Auditory P3a Deficits in Male Subjects at High Risk for Alcoholism

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Background: *Substantial evidence indicates that alcoholism is biologically mediated by a genetic predisposition. As the decreased P300 (P3b) event-related brain potential component does not recover with prolonged abstinence, it is unlikely to be related to drinking history but is more likely to be genetically influenced. This is supported by findings that P3b amplitudes are reduced in subjects at high-risk compared to low-risk for alcoholism. Although there are few studies of P3a in HR subjects, lower P3a amplitudes have been reported with a novel nontarget stimulus paradigm, as well as with a difficult three-stimulus visual paradigm. Using a similar three-tone auditory paradigm in which the discriminability between the target and standard tone is difficult, the P3a component can also be reliably elicited with a rare nontarget perceptually distinct stimulus. This technique was employed in young adult subjects at low-risk and high-risk for alcoholism.*

Methods: *A total of 17 low-risk and 24 high-risk male subjects were employed as subjects in an auditory paradigm that yielded a large amplitude P3a with a centro-frontal maximum to the nontarget and a robust low amplitude prolonged P3b with a parietal maximum amplitude to the target stimulus. Current source density maps were derived to assess topographic differences between low-risk and high-risk subjects.*

Results: *The high-risk group manifested significantly lower P3a amplitudes than the low-risk group at the frontal electrodes to rare nontarget stimuli. High-risk subjects also demonstrated a more disorganized current source density map for P3a compared to low-risk subjects.*

Conclusions: *The reduction of P3a in the high-risk group may be due to cortical dysfunction including the frontal and prefrontal cortex. The lower P3a amplitude coupled with more disorganized current source density maps suggest inefficient brain functioning in high-risk subjects.*
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Introduction

A good deal of evidence suggests that alcoholism is biologically mediated (Cloninger 1987; Schuckit 1980). In particular, male children of alcoholic parents raised by nonalcoholic foster parents are at higher risk for developing alcoholism than are the biological children of nonalcoholic parents (Cloninger et al 1981; Goodwin 1979). Event-related potential (ERP) differences have been reported between abstinent alcoholics and control subjects, especially low amplitude P3(00) in abstinent alcoholics (Pfefferbaum et al 1991; Porjesz et al 1987a, 1987b). Despite the characteristic low P3 amplitude consistently reported in alcoholics, the role of chronic alcohol abuse on the diminished P3 voltages observed in alcoholics is unclear. As the P3 component does not recover with prolonged abstinence (Porjesz and Begleiter 1985), it seems unlikely to be related directly to the patient's drinking history (Pfefferbaum et al 1991), but rather seems to be genetically influenced (Almasy et al 1999; Begleiter et al 1998; Katsanis et al 1997; O'Connor et al 1994; van Beijsterveldt 1996).

Begleiter et al (1984) assessed ERPs in preteen subjects at-risk for alcoholism using a complex head-orientation paradigm that employed both easy and difficult conditions. P3 amplitudes were significantly smaller in the high-risk group (HR) compared to the low-risk group (LR), especially in the difficult condition. These findings have been replicated using the identical head orientation paradigm, both in prepubescent and in postpubescent boys at risk for alcoholism (Hill and Steinhauer 1993; O'Connor et al 1986) as well as with other visual paradigms (Berman et al 1993; Noble 1990; Porjesz and Begleiter 1990; Whipple et al 1988, 1991); however, a comprehensive meta-analysis of at-risk P3 studies indicated that P3 amplitude difference were most evident in young prepubescent male subjects when a difficult visual discrimination task was used. The results in older offspring were more variable, particularly those involving easy auditory tasks (Polich et al 1994).

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In addition, a type of P300 can be elicited with intrusive or novel stimuli (e.g., dog barks, abstract color forms, etc.) to which the subject does not respond, such that an earlier potential called P3a is generated, which seems to be distinct from the later P300 or P3b component (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); however, recent reports indicate that P3a amplitude is directly affected by the discrimination difficulty between the target and standard stimuli and not upon 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 (Knight 1996; Potts et al 1996), and readily habituates. Hence, P3a reflects the initial response to an incoming signal, and P3b indexes the attentional and mnestic operations engaged during subsequent stimulus processing (Knight 1990; McCarthy et al 1997). Although the majority of ERP studies in HR subjects have used P3b tasks, there are a few studies of P3a. Using a novel nontarget stimulus paradigm in HR subjects, smaller P3a amplitudes were observed for HR compared to LR over the occipital region without significant differences in P3a latency, behavioral performance, or current source density (CSD) maps of novel P3 (van der Stelt et al 1998). Similarly, smaller P3a amplitudes were found in HR subjects using a difficult three-stimulus visual paradigm (Rodriguez Holguin et al 1999a). Thus, P3a deficits in HR subjects may exist, but the nature of these effects is not yet clear.

This Study

A critical factor for delineating P3a amplitude effects in HR subjects seems to be the nature and modality of the discrimination task. This study was conducted to ascertain whether P3a from a difficult auditory three-tone paradigm would be affected by the genetic predisposition toward alcoholism. This issue is important because it is suggested that P3a reflects frontal lobe function. Comparable groups of LR and HR were assessed, and both ERP and 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 LR and HR subjects, all of whom were right-handed male subjects. All subjects provided informed consent and received pecuniary remuneration for their participation. Exclusionary criteria for both groups included major medical problems, CNS medication, a history of psychiatric problems and/or drug abuse. Prospective subjects were screened with a questionnaire that detailed alcohol/drug use and the medical and psychiatric histories for both himself and his relatives. Inclusion in the LR group initially depended on both the responses to the questionnaire and the requirement that none of the LR candidate's first-or second-degree relatives be diagnosed as alcoholic. In contrast, the HR group consisted of young adult, nonalcoholic male subjects recruited using the same methods. Inclusion in the HR group required that at least the subject's father be classified as alcohol dependent, but if the mother was alcoholic that individual was excluded.

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

	High-risk	Low-risk
Sample size	24	17
Age (years)	22.8 (1.8)	22.9 (1.8)
Education (years)	12.2 (1.4)	13.4 (2.2)
Drinking days/week	4.9 (5.4)	1.9 (2.1)[a]
Drinks/occasion	4.1 (4.1)	2.1 (2.2)[a]
Density	2.1 (1.3)	0

Density: the number of alcoholics within first- or second-degree relatives.
[a] $p < .05$.

Subjects came to the laboratory and were given a detailed psychiatric interview that focused on drug and alcohol use (quantity/frequency), the medical and psychiatric histories for both himself and his first and second-degree relatives. Some subjects (both the LR and HR) 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 employs both DSM-III-R and Feighner criteria to define alcoholism (Bucholz et al 1994). Interviews with additional family members were also obtained to validate the family history information. All subjects were asked to abstain from alcohol for 48 hours before testing. A breathanalyser test was administered on the day of testing, and individuals with values greater than zero were excluded. Urine screens on the day of testing were employed to exclude subjects manifesting drug use.

ERP Paradigm and Recording

Subjects were seated in a reclining chair located in a sound-attenuated and shielded room. They were instructed to fixate on a point in the center of a computer display located 1 m away from their eyes. The subject was presented with 350 binaural tones through headphones at 103 dB SPL (10-msec rise/fall, 40-msec plateau) and an interstimulus interval of 1.5 sec, with 280 standard (1630 Hz), 35 target (1530 Hz), and 35 rare nontarget (670 Hz) stimuli. The target and standard stimuli were difficult to discriminate from each other, but the rare nontarget stimulus was readily perceived. 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 rates 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 rare nontarget. The experiment concluded when all 350 stimuli had been presented.

An electrode cap with 61 electrodes (ECI, Electrocap International) was used that included the 10–20 system and 42 additional sites: 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, P.O.1, P.O.2, P.O.7, and P.O.8 (Electrode Position Nomenclature, American Electroencephalographic Association 1991). Scalp electrodes were referred to the nose, with a ground electrode on the forehead, and the impedances reduced to 5 kΩ or less. 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 EPA-2 amplifiers (Sensorium, Inc.), with a 0.02- to 50-Hz bandpass interfaced to a Concurrent 5550 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 (EMG, EOG, saturation > 73.3 μV) were performed off-line.

ERP Data Analysis

The P3a component was obtained from the rare nontarget, and the P3b component was obtained from the target stimuli; they were defined as the largest positive-peaks 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 (FP1, FP2, FPZ, AF1, AF2, AF7, AF8, AFZ, F1, F2, F3, F4, F5, F6, F7, F8, FZ), central (FC1, FC2, FC3, FC4, FC5, FC6, FCZ, C1, C2, C3, C4, C5, C6, CZ), parietal (CP1, CP2, CP3, CP4, CPZ, P1, P2, P3, P4, PZ), occipital (P.O.1, P.O.2, P.O.7, P.O.8, POZ, O1, O2, OZ), left temporal (FT7, T7, TP7, CP5, P7, P5), and right temporal (FT8, T8, CP6, TP8, P6, P8) regions. The mean amplitude computed over electrodes within each region was employed as the dependent amplitude measure. Multivariate analyses of variance (MANOVA) were performed to compare the two groups (2 groups × 6 regions). Analyses of variance (ANOVA) were used to compare group differences for P3a amplitude in each region. As there was a significant difference between groups in mean years of education and mean drinks per month, these two variables were employed as covariates in the analysis of P3a amplitude in the frontal region (ANCOVA).

Current Source Density Analysis

Scalp ERPs 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

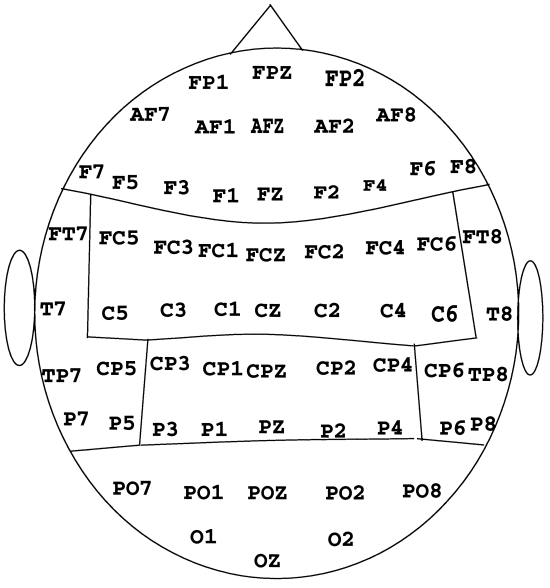
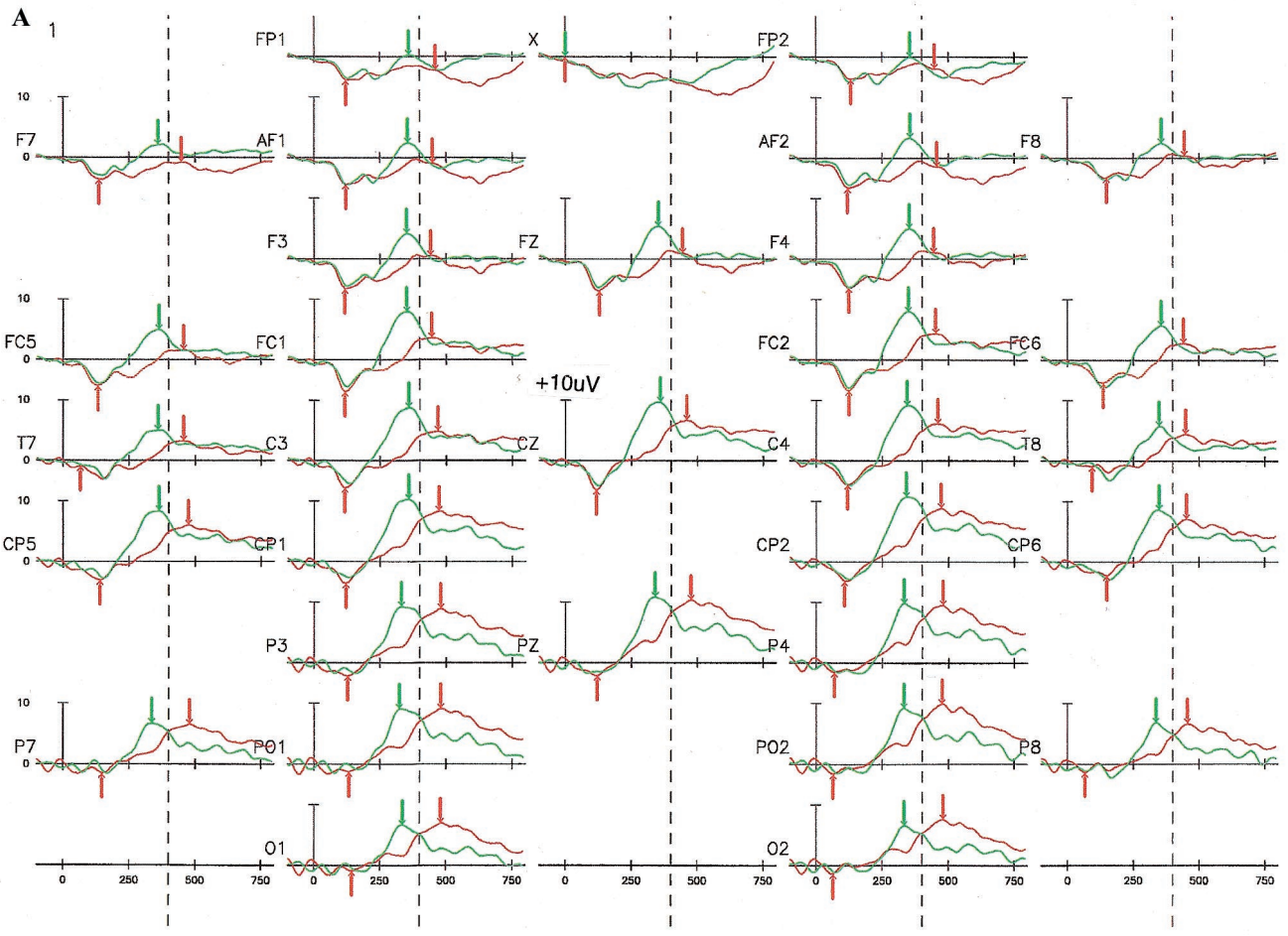


Figure 1. Schematic illustration of the electrode montage and six regional groupings (frontal, central, parietal, occipital, right temporal, left temporal) used in the statistical analyses of the event-related brain potential and current source density data.

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 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). Topographic CSD maps were constructed for both groups using the rare nontarget amplitudes measured at the average peak latency (Wang and Begleiter 1999). 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.

To increase the analytical sensitivity, CSD maps were also derived from 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

Figure 2. **(A)** Event-related potential grand averages for target (red) and rare nontarget (green) stimuli for 30 electrode sites from the high-risk subjects ($n = 24$). **(B)** Event-related potential grand averages for target (red) and rare nontarget (green) stimuli for 30 electrode sites from the low-risk subjects ($n = 17$).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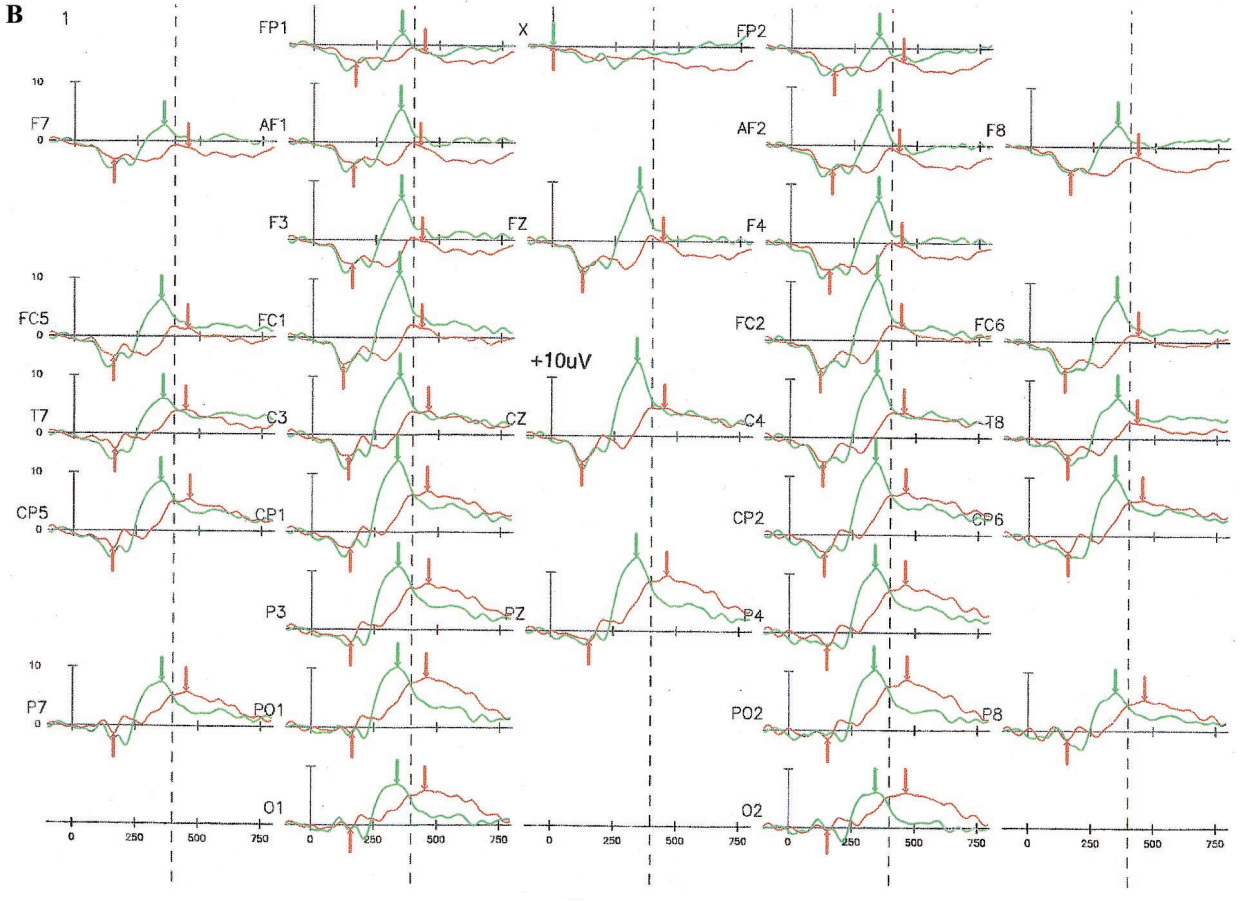
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correlation coefficient (Pearson *r*) computed between groups using the CSD value across electrodes within each of the topographic regions will be zero. If the CSD scalp topography shapes are not different, the correlation coefficient will be significantly 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 *z* transformation of *r* was applied to the correlations obtained from each sampling, and for each *z* value, group differences were assessed using a *t* test.

Results

Task Performance

The mean percentage of errors was 2.3%, with no statistically reliable group differences found for any stimulus category ($p > .10$); the error rate was the same for rare nontarget stimuli in both LR and HR groups (1%, $p > .1$). Response times were not significantly different between the LR and HR groups (525 vs. 547, $p > .10$). Thus, task performance was equivalent for each group.

ERP Analyses

Figure 2 illustrates the grand average ERPs for rare target and rare nontarget conditions for the LR and HR groups. Figure 3 illustrates the mean P300 amplitudes from the rare nontarget (P3a) and target (P3b) stimulus for each subject group.

Intragroup 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 × 4 midline electrodes) MANOVA to determine whether the two groups differed with respect to whether the three-stimulus paradigm produced similar P3a and P3b outcomes. Low risk subjects manifested significantly larger overall P3a than P3b amplitudes [$F(1,16) = 22.1$, $p < .001$], and increasing amplitudes from the frontal to parietal/occipital electrodes [$F(3,48) = 9.2$, $p < .001$], with a stimulus type × electrode interaction [$F(3,48) = 2.3$, $p > .05$]. P3a had a consistently shorter peak latency than P3b [$F(1,16) = 119.3$, $p < .001$], and no other reliable outcomes obtained ($p > .50$ in all cases). High risk subjects produced larger P3a compared to P3b amplitudes [$F(1,23) = 7.2$, $p < .01$], similar increases across the midline [$F(3,69) = 10.2$, $p < .001$], and no stimulus type × electrode interaction [$F(3,69) = 10.2$, $p > .05$]. P3a latency was shorter than P3b [$F(1,23) = 246.7$, $p < .001$], with no other reliable outcomes obtained ($p > .9$ in all cases). In sum, both subject groups produced similar P3a and P3b latency and amplitude patterns (Figure 4).

Nontarget P3a

P3a amplitude from the rare nontarget stimulus was assessed using a two-factor (2 groups × 6 regions) MANOVA. Low risk subjects demonstrated larger amplitudes overall than HR [$F(1,41) = 9.9$, $p < .01$], with reliable regional differences also obtained [$F(5,205) = 102.2$, $p < .001$]. Furthermore, there was a significant group × region interaction ($p < .05$).

A one-factor ANOVA was used to compare group differences for P3a amplitude in each region. In the frontal region, HR subjects evinced a significantly lower amplitude than LR subjects did [$F(1,41) = 16.1$, $p < .001$]. No significant differences were found between the two groups in other brain regions ($p > .05$ in all cases). P3a latency was assessed similarly and no significant outcomes were obtained ($p > .20$ in all cases). Hence, the rare nontarget stimuli elicited different P3a amplitudes for the LR compared to HR subjects, and regional differences were observed only in the frontal region. As indicated in Table 1, risk group comparison for number of drinking days/week and drinks/occasion revealed significant reliable differences. Therefore, rare nontarget P3a amplitude in the frontal region was analyzed using an analysis of covariance (ANCOVA) with the mean drinks/week and the mean drinks/occasion as covariates. In both analyses, the HR group had a significantly lower amplitude than the LR group in the frontal region.

Target P3b

Similar analyses were performed for P3b, but we did not obtain significant differences between the HR and LR groups for amplitude and latency.

Current Source Density Analysis

Figure 5 illustrates the CSD maps for the rare nontarget and the target in both groups. Both groups demonstrated stronger anterior current source density distributions for the rare nontarget (P3a) compared to the target (P3b). Table 2 summarizes the statistical analyses for the P3a and P3b CSD maps. Low risk subjects manifested stronger current density than HR subjects for the rare nontarget. There were more sources and sinks in the CSD maps for the HR than for the LR group. For the rare nontarget, the HR group demonstrated predominant sources in one portion of right central, midparietal, and left temporal areas; sinks occurred in right frontal and right temporal regions. The LR group demonstrated predominant sources in the entire central, parietal and

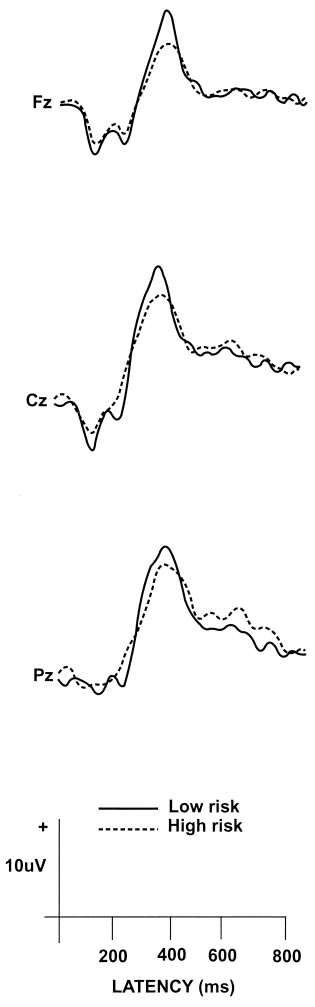

Figure 3. Low-risk and high-risk subject grand average event-related potentials from rare nontarget stimuli from the midline electrodes.

occipital regions; sinks occurred in the right frontal region. For the target, the HR group demonstrated predominant sources in the parieto-occipital region; sinks occurred in the right frontal region. The LR group also demonstrated predominant sources in the parieto-occipital region; sinks occurred in the right and left front-temporal region. On visual inspection it appears that the CSD maps for the target (P3b), were more similar between the two groups than were the CSD maps for the rare nontarget (P3a); however, the bootstrap analysis method indicated that the distributions between HR and LR were significantly different for both the rare nontarget ($p < .0001$) and the target ($p < .0001$) CSD maps in all regions (Figure 5).

Discussion

This study employed an auditory three-stimulus paradigm to elicit the P3a and P3b components in LR and HR subjects. Because the difficult auditory target/standard discrimination employed in this study elicited reliable group differences for the P3a from the rare nontarget stimulus (Comerchero and Polich 1998, 1999; Katayama and Polich 1998), it is reasonable to conclude that task difficulty is a critical variable for demonstrating high risk versus low risk P3a effects (Polich and Bloom 1999; Polich et al 1994). Although the subject groups demonstrated similar distributions of amplitude and latency for the rare nontarget and target stimuli, P3a amplitudes were smaller overall for the HR compared to the LR group. Regional analyses revealed that the HR subjects had significantly lower P3a amplitudes in the frontal region compared to the LR subjects. Different CSD patterns were also found between groups, which suggest that neuroelec-

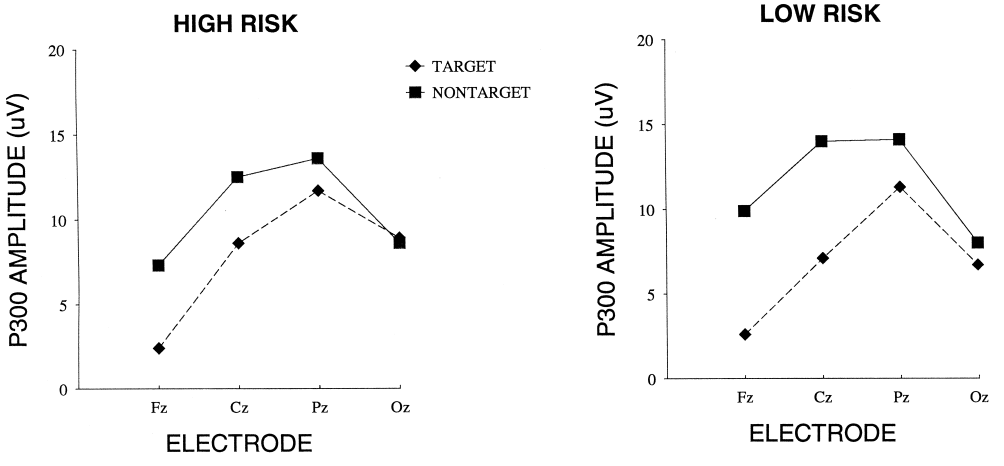

Figure 4. Mean P300 peak amplitudes from the low-risk and high-risk subjects for the target and nontarget stimuli as a function of midline electrode sites.

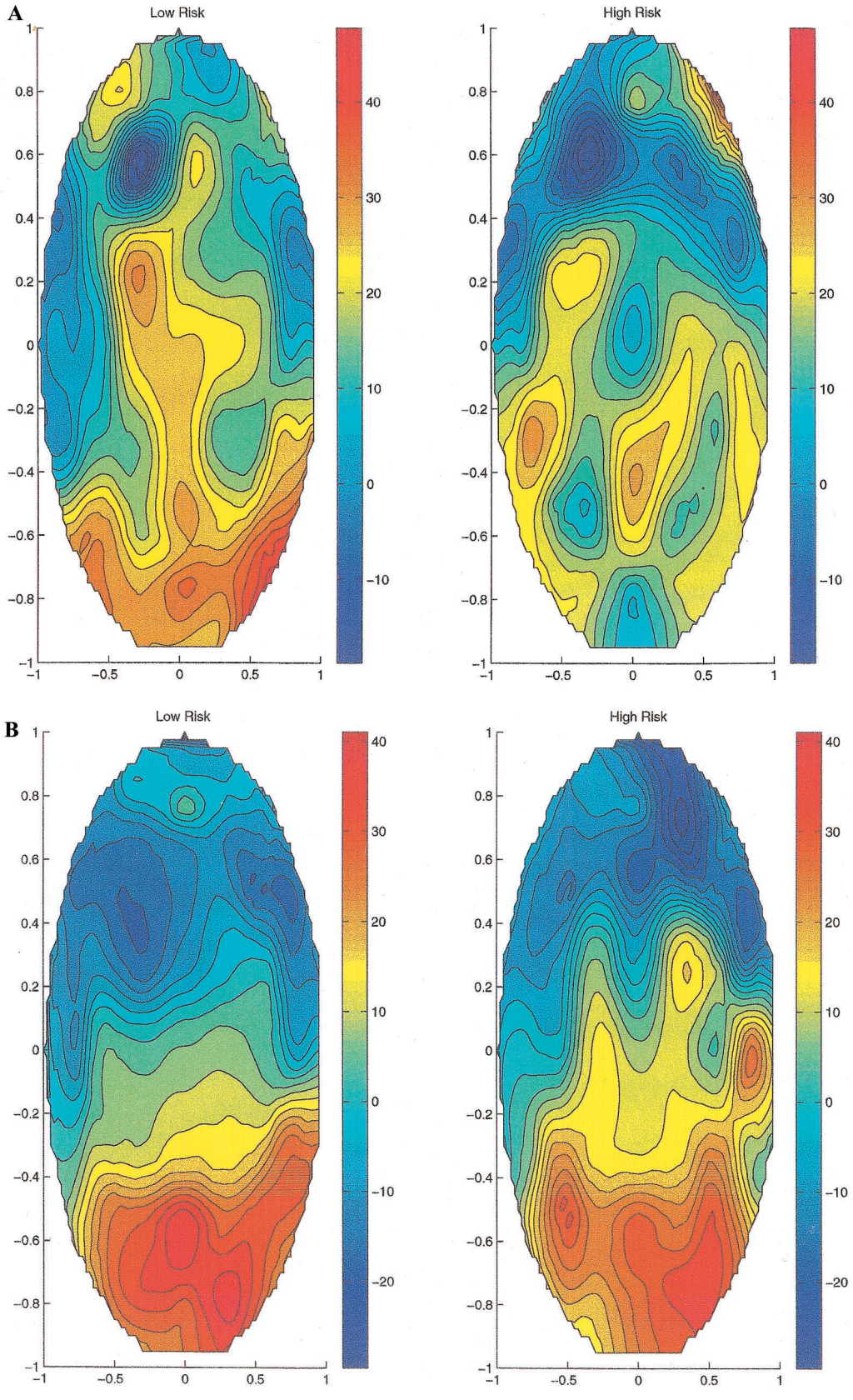

Figure 5. **(A)** Current source density maps of P3a from the rare nontarget stimuli for low- and high-risk subjects (unit, $\mu V/r^2/cm^2$ [r, head radius]). **(B)** Current source density maps of P3a from the target stimuli for low- and high-risk subjects (unit, $\mu V/r^2/cm^2$).

Table 2. Mean *z* Score Values from the Current Source Density Comparisons for Each Major Electrode Region for Rare Nontarget P3a and Target P3b

	P3a			P3b		
Region (df = 398)[a]	HR vs. LR	Random-1 vs. Random-2	*t* value (df = 398)[a]	HR vs. LR	Random-1 vs. Random-2	*t* value
Frontal	2.61	2.28	8.0	3.06	2.79	9.0
Central	2.91	2.64	6.3	3.30	3.01	8.5
Parietal	2.54	2.11	10.7	2.92	2.68	7.2
Occipital	2.71	2.34	9.3	3.11	2.86	8.7
Right temporal	2.54	2.31	4.8	3.03	2.56	11.9
Left temporal	2.45	2.08	4.9	2.89	2.61	8.8

See Figure 1 and text for details. HR, high risk; LR, low risk.
[a]All statistical outcomes obtained $p < .0001$.

tric mechanisms underlying the P3a component were different for the two groups.

Although difficult tasks have been found to more readily differentiate P3b amplitude to targets between HR and LR subjects (Polich et al 1994), when target and standard discriminations are *extremely* difficult, less differentiation has been reported between alcoholics and controls (Porjesz et al 1987b) and HR and LR (Porjesz and Begleiter 1996). P3b amplitude decreases and latencies become prolonged with increasing task difficulty in normal subjects (Ford et al 1979; Johnson and Donchin 1978; Ritter et al 1972; Towey et al 1980), which has been suggested to be due to equivocation (Ruchkin and Sutton 1978). As both the controls and alcoholics have difficulty discriminating the target and standard for these difficult discrimination tasks, there is a "floor effect" with both groups manifesting low P3bs. Thus, this is not a typical P3b paradigm but rather this extremely difficult discrimination between target and standard is used to elicit a large clear P3a to the rare nontarget (Comerchero and Polich 1998, 1999; Hada et al in press; Katamaya and Polich 1998; Rodriguez Holguin et al 2000). As Figure 4 indicates, with this atypical paradigm, P3a is actually larger than P3b, and the P3bs are indeed prolonged and of a low amplitude in both groups.

P3a, HR for Alcoholism, and Frontal Lobe Dysfunction

Although the precise location of the P3a generator is unknown, the frontal cortex is implicated because the response is markedly affected by frontal cortex damage. Patients with circumscribed lesions of dorso-lateral frontal cortex demonstrated a reduction in P3a, with relative sparing of P3b for different (auditory, visual, and somatosensory) modality; lesions of temporal-parietal junction produce near abolition of P3b (Knight 1984; Yamaguchi and Knight 1991). Hence, the integrative functions of the temporal-parietal junction (Halgren et al 1995; Yamaguchi and Knight 1991) and hippocampal involvement (Johnson 1993; Polich and Squire 1993) are necessary generators of the P3b, although these neural loci cannot be the sole generators of the P3 (Knight 1996). Similarly, single photon emission tomography during a three-tone (novel) auditory discrimination task, demonstrated that P3a amplitude was positively correlated with anterior cingulate tracer uptake, and negatively correlated with temporal cortical activity (Ebmeir et al 1995). Magnetic resonance imaging (MRI) results also have found that P3 components recorded during both automatic and effortful attention correlated with frontal and parietal gray matter volumes (Ford et al 1994). In addition, evidence from the lesion literature indicates that P3b persists even following severe hippocampal lesions; P3a seems to be much more sensitive to hippocampal lesions (Knight 1996). Thus, differential effects of frontal lesions on P3a and P3b argue for a distinctive frontal cortex contribution to P3a generation, and at least partially different generator locations for P3a and P3b.

Several neuroimaging studies of alcoholics suggest that alcoholics with cortical atrophy on CT scan manifested lower P3 amplitudes than alcoholics without cortical atrophy (Begleiter et al 1980). MRI assessment has found that volume losses in the diencephalon, the caudate nucleus, dorsolateral frontal and parietal cortex, and mesial temporal lobe were the most prominent in alcoholics (Jernigan et al 1991). Furthermore, older alcoholics demonstrate a selective deficit in prefrontal gray matter relative to the younger alcoholic group and the cortical white matter volume deficit in the older alcoholics was especially severe in the prefrontal and frontal regions (Pfefferbaum et al 1997). Alcoholics also showed decreased local cerebral metabolic rate for glucose (LCMRglc) in the medial frontal area in comparison with the normal control subjects with PET procedures. The severity of clinical neurologic impairment (especially in the performance on the Wisconsin Card Sorting Test), was significantly cor-

related with the degree of hypometabolism in the medial frontal region of the cerebral cortex (Adams et al 1993; Gilman et al 1996; Shimamura 1995). In sum, these neuroimaging studies suggest that alcoholics have a dysfunction in the frontal lobe, especially the prefrontal region. The present results indicate that HR subjects manifest low P3a amplitudes, particularly over the frontal region. Similar P3a deficits have recently been reported in alcoholics using the same three-tone paradigm (Hada et al in press). As both the alcoholic and the HR groups manifest similar dysfunction, this supports the conclusion that the dysfunction antecedes the development of alcoholism and may be genetically mediated.

P3a, HR for Alcoholism, and CSD

The most prominent current sources are apparent more anteriorly for the rare nontarget compared to the target stimulus in both groups, a finding consistent with the previous potential distribution studies (Courchesne et al 1975; Knight 1984). Current source density maps were more organized in the LR than the HR groups for both target and rare nontarget, whereas they seem disorganized for the rare nontarget in the HR group. The difference in distribution of CSD maps to the rare nontarget stimulus between LR and HR suggests that HR subjects 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 (Courchesne et al 1975; Ebmeier et al 1995; Friedman et al 1993, 1994; Knight 1984; Yamaguchi and Knight 1991). 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; however, it is suggested that the frontal lobe plays an important role in determining the difference in CSD maps between alcoholics and controls. The weaker sources to rare nontargets coupled with the lack of organization in the CSD maps of HR compared to LR, suggests that HR subjects 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 HR subjects, perhaps reflecting underlying CNS hyperexcitability that is genetically mediated.

P3a, CNS Disinhibition, and Predisposition for Alcoholism

There have been a number of functional models proposed to account for P3 amplitude, namely: context updating (Donchin and Coles 1988), closure (Verleger 1988), and CNS inhibition (Desmedt 1980). Recent reports have found that when both go and no-go are used to elicit the P3 component, reduced amplitude for both alcoholics and HR individuals were obtained (Cohen et al 1997a, 1997b). In keeping with various neurophysiological accounts of the P3 ERP component (Desmedt 1980; Lutzenberger et al 1978), low P3 voltage may be an index of CNS disinhibition (Begleiter and Porjesz 1999; Cohen et al 1997a, 1997b; Porjesz and Begleiter 1996, 1998; Ramachandran et al 1996). Several investigators have proposed that the P3 component of the ERP is largely caused by a widely distributed inhibitory event which operates under various processing functions (Halgren et al 1986; Rockstroh et al 1992; Smith et al 1990; Woodward et al 1991). Other sources, such as the temporal-parietal junction (Knight et al 1989) and the magnocellular or intralaminar tuning mechanisms that regulate cortical excitability (Velasco et al 1986; Yingling and Hosobuchi 1984) could also modulate the polarization of neocortical apical dendrites known to be the primary contributor to the scalp EEG (Elbert and Rockstroh 1987). A somewhat different mechanism for controlling pyramidal cells by the P3 has been proposed such that the P3 component arises in part when propagation of lateral inhibition through the reticular nucleus decreases thalamocortical pathways and cortical projection sites not driven by the task stimulus relative to the pathways activated by the specific stimulus (Roberts et al 1994). Other investigators have invoked a resolution/relaxation hypothesis, that asserts that the P3 positivity constitutes an inhibitory resolution of preceding excitatory negativity (Deecke et al 1984). Finally, it has been proposed that negative shifts in ERPs indicated enhanced excitability of neural networks, whereas positive shifts were indicative of decreased excitation (Birbaumer et al 1990; Rockstroh et al 1989). It may be that slow positive potentials such as the P3 component of the ERP indicate an inhibitory process, namely a disfacilitated state of neuronal networks.

Although most of these studies have been conducted on P3b or Go and No-Go P3, there have been several P3a studies indicating that CNS disinhibition is associated with frontal lobe function. As measured by somatosensory P3a and other neurophysiological tests, humans with prefrontal damage showed increased distractibility and impaired gating of inputs to primary auditory and somatosensory cortex (Knight et al 1989; Woods and Knight 1986; Yamaguchi and Knight 1990). Additional evidence from animal experiments suggests that the prefrontal cortex is important for the early selection of sensory inputs and that damage to this area in animals and humans results in disinhibition of input to primary cortical regions (Knight et al 1989; Skinner 1976; Yamaguchi and Knight 1990; Yingling et al 1976). Thus, the present findings support

the conclusion that HR subjects manifest a P3a amplitude reduction reflecting CNS disinhibition.

A pleiotropic model has been suggested by COGA results (Porjesz et al 1998), where the genotype is hypothesized to indicate a low voltage P3 as a predisposing factor for the future development of a number of disinhibitory conditions such as alcoholism, substance abuse, attention-deficit-hyperactivity disorder, and antisocial behavior (Iacono 1998). Both antisocial personality disorder (ASPD) and family history of alcoholism predispose individuals to alcoholism, and individuals in both of these groups manifest low P3 sec (Hesselbrock et al 1993). Because P3a amplitude reductions have not only been found in alcoholics (Hada et al in press; Pfefferbaum et al 1991; Realmuto et al 1993; Rodriguez Holguin et al 1999b) but also in HR subjects (Rodriguez Holguin et al 1999a) as well as in this study, it is suggested that the P3a amplitude reduction is also a heritable trait. It satisfies some of the conditions necessary for a phenotypic marker of a psychiatric disease (Porjesz et al 1998). It is present in patients during symptom remission, and occurs among first-degree relatives of affected individuals at a rate higher than that of the normal population. Although the P3b has been found to be highly heritable (Almasy et al 1999; Begleiter et al 1998; Eischen and Polich 1994; Katsanis et al 1997; O'Connor et al 1994; Polich and Burns 1987; van Beijsterveldt 1996), this still remains to be established for P3a. Therefore, similar to the findings for P3b, the P3a amplitude reduction may reflect a predisposing factor for alcoholism, indicating underlying CNS disinhibition.

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