0145-6008/02/2603-0303$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 26, No. 3
March 2002

Alcohol-Related ERP Changes Recorded From Different Modalities: A Topographic Analysis

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Background: There is controversy in the literature regarding the relationship between event-related-potential (ERP) abnormalities in abstinent alcoholics and stimulus-processing modality (i.e., visual versus auditory). The first purpose of this study was to address questions about whether ERP abnormalities observed in alcoholics are modality specific. The second purpose was to employ current source density (CSD) analyses to investigate topographic differences between alcoholics and controls within each modality.

Methods: Data were collected from 30 sober male alcoholics and 39 normal males in a typical auditory oddball task and in a visual oddball paradigm with novel stimuli, with an extensive set of 61 scalp electrodes. Visual and quantitative assessment of CSD maps as well as analyses of variances on both raw and normalized ERP data were performed.

Results: Positive findings were limited to the N1 and P3 components. The visual N1 amplitude was significantly smaller in alcoholics than in controls at the parietal region; no significant group differences in N1 were found in the auditory modality. Alcoholics had widespread reductions in P3 amplitudes in both modalities compared with controls, although in the frontal region this effect was partially due to the influence of age. These P3 reductions in alcoholics were statistically more pronounced in the posterior compared with the anterior regions regardless of modality. Topographically, sources in CSD maps were weaker in alcoholics than in controls; in the frontal and central regions, the weakness was more pronounced in the auditory modality but, in parietal and occipital regions, it was more pronounced in the visual modality.

Conclusions: The results suggest that, in abstinent alcoholics, abnormalities in auditory ERPs may be localized to more anterior sources, while abnormalities in visual ERPs may be localized to more posterior sources. ERP topographic features are more sensitive than amplitude measurements in assessing alcoholic-related modality effects.

Key Words: Topography, Alcoholics, P3, N1, Modality, CSD.

EVENT RELATED POTENTIALS (ERPs) recorded in the oddball paradigm have provided abundant measurements that differentiate groups with and without alcohol dependence (Glenn et al., 1996; Porjesz and Begleiter, 1996). The most robust ERP feature is the lower P3 amplitude in abstinent alcoholics (Cohen et al., 1995; Emmerson et al., 1987, Glenn et al., 1994, Pfefferbaum et al., 1987; Porjesz et al., 1980; Porjesz and Begleiter, 1987); decreased N1 amplitude as well as prolonged N2 and P3 latencies are less consistent findings (Glenn et al., 1996; Porjesz and Begleiter, 1987; Romani and Cosi, 1989). The typical oddball task given to sober alcoholics requires effortful or controlled processes, because subjects are making a button-press response or mentally counting the number of target stimuli (Pfefferbaum et al., 1991; Porjesz et al., 1980). The target stimulus is usually the oddball which appears randomly and less frequently in a series of more frequent and physically different (i.e., high versus low tone or triangle versus square shapes) stimuli in either the auditory or visual modality; in a dual-modality paradigm, it is the attended oddball within one modality with respect to the rare stimulus of the other modality (Porjesz and Begleiter, 1983). In precise terms, the target-elicited P3 in such paradigms is actually the P3b component, and the reduction in its amplitude is a widely observed phenomenon in alcoholics (Porjesz and Begleiter, 1996). This observation is further corroborated by single trial analyses, which take the variability of latency into consideration (Pfefferbaum et al., 1991). In contrast, some investigations of P3b have failed to observe an amplitude deficit in male (Hill et al., 1995,1999; Steinhauer et al., 1987) and female (Hill et al., 1999; Parsons, 1994; Parsons et al., 1990) alcoholics and in auditory (Hill et al., 1995,1999; Parsons et al., 1990; Steinhauer et

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Received for publication January 31, 2001; accepted December 5, 2001.

This research was supported by NIH Grants AA05524 and AA02686 (HB, BP).

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al., 1987) and visual (Hill et al., 1999; Parsons, 1994; Parsons et al., 1990) paradigms. In addition, the P3 voltage responses to novel, nontarget stimuli (P3a) (Biggins et al., 1995), or no-go stimuli (Pfefferbaum et al., 1987) do not manifest differences between alcoholics and controls. However, recent studies (Hada et al., 2000; Holguin et al., 1999) report that the P3a amplitude is lower in alcoholics than controls to rare deviant nontargets. The N1 and N2 components are thought to be more passive and less target-dependent (Naatanen and Picton, 1987; Ritter et al., 1984) compared with the target-elicited P3, which reflects a relatively controlled process (Bashore and van der Molen, 1991). While a lengthened N2 latency without the concomitant amplitude reduction has been reported (Glenn et al., 1993; Porjesz et al., 1987), decreased N2 without prolonged latency has also been reported (Realmuto et al., 1993). Mixed reports also have been observed with regard to the N1 amplitude reduction (Kaseda et al., 1994; Miyazato and Ogura, 1993; Oscar-Berman, 1987; Realmuto et al., 1993), especially when target and nontarget elicited ERPs were both examined (Glenn et al., 1996).

Further, although these ERP aberrations were observed in auditory, visual, and dual-modality oddball paradigms, it seems that, in alcoholics, paradigms employing visual stimuli are most likely to elicit decreased P3 and N1 amplitudes (Ciesielski et al., 1985; Cohen et al., 1995; Glenn et al., 1993; Parsons, 1994; Steinhauer et al., 1987). The inconsistency among studies mentioned above could be due to a number of variables: (1) different percentages of alcoholic subjects with positive family histories (Patterson et al., 1987), a variable considered to be an important contributor to the observed P3 amplitude reduction in alcoholics (Cohen et al., 1995; Pfefferbaum et al., 1991); and/or (2) differences in subjects' ages (Glenn et al., 1996; Picton et al., 1984); and/or, (3) differences in difficulty level (Porjesz et al., 1987). It is possible that ERPs in different modalities may be differentially sensitive to alcoholism (Pfefferbaum et al., 1991). In Pfefferbaum et al. (1991), alcoholics showed smaller P3 amplitudes in both auditory and visual paradigms but had later and more frontally distributed P3 amplitudes only in the visual paradigm. While studies showed controversially that visual and auditory P3 components may involve different neural generators (Ji et al., 1999; Johnson, 1993; Naumann et al., 1992), studies of N1 and N2 components agreed that these negative components are actually modality-dependent (Naatanen and Picton, 1987; Ritter et al., 1984). Considering that different topographic regions may manifest peak activity to the same stimuli in different modalities, it is natural to hypothesize that there may be differences in sensitivities between alcoholics and controls to modality-specific features of stimuli. Such sensitivity differences may be partly responsible for the diverse results found in the literature regarding whether there are ERP changes in alcoholics using different oddball paradigms. Thus, one of the purposes of the present study is to further investigate the modality specific ERP features of alcoholics by directly comparing auditory and visual ERPs obtained in the same subjects with an extensive set of scalp-recording sites (61 sites).

By employing 61 scalp-recording sites, it is possible for us not only to conduct regional analyses of ERP data between auditory and visual paradigms in alcoholics but also to provide a better resolution of scalp topography in terms of current source density (CSD) maps. Therefore, besides cross-validation of ERP amplitude and latency changes in alcoholics, the scalp topography based on 61 scalp sites enables us to extend our investigation to the topographic features of P3 components in alcoholics and healthy controls within and across sensory modalities. By performing topographic analyses of ERP data in two sensory modalities in alcoholics, we attempt to advance the understanding of source localization of alcoholic ERP changes (Oades et al., 1995).

In summary, this study examines the ERP differences between sober alcoholics and normal controls, based on data recorded from 61 scalp electrode sites to both auditory and visual stimuli. Neither any modality difference by itself nor any group difference alone is emphasized in this study. Rather, our interests emphasize those group differences that appeared true/stronger in one modality and false/weaker in another modality or those modality differences that seemed true/stronger in one subject group and false/weaker in the other subject group.

METHODS

Subjects

Thirty male experimental subjects (30.33 ± 4.31, between 21 and 37 years old) and 39 male control subjects (24.67 ± 3.30, between 20 and 33 years old) participated in the experiment. Alcoholics were recruited from Kings County Hospital; all individuals met DSM-III-R criteria for alcohol dependence and had been detoxified in a 30-day treatment program prior to testing. However, they were neither released to us nor to their own community unless they were no longer in withdrawal. Table 1 presents MMSE (Mini Mental Status Examination) scores, education, age of onset, drinks per day, and number of drinking days per month. Controls were recruited either through notices posted in the SUNY Health Science Center or via newspaper ads.

Table 1. Demographic Variables for Alcoholics and Controls (Mean, SD, and Range)

Groups	Years of education	MMSE	Age at onset of drinking (yrs)	Drinking days per month*	Drinks per occasion*
Alcoholics	11.6 (2.49)	27.5 (2.75)	14.3 (5.11)	23.0 (9.57)	15.1 (16.9)
(n = 30)	(5–16)	(19–30)	(4–31)	(0–31)	(0–70)
Controls	15.5 (2.23)	28.8 (1.50)	Not applicable	2.49 (4.54)	1.38 (1.41)
(n = 39)	(10–20)	(24–30)		(0–25)	(0–5)

* Data are for the 6 months prior to treatment.

The screening procedure required each control and alcoholic individual to fill out a questionnaire detailing alcohol and drug use and the medical (including psychiatric) histories for both himself and his relatives. Inclusion in the control group depended on both the responses to the questionnaire and the requirement that none of the candidate's first- or second-degree relatives be diagnosed with any kind of alcohol-related disorder. Exclusionary criteria for both groups included major medical problems, a current requirement for medication with effects on the central nervous system (CNS), or a history of psychiatric problems. These clinical data were obtained with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994), an instrument developed by COGA (Collaborative Study on the Genetics of Alcoholism) that uses both DSM-III-R and Feighner criteria for the determination of alcoholism (Begleiter et al., 1995). Subjects were neither excluded from the study for having ever had psychotropic medications for purposes other than detoxification nor for being polydrug abusers with dependencies on other drugs secondary to alcoholism. Subjects were requested to abstain from alcohol and other CNS-acting substances for 5 days prior to testing. A second questionnaire, administered on the day of testing, documented drug use (alcohol, marijuana, cocaine, hallucinogens, methadone, tranquilizer, antidepressants, neuroleptics, other prescribed medications, nicotine, caffeine) over the previous 5 days and the several hours prior to testing. The subject's responses to these questions could be cause to cancel the session and reschedule. Further, on the day of testing, the subjects were given both a urine screen and a breathalyzer. Positive findings on the former would exclude the subject's ERP data from any analyses, whereas a value greater than zero on the latter would be cause to cancel the session and reschedule. All subjects were right-handed and had normal or corrected normal vision. Although the subjects were not given an audiometric exam, no one in either group had difficulty hearing the tones or discriminating between them, nor was anyone excluded from the study because of a hearing problem. Males were used exclusively to maximize the likelihood of obtaining cognitive-based hemispheric differences (Halpern, 1992).

Recording Procedure and Stimuli

EEG activity was recorded monopolarly using a 61-lead electrode cap (Electro-cap International, Inc., Eaton, OH) referred to the nose, with the impedances kept below 5 kOhms and a forehead ground. The vertical and horizontal electro-oculogram (EOG) were recorded. The signals were amplified with a gain of 10,000 by a set of amplifiers (Sensorium, Charlotte, VT) with a bandpass of 0.02–50 Hz, and recorded on a Concurrent 5550 computer (Concurrent Computer Corp., Atlanta, GA) with subsequent 32-Hz low-pass digital filtering. The sampling rate was 256 Hz. The total length of the ERP epoch was 1500 msec for the auditory paradigm and 1620 msec for the visual paradigm, including a prestimulus baseline of 187 msec. After digital filtering, the prestimulus baseline epoch was 125 msec. Trials with artifacts (>73.3 μv) were rejected online.

For the auditory P3, the subject was presented with up to 400 binaural stimuli with uniform interstimulus interval (ISI) of 1500 msec. There were two types of stimuli: a 600-Hz low tone and a 1600-Hz high tone. Each stimulus had a 60-msec duration (10 msec r/f, 40-msec plateau) and an intensity level of 60 dB sound pressure level (SPL). The rare and frequent (standard) tones had 12.5% and 87.5% probabilities of occurrence, respectively. The designation of the low- or high-frequency tone as the rare stimulus was alternated across subjects. The auditory stimuli were presented binaurally through headphones (model ER-3A Tubephone Insert Earphones, 50-ohm impedance; Etymotic Research, Elk Grove Village, IL); the ear piece and a short length of the Tubephone were fitted under the electrode cap, and the individual left and right transducer cases were situated on either side of the neck.

Visual P3s were elicited with 280 stimuli presented on a computer monitor for a duration of 60 msec, with an interstimulus interval of 1.6 sec. The target (12.5% of total stimuli) was a white letter "X" (4×4 cm, $2.9° \times 2.9°$), the standard nontarget (75%) was a white square (4×4 cm, $2.9° \times 2.9°$), and the novel stimuli (12.5%) consisted of nonrepeating colored geometric shapes (5×5 cm, $3.6° \times 3.6°$) arranged in variegated patterns. The subject was seated in a reclining chair located in a sound-attenuated RF-shielded room (IAC, Industrial Acoustics, Bronx, NY) and fixated on a point in the center of a computer display located 1 m away from his eyes.

Subjects were instructed to press a mouse button with their forefinger (response hand was counterbalanced across subjects) whenever a target was detected and to refrain from responding when the novel or standard stimuli occurred. The button-press action terminated a clock started at stimulus onset and defined the response time. The auditory experiment could be terminated after as few as 100 artifact-free trials (a minimum of 25 target and 75 nontarget trials) were acquired. The visual experiment terminated automatically after a minimum of 25 target stimuli, 150 nontarget stimuli, and 25 novel, artifact-free trials had been acquired, or when all 280 stimuli had been shown. The designation of the modality sequence (visual first or auditory first) was alternated across subjects.

Trials (both visual and auditory paradigms) with response times >1000 msec were rejected. The ERPs from accepted trials were automatically placed in target, novel (visual only), and nontarget response categories for subsequent summation, averaging, and statistical analysis. Response speed was emphasized, but not at the cost of accuracy.

Data Analysis

Initially, it should be noted that the following data analyses reflect a retrospective study of existing data rather than a prospective study designed to address modality-related P3 differences both within and between subjects. Both the auditory and visual P3 data were acquired over a narrow time period on the same day for a given individual and under the same experimental conditions for all subjects.

A semiautomatic peak detection program was employed to analyze the average ERPs to target, standard nontarget, and novel (visual only) stimuli. This paper reports only target data analysis. An auditory P3 was selected as the largest positive peak within a time window from 215 to 430 msec. Visual P3 was selected as the largest amplitude peak within a time window from 215 to 530 msec. Pz was used for the peak detection of P3. N1, P2, and N2 were measured respectively as the maximum negative peaks in the latency range of 62–183 msec for auditory N1, 78–195 msec for visual N1; the maximum positive peak in the latency range of 117–238 msec for auditory P2, 144–300 msec for visual P2; the maximum negative peak in the latency range of 152–281 msec for auditory N2, and 218–355 for visual N2. Fz was used for the peak detection of all of these components except for visual N1, which was most clearly visualized at Oz. Peak amplitudes were measured with respect to a 125-msec prestimulus baseline. Latencies were measured from the time of stimulus onset to the peak of each component. All the measurements were qualified by separate visual inspection. The grand mean ERPs at three electrodes over the scalp (Fz, Cz, Pz) elicited by target stimuli for both modalities and both groups are presented in Fig. 1 (upper: control auditory ERP versus alcoholic auditory ERP; bottom: control visual ERP versus alcoholic visual ERP).

Statistical analyses of ERP data were only conducted on artifact-free trials with correct behavioral responses. Five regional groupings of the 61 electrodes were created for regional analysis, as illustrated in Fig. 2. MANCOVAs (SAS v6.11, Proc GLM, SAS, Cary, NC) (group + modality + age + modality $\times$ group + group $\times$ age) were used to perform between group comparisons for P3, N2, and P2 amplitudes and latencies in each of the five brain regions. Multivariate analyses of variance (MANOVAs) (SAS v6.11, Proc GLM) were used to evaluate modality effects when alcoholic and control subjects were examined separately.

For individual ERP measurements, auditory N1 is difficult to detect at posterior electrode sites, while the visual N1 is difficult to recognize at anterior electrode sites. Therefore, regional analyses of N1 amplitudes and latencies were not performed across modalities; instead, the analyses were conducted in the frontal and central regions for the auditory N1 and in the parietal, occipital, and temporal regions for visual N1.

Topographic analyses were performed on both raw and normalized ERP data. The raw ERP amplitudes were normalized by the MinMax procedure described by McCarthy and Wood (1985). The minimum and maximum grand mean ERP amplitudes were found separately for each

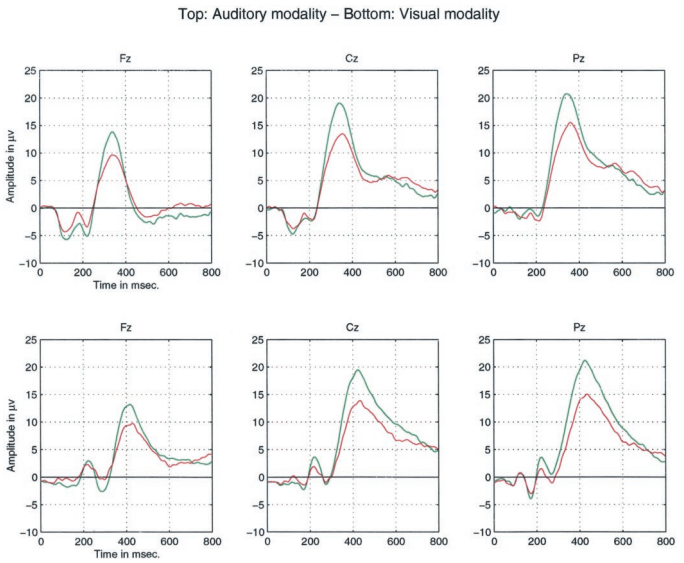

Fig. 1. Grand mean ERPs over three scalp sites (Fz, Cz, Pz). The upper row presents auditory target responses (alcoholics [red] versus controls [green]); the bottom row presents visual target responses (alcoholics [red] versus controls [green]).

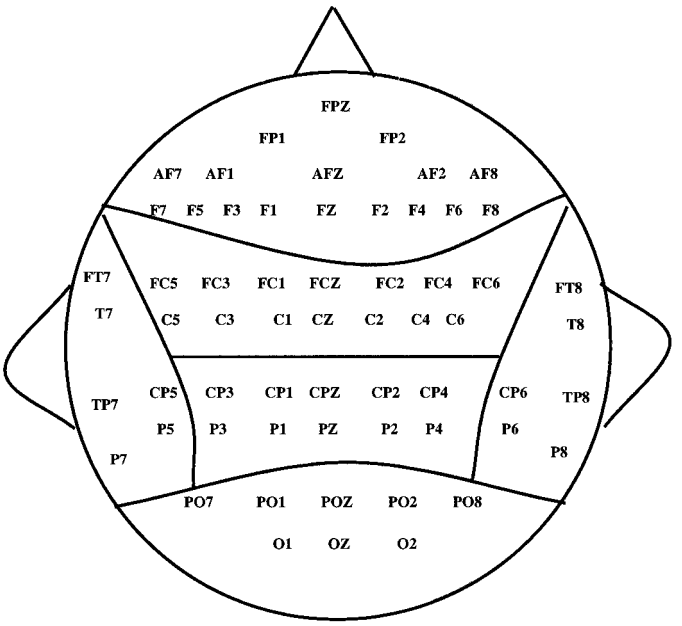

Fig. 2. The recording electrode (n = 61) montage and the regional groupings used in the statistical analyses.

group and each modality. The minimum grand mean amplitude was subtracted from the raw amplitude at each location, then divided by the difference between maximum and minimum amplitudes. Both normalized and raw datasets were subjected to repeated measures analyses of variance (ANOVAs). The coronal effect (frontal, central, parietal, and occipital) was tested along five sagittal planes (far left: *F*7/5, T7/C5, P7/5; midleft: *F*3/1, C3/1, P3/1; midline: AFz/Fz, FCz/Cz, CPz/Pz, POz/Oz; midright: *F*4/2, C4/2, P4/2; far right: *F*8/6, T8/C6, P8/6); the laterality effect (left, right) was tested for five brain regions separately. Univariate, modified univariate (Greenhouse-Geisser corrections), or multivariate results were reported where appropriate.

In addition, topographic maps were created by employing a reference-free model (Perrin et al., 1989; Wang et al., 1994). The CSD (unit: $\mu V/r^2/cm^2$) maps were created by using the spherical spine method to obtain the second spatial derivative of the voltage fields. Positive values of the current source density indicate local current flow out of the skull, whereas negative values indicate current flow into the skull.

RESULTS

Behavioral Data

The response time (msec) for alcoholics (auditory: 428.68 ± 114.68; visual: 458.34 ± 74.41) was generally longer than for controls (auditory: 378.09 ± 69.62; visual: 451.47 ± 77.38) though without statistical significance [$F(1,132) = 3.96, p = 0.05$]; however, all subjects [group × modality: $F(1,132) = 2.29, p = 0.13$] took significantly less time to respond to target stimuli in the auditory modality than in the visual modality [$F(1,132) = 14.43, p < 0.001$].

ERPs

Modality Differences The peak amplitudes and latencies for P3, N2, and P2 over four midline scalp sites were plotted in Figs. 3, 4, and 5, respectively (part "a" for amplitude, part "b" for latency). Figure 3a illustrates that group differences in P3 amplitude are stronger than modality differences and that, within groups, P3 amplitudes at midline electrodes look very similar between modalities. Figure 4a indicates that, in controls, the modality difference in N2 peak amplitude is relatively stable across four scalp sites, resembling the modality difference in the P3 peak; however, in alcoholics, the modality difference in N2 peak amplitude varied over the scalp sites. Figure 5a indicates that the modality difference in P2 peak amplitude was more pronounced at the anterior sites than at the posterior sites for both groups. Compared with Figs. 3a, 4a, and 5a, the distinguishing feature in Figs. 3b, 4b, and 5b was that the ERP latencies were more differentiated by modality than by group.

MANCOVAS and MANOVAS

Table 2a summarizes the modality effect obtained from MANCOVAS and MANOVAS performed on P3 responses. For P3 amplitudes there is a significant age × group effect [MANCOVA, $F(17,116) = 1.87, p < 0.05$], which indicates that for each group, age has a different influence on P3 amplitudes recorded at frontal sites. This interaction makes any differences between the two groups at frontal sites less statistically sound due to the violation of the parallel requirement in conducting MANCOVA. Nevertheless, at central and occipital regions, overall modality effects are obtained without any significant interaction effects (Table 2a). Further examination of means in each modality for each of the 13 peak amplitudes in the central region and 8 peak amplitudes in the occipital region failed to reveal a clear pattern regarding which modality evinced a larger P3. Some electrodes recorded larger P3 amplitudes in the auditory modality while others in the same region

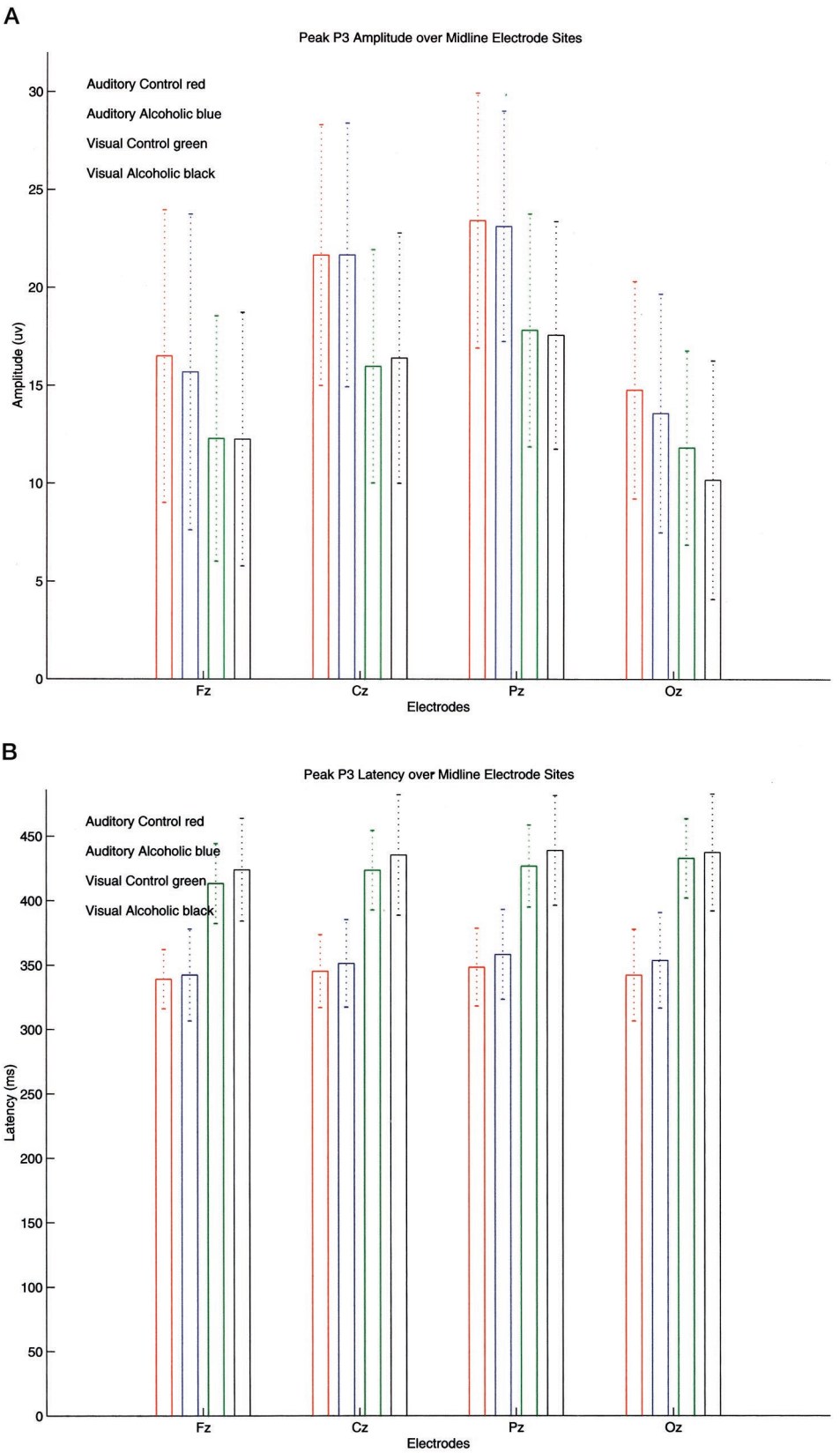

Fig. 3. (a) Peak P3 amplitude and SD; (b) Peak P3 latency and SD over midline electrode sites.

recorded larger P3 amplitudes in the visual modality. On the other hand, when electrode sites were considered as repeated measurements and modality was examined as a between-subject effect, the significant modality effects in Table 2a were no longer significant at frontal, central, and occipital regions.

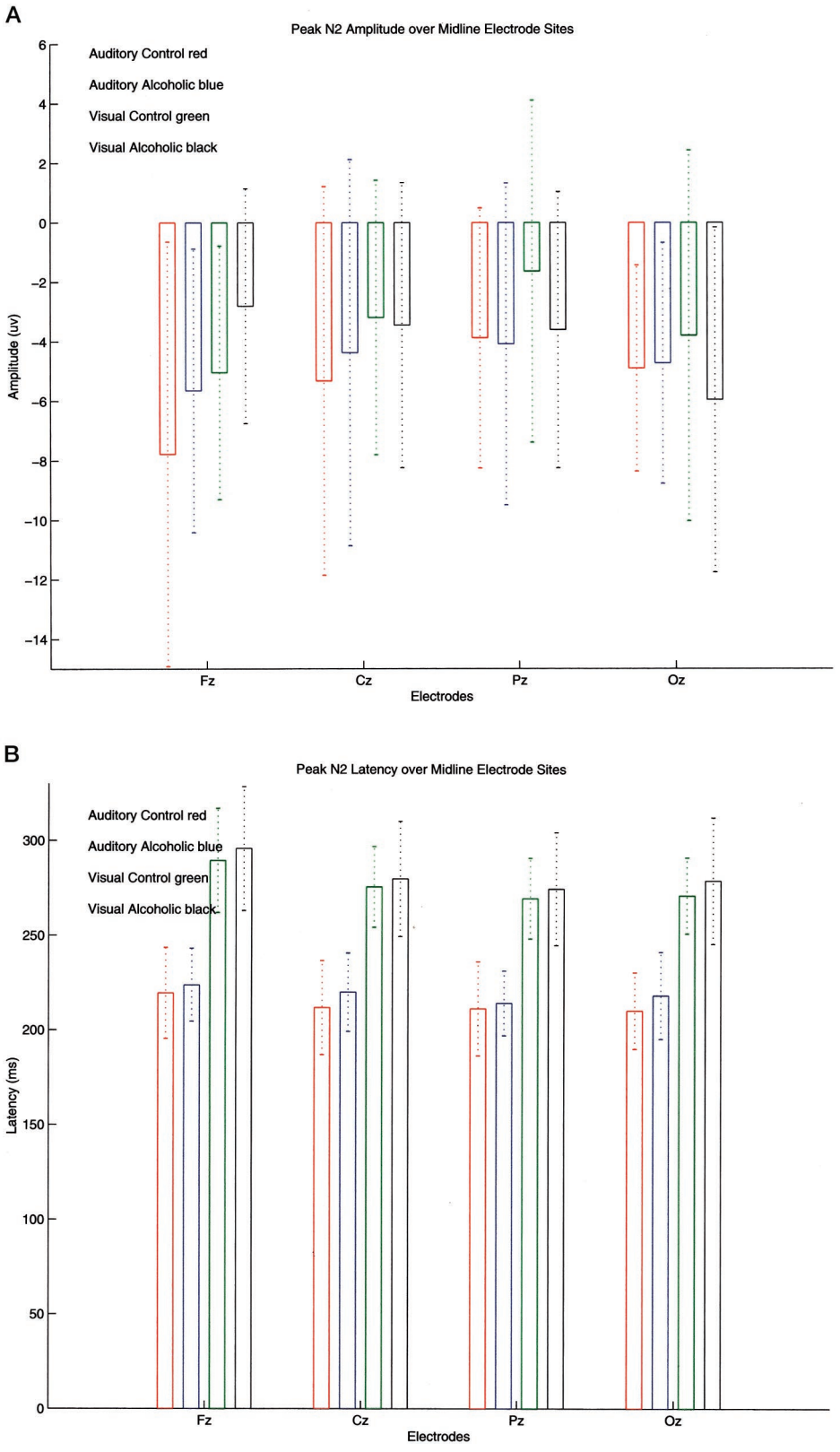

Fig. 4. (a) Peak N2 amplitude and SD; (b) Peak N2 latency and SD over midline electrode sites.

The results of MANOVA (examining modality effects separately for the two groups) indicated that while no significant modality effect was obtained over all brain regions in alcoholics, significant modality effects were observed for controls in frontal and central areas (Table 2a), where visual P3 amplitude tended to be larger than auditory P3 amplitude.

For P3 latencies, the modality effect was significant for

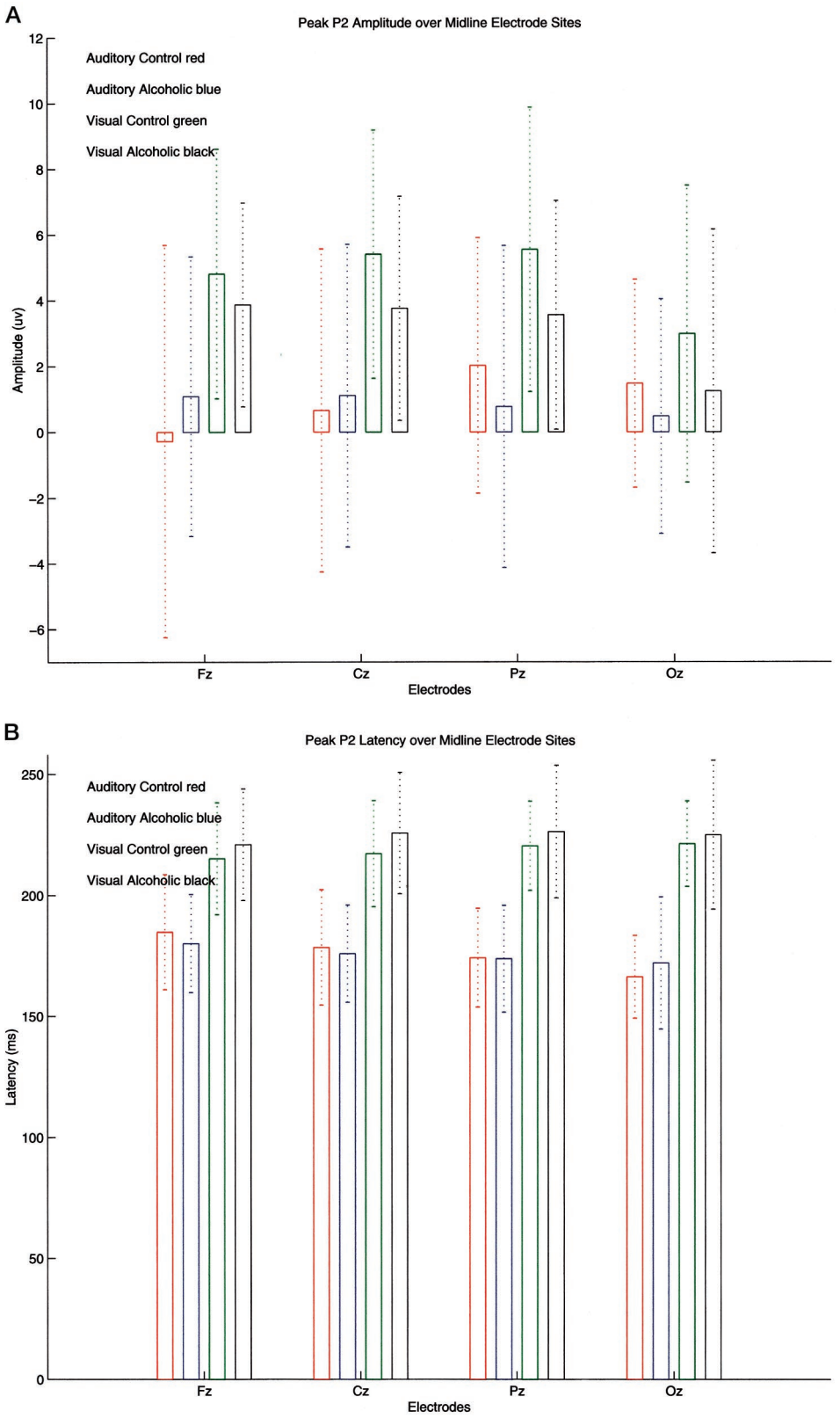

Fig. 5. (a) Peak P2 amplitude and SD; (b) Peak P2 latency and SD over midline electrode sites.

both groups at all five brain regions and remained significant when the two groups were included in a single MANCOVA model with age as a covariate (Table 2a). The lack of an interaction between group and modality/age as well as examinations of the mean latency values in each brain region indicate that, regardless of group, visual P3 is generally later than auditory P3.

N2 and P2. Table 2b summarizes the results of MAN-

Table 2a. The Modality Effect for P3 (*df*, *F*)

	Amplitude						Latency					
			MANOVA						MANOVA			
	MANCOVA		Controls		Alcoholics		MANCOVA		Controls		Alcoholics	
Region												
Frontal	(17,116)	1.79*	(17,60)	1.96*	(17,42)	1.08	(17,116)	14.6***	(17,60)	10.6***	(17,42)	5.77***
	Age × group	1.87*										
Central	(14,119)	2.78**	(14,63)	2.69**	(14,45)	1.24	(14,119)	18.0***	(14,63)	11.4***	(14,45)	7.23***
Parietal	(10,123)	1.41	(10,67)	0.88	(10,49)	1.66	(10,123)	20.6***	(10,67)	14.4***	(10,49)	7.62***
Occipital	(8,125)	3.17**	(8,69)	1.75	(8,51)	1.62	(8,125)	30.4***	(8,69)	21.5***	(8,51)	11.0***
Temporal	(12,121)	1.27	(12,65)	0.80	(12,47)	1.14	(12,121)	24.1***	(12,65)	17.0***	(12,47)	9.30***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 2b. The Modality Effect for N2 and P2 (*df*, *F*)

		N2		P2	
	df	Amplitude	Latency	Amplitude	Latency
Region					
Frontal	(17,116)	3.49***	19.0***	2.77***	9.07***
Central	(14,119)	1.80*	24.3***	3.49***	13.6***
Parietal	(10,123)	3.67**	27.6***	4.29***	22.5***
Occipital	(8,125)	5.73***	33.0***	6.20***	28.7***
Temporal	(12,121)	4.77***	32.0***	8.51***	23.9***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

COVAs used to examine modality effects on N2 and P2. For N2 and P2 amplitudes, significant modality effects were obtained in all regions without concomitant interactions between group × modality or age. The modality effect on peak N2 amplitude was caused by the more negative N2 in the auditory modality compared with the visual modality. The P2 modality effect was caused by a larger P2 in the visual modality compared with the auditory modality.

Similar to P3 latencies, N2 and P2 latencies were later in the visual than the auditory modality. Due to the problems described previously, no comparisons across modalities were made for N1.

ERPs

Modality Specific/Nonspecific Group Difference

Peak Amplitudes. As presented above, the age × group effect in regional MANCOVAs was not significant except at frontal scalp sites. Thus, for central, parietal, occipital, and temporal regions, the age × group effect was not examined. P3 amplitudes were significantly different between alcoholics and controls at central [$F(14,120) = 2.99$, $p < 0.001$]; parietal [$F(10,124) = 3.17$, $p < 0.01$]; occipital [$F(8,126) = 2.75$, $p < 0.01$]; and temporal [$F(12,122) = 3.12$, $p < 0.001$] regions, but none of these effects was modality specific (group × modality interactions were not significant). In both modalities, P3 amplitudes were lower in alcoholics than in controls (Fig. 3a). In the frontal region, the P3 amplitude difference between alcoholics and controls [$F(17,116) = 1.86$, $p < 0.05$] was confounded by the influence of age. No modality specific or modality nonspecific group differences were found in P2 and N2 amplitudes. In the frontal and central regions, auditory N1 amplitudes were not significantly different between alcoholics and controls; visual N1 amplitudes were significantly smaller in alcoholics than in controls in the parietal region [$F(10,57) = 2.10$, $p < 0.05$] but not in the occipital [$F(8,59) = 0.42$, $p = 0.91$] or temporal [$F(12,55) = 0.61$, $p = 0.83$] regions.

Peak Latencies. P3 latencies were not different between alcoholics and controls in any of the five brain regions; this nonsignificant group effect was modality nonspecific (as indicated previously, none of the group × modality interactions was significant). Similar results were obtained for P2, N1, and N2 latencies.

P3

Topographic Profile. We first analyzed the coronal effect (frontal, central, parietal, and occipital) and its interactions with groups and modalities along five sagittal planes (far left, midleft, midline, midright, and far right). Then, we analyzed the laterality effect (left versus right) and its interactions with groups and modalities for each of the five brain regions (frontal, central, parietal, occipital, and temporal). Unless otherwise specified, the age × group effect was not significant in any of the following analyses.

Coronal Effect. Along the far left sagittal plane, the coronal (frontal, central-temporal, parietal-temporal) × modality effect [$F(2,131) = 3.93$_norm or 4.32_raw, $p < 0.05$] and modality effect [$F(6,127) = 3.06$_norm or 2.29_raw, $p < 0.05$] were significant, while the coronal × group or coronal × group × modality interactions, as well as all other effects were not significant. Along the midleft sagittal plane, except for the modality effect [$F(6,127) = 3.29$_norm or 3.53_raw, $p < 0.01$], none of the other effects was significant. Along the midline electrode sites, P3 had a parietal maximum distribution [$F(3,130) = 3.63$_norm or

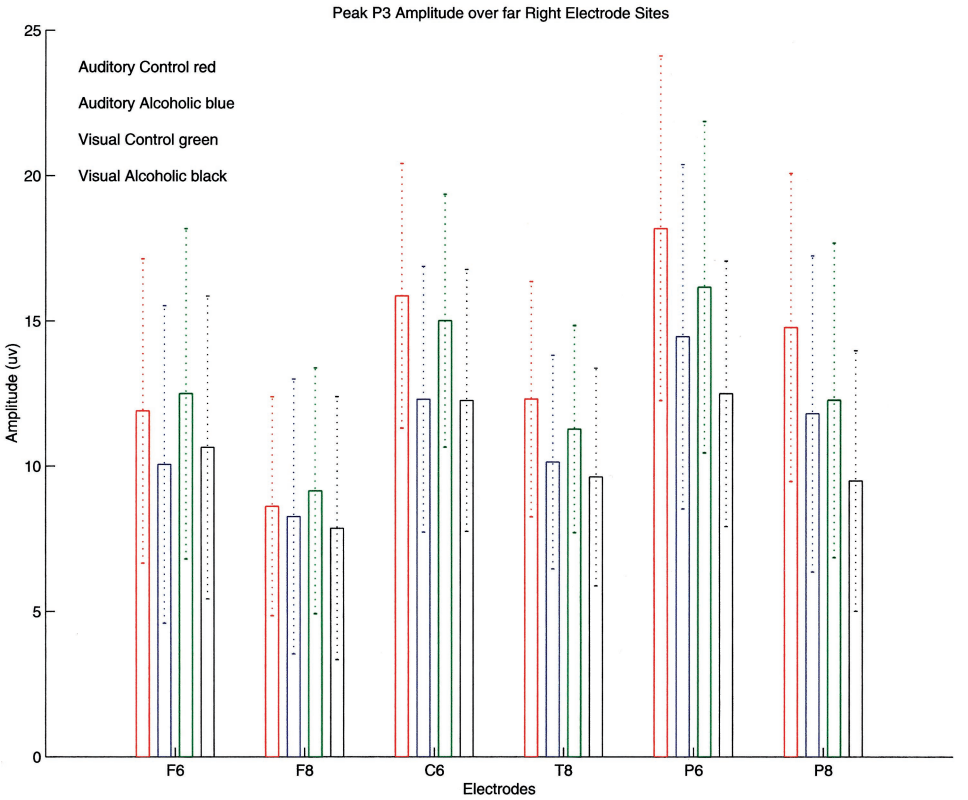

Fig. 6. (a) Peak P3 amplitude and SD over far right electrode sites.

3.41_raw, $p < 0.05$]. Furthermore, none of the group, modality, group × modality, nor their 3-way interactions with coronal effect (frontal, central, parietal, and occipital) was significant in either raw or normalized datasets. Along the midright sagittal plane, coronal [$F(2,131) = 3.49$_norm or 3.82_raw, $p < 0.05$] and modality effects [$F(6,127) = 3.66$_norm or 3.27_raw, $p < 0.01$] were significant; whereas the coronal (frontal, central, parietal) × modality effect [$F(2,131) = 3.22, p < 0.05$] was significant with normalized data, it was not significant with raw data [$F(2,131) = 2.34$, $p = 0.10$], and all the other effects were not significant. Along the far right sagittal plane, coronal × group [$F(2,131) = 3.25$_norm or 3.42_raw, $p < 0.05$] and coronal × modality interactions [$F(2,131) = 3.57$_norm or 3.60_raw, $p < 0.05$] were significant, while the modality effect was significant with normalized data [$F(6,127) = 2.90, p < 0.05$] but not in raw data [$F(6,127) = 1.83, p = 0.10$]; all the other main and interaction effects were not significant. The significant interactions between coronal and group/modality are illustrated in Fig. 6 which reveals that group and modality differences in P3 amplitude were more pronounced in the posterior compared with the anterior regions.

Laterality Effect. From the frontal to the temporal region, the laterality (left versus right) × group effect was significant only in the central region and only with normalized data [$F(1,132) = 4.39, p < 0.05$]; it was not significant with raw data [$F(1,132) = 3.16, p = 0.08$]. At central electrodes, the modality effect was significant with both normalized and raw data [$F(12,121) = 3.56$_norm or 3.29_raw, $p < 0.001$]. Figure 7 demonstrates that a left-smaller-than-right trend in central electrodes is more pronounced in alcoholic subjects than in control subjects; this trend is generally less visible in the visual modality. No laterality effect nor any 3-way interactions were significant in other regions.

Family History

Additional analyses were performed to examine the effects of family history on both auditory and visual P3. The alcoholic subjects were divided into both a low-density (LD) and a high-density (HD) group. The LD group ($n = 17$) consisted of individuals with either 0 or 1 alcoholic relatives (X = 0.24[0.44] relatives/individual), while the HD group ($n = 11$) consisted of individuals with either 3, 4, or 5 alcoholic relatives (X = 3.64[0.92] relatives/individual). Comparisons between the groups were made using both auditory P3 and visual P3 responses recorded at Pz. The results of these analyses yielded one group difference in an unexpected direction, i.e., auditory P3 amplitude was greater in the HD group than the LD group (HD: X = 22.4 uV versus LD: X = 15.2 uV; $p < 0.0008$). However, given the small number of subjects in each group, we do not give any physiologic significance to this result.

Current Source Density

Figure 8 presents CSD maps around P3 peak latency, as well as 50 msec before and after peak latency, for each

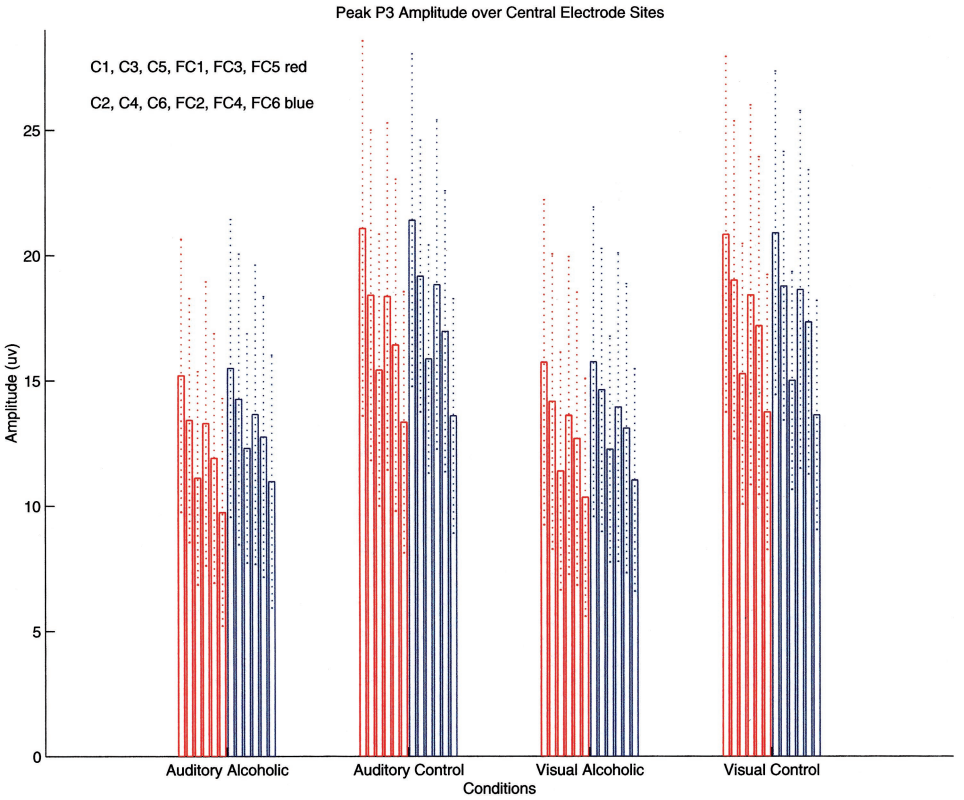

Fig. 7. Peak P3 amplitude and SD over central electrode sites. Red bars represent P3 amplitudes from left sites; blue bars represent P3 amplitudes from right sites.

modality and group. The 50 msec before and after the peak latency were chosen to reflect the dynamic changes of the source pattern that, on visual inspection, appear to last about 100 msec.

Auditory P3. Visual assessment of the two CSD maps at peak latency in the auditory modality revealed little difference between alcoholics and controls, except that the sources (red spots) around the Pz electrode and frontal-temporal region in alcoholics seemed weaker than those in controls. However, the dynamic changes in the source pattern were quite different between alcoholics and controls; the appearance of the left frontal-temporal source was more prominent in controls compared with alcoholics, and the diffusion of sources after peak latency seems more widely distributed in controls compared with alcoholics.

Visual P3. In the visual modality, the sources around both parietal and right frontal-temporal regions were much weaker in alcoholics than in controls, and the parietal sources tended to diffuse rightward only in control subjects.

Topographic Symmetry. To obtain a quantitative assessment of the topographical symmetry of CSD maps of different groups under different modalities at different time points, an analysis applying a bootstrap method (Ji et al., 1998; Srebro, 1996) was performed for each group. For each subject, a CSD map was calculated for the average of five consecutive sample points around 50 msec before peak latency, at peak latency, and 50 msec after peak latency. Then, 30 maps for the alcoholic group (39 maps for the control group), chosen randomly with replacement from the 30 subject maps, were averaged. This was done 200 times to provide a basis for statistical analysis. For the left frontal-right frontal comparison, the midline points produced by the current density calculation were removed, leaving 293 points on each side for the symmetry calculation. The Pearson correlation (r) between the left and right points for each of the 200 maps was calculated and then subjected to the Fisher Z transform, in order to apply a Student's t test to the values. Pooled datasets were formed by randomly taking data from either the left or right frontal sites. The Pearson correlation between the 200 maps and a nonidentical permutation of them was calculated and then subjected to the Fisher Z transform. To determine whether the degree of symmetry in the maps was statistically significant, a two-sample Student's t test was applied to the left-right data and the pooled data. The left-right correlations were all significantly different ($p < 0.001$) from the pooled correlations, indicating the statistical significance of the measures of symmetry of the CSD pattern over the frontal hemisphere. This is a necessary condition for the intergroup comparisons. If, on the other hand, the correlations were not different between the left-right and the pooled data, then either the left and right data are close to identical or there is too much variability between subjects for any comparisons to have statistical significance.

Table 3 summarizes the mean and standard deviation of correlations for each group under each modality and at each time

point. The alcoholic group has a significantly smaller correlation ($p < 0.0001$) than the control group, indicating greater asymmetry. Inspection of Table 3 and Fig. 8 demonstrates that, in the visual modality, the lateral frontal sources are more asymmetrical in the alcoholic group relative to the control group, especially around the time before peak latency; however, over time, the lateral frontal sources become less asymmetrical.

DISCUSSION

N1, N2, P2

The topographic morphology of the N1 wave manifested visually discernible differences between the auditory and visual modality, with auditory-anteriorly and visual-posteriorly distributed patterns; this was true for both alcoholics and controls. However, alcoholics compared with controls manifested a statistically significant reduction of N1 responses in the parietal region but only to visual stimuli. This is partially consistent with studies of Parsons et al. (1990), Patterson et al. (1987), and Pfefferbaum et al. (1979), in which visual N1 was found to be reduced in alcoholics at Cz and Pz while auditory N1 did not demonstrate sensitivity to alcoholism itself (rather to family history). Although this study and studies by Kathmann et al. (1996) and Glenn et al. (1993) did not find a group effect for auditory N1, both Miyazato and Ogura (1993) and Glenn et al. (1994) demonstrated reduced auditory N1 amplitudes at frontal and central regions in alcoholics. According to Naatanen and Picton (1987), the N1 responses to auditory stimuli consist of at least three components, which reflect the physical and temporal aspects of the stimuli and the general state of the subject. Whereas auditory N1 has a frontocentral distribution (Naatanen and Picton, 1987), visual N1 is recorded more posteriorly on the scalp (Perrault and Picton, 1984). The overlapping structure of these subcomponents may contribute to the incon-

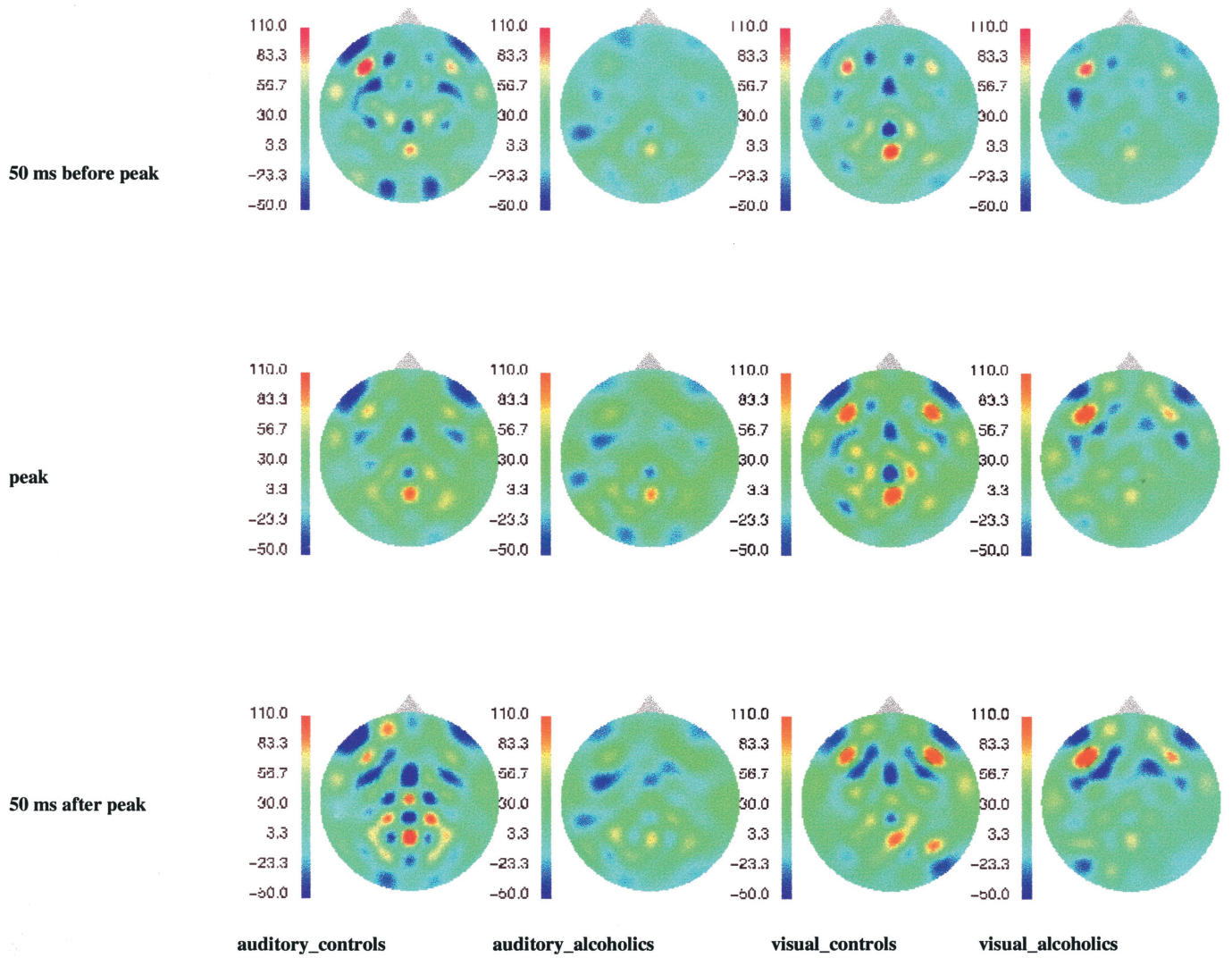

Fig. 8. Current source density maps of target P3 sec around 50 msec before peak latencies (the upper row), at peak latencies (the middle row), and 50 msec after peak latencies (the bottom row) for controls in the auditory modality (1st column), alcoholics in the auditory modality (2nd column), controls in the visual modality (3rd column), and alcoholics in the visual modality (4th column). The unit for the scale is $\mu V/r^2/cm^2$, r = radius of head.

sistent findings regarding N1 reduction between modalities and across studies. As the N1 wave is not considered to be a unitary event and there is no direct evidence indicating which unique aspects of the present N1 are reflected in this visual paradigm, the reduced N1 electrical voltages at parietal brain regions of alcoholics cannot be interpreted along any single underlying cerebral process. However, the N1 wave obtained in a similar visual paradigm (Knight, 1997) manifested prominent reductions in cerebrovascular stroke patients with prefrontal and posterior cortical lesions; the distribution pattern of the N1 reductions in these patients suggested that the visual N1 may be related to a net excitatory prefrontal pathway to extrastriate regions active during sustained attention. The observed visual N1 reduction may reflect the fact that communication among structures in the visual attentional network is poor in alcoholics. Therefore, one is more likely to record altered N1 responses from alcoholics in centroparietal scalp sites despite the experimental evidence that N1 appears to be generated in frontal and/or temporal regions (Naatanen and Picton, 1987).

Consistent with other studies (Kathmann et al., 1996; Parsons et al., 1990; Pfefferbaum et al., 1991; Romani and Cosi, 1989), there are no positive findings regarding the N2 and P2 components. Among the ERP components examined, the test-retest correlations are higher for N1 and P3 amplitude for both alcoholic and control subjects compared with the other ERP measurements (Sinha et al., 1992). The relatively weak reliability of the P2 and N2 components may, to some extent, account for the common negative findings.

P3

The results demonstrated that alcoholics showed P3 amplitude reductions at almost every scalp site in both modalities, although, at frontal sites, this reduction could, in fact, reflect the influence of age. The P3 amplitude reduction is in accord with the majority of reports (Cohen et al., 1995,1997; Glenn et al., 1994,1996; Kathmann et al., 1996; Miyazato and Ogura, 1993; Parsons, 1994; Parsons et al., 1990; Pfefferbaum et al., 1987,1991; Porjesz et al., 1980,1987; Realmuto et al., 1993). Under most testing conditions, the midline electrodes, especially Pz, were reported to manifest P3 alterations; the present study demonstrated that P3 reductions are more widespread. The robust P3 reduction also has been found in other alcohol-related groups of subjects: namely, children at high risk (Begleiter et al., 1984) and normals following acute ethanol ingestion (Hamon and Camara, 1994). However, the auditory P3 does not always differentiate alcoholics from controls (Hill et al., 1995; Parsons et al. 1990; Steinhauer et al., 1987), even if the two groups were significantly different in familial density of alcoholism, a very important codeterminant in the observed P3 amplitude reduction of alcoholism (Cohen et al.,1995; Pfefferbaum et al., 1991). To date, P3 amplitude reductions have been associated with: (1) acute neurotoxic effects of alcohol (Hamon and Camara 1994; Oscar-Berman, 1987); (2) sober alcoholics with prolonged abstinence (Porjesz and Begleiter, 1985); (3) antecedent of alcoholism (Begleiter et al., 1987); (4) gender (Hill and Steinhauer, 1993; Parsons et al., 1990); (5) familial loading for alcoholism (Benegal et al., 1995; Cohen et al., 1995; Pfefferbaum et al., 1991); (6) neurodevelopmental lag (Hill et al., 1995); and (7) paradigm parameters used to elicit P3, such as sensory modality and task difficulty (Polich et al., 1994), etc. The interactions among these factors may enhance or suppress P3 vulnerability. For example, although Hill et al. (1995) interpreted the discrepancy between their positive findings (reduced P3) in boys at risk and their negative finding (normal P3) in high-risk adult males (who were not the same boys grown up) as a developmental lag, it is also possible that the auditory paradigm, intense familial loading, and the alcohol naive state of the subjects interacted to suppress P3 alterations. After all, our results confirm the vulnerability of P3 amplitude in both the visual and auditory modality to the sober state of alcoholics; it is still unresolved whether it is the predisposition of the alcoholics or it is the persistent chronic neurotoxic effect of alcohol. Furthermore, alcoholics in this group displayed more hemispheric P3 differences among central electrodes (left-smaller-than-right) than controls, indicating that the P3 amplitude aberration in alcoholics is more pronounced in the left compared with the right hemisphere, especially in the auditory modality.

This latter finding resembles that from Miyazato and Ogura (1993) who reported an auditory P3 reduction only at left centrofrontal sites in alcoholics. However, in contrast to those observations, the P3 deficit described herein had a far greater anterior-posterior extent and involved both left and right hemispheres. Thus, the left-worse-than-right description as applied to the current results refers to a widespread P3 deficit in which the magnitude of the deficit was greater in the left central region than the right.

Reduced P3 amplitude as well as hemispheric asymmetry in the magnitude of the deficit also has been documented in schizophrenics (O'Donnell et al., 1999; Potts et al., 1998; Salisbury et al., 1999). It has been proposed that this pattern may reflect abnormalities in the P3 generators located in the temporal lobe as well as anatomic asymmetries in the temporal lobe and/or associated structures. Imaging studies suggest an anatomic basis for the asymmetry in the electrophysiological deficit, with reports of decreased tissue volumes in both the left angular gyrus (Niznikiewicz et al., 2000) and left planum temporale (Hirayasu et al., 2000; Kwon et al., 1999). In contrast, although imaging studies in alcoholics have revealed numerous anatomic deficits (e.g., decreased white matter and gray matter, increased sulcal CSF volumes, and increased ventricles) (Pfefferbaum et al., 1998; Sullivan et al., 1998), they have not documented the

asymmetries observed in schizophrenics; possibly, these differences are below the detection threshold for MRI. Given the evidence that alcoholism is characterized by etiologic heterogeneity, it may be that the left-worse-than-right pattern in the P3 deficit describes an alcoholic subtype. In this context, imaging studies might prove valuable in determining whether structural abnormalities underlie the topography of electrophysiological deficit.

P3 and Age

In general, aging reduces P3 amplitude (0.18 uV per year) in a similar way for both auditory and visual modalities (Picton et al., 1984). In this study, the average age of the alcoholic group was approximately 6 years greater than that of the control group. Therefore, the group comparison could be affected by the age difference. Our results revealed that the age effect on P3 amplitude is different for alcoholics and controls (significant age by group effect) only in the frontal region (i.e., the rate of reduction of P3 amplitude with age manifests group differences frontally) but not elsewhere. In contrast, the decreased auditory and visual P3 amplitudes generated in other regions by the alcoholics did not reflect the age difference between the groups. Anderer et al. (1996) demonstrated that in the normal population, the age-amplitude relationship in the frontal region is not as linear as in parietal and occipital regions. This may contribute to the significant age $\times$ group interaction observed in the frontal region, but not in other brain regions. The differential effect of age on alcoholics and controls was also observed by Realmuto et al. (1993), who reported that, in controls, there was a significant negative correlation between age and P3 amplitude at both Fz and Pz; in contrast, no correlation was found in alcoholics at Pz. In addition, in the frontal region, the controls had larger P3 responses to visual compared with auditory stimuli; this modality difference was not observed in alcoholics. In the present study, because the alcoholics were generally older than the controls, the significant (controls) versus non-significant (alcoholics) modality effect in the frontal region could be caused by the age difference and/or the absence/presence of alcoholism. To address this question, it would be necessary to obtain separate regression functions for visual P3 amplitude with age and auditory P3 amplitude with age. However, this would require a larger number of subjects than that in the present study.

P3

Modality and Task Difficulty. One aspect of this study that may be considered problematic is that it compared responses between an easy, two-stimulus auditory paradigm and a difficult, three-stimulus visual paradigm. Consequently, one may offer that any modality-related difference in P3 is confounded by a difference in task difficulty. Several lines of evidence suggest this difference had little effect on the results.

First is the fact that, to accurately assess modality-related differences in P3, one needs to equate the stimuli in each modality. This requires that a cross-modality matching procedure be used with each subject to generate stimulus sets that are subjectively equal along some dimension (e.g., intensity). Moreover, the procedure would need to be repeated for each stimulus category. Whereas it would be time consuming but rather simple for frequent and rare stimuli in a basic oddball paradigm, it would be inordinately difficult, if not impossible, to generate sets of novel stimuli. To the authors' knowledge, no studies of modality-related differences in P3 have used this degree of experimental rigor.

Second are the results from a recent review (Porjesz and Begleiter, 1998) that suggest that the effect of task difficulty may be equivocal. The authors reported that identical results have been obtained with tasks at different levels of difficulty. Moreover, some aspects of task difficulty, e.g. discrimination, alter P3 characteristics whereas other aspects, e.g. response selection difficulty do not. The authors also suggested that task difficulty is not necessarily a continuum along which P3 results can be explained.

Last is the observation that, even if the present results were influenced in part by differences between the two paradigms, these differences were common to both groups. In this context, the possible confound still does not diminish our most important findings (i.e., significant within and between groups differences in controls and alcoholics that likely reflect group differences in stimulus processing rather than differences in experimental design).

P3 Topography

The topographic profile analysis for group differences along the far right sagittal plane revealed that the P3 reductions in alcoholics were statistically more pronounced in the posterior compared with the anterior regions (Fig. 6). Furthermore, the P3 amplitude reduction in the central region in alcoholics is more pronounced in the left than in the right hemisphere. Several studies (Anderer et al., 1996; Friedman et al., 1993) have demonstrated that, with advancing age, there is a shift to a relatively more frontally oriented P3 amplitude distribution and therefore a more equal distribution across the scalp. Thus, in alcoholics, their greater age may exaggerate the P3 amplitude difference between anterior and posterior areas (Pfefferbaum et al., 1991). As a consequence, the large amplitude differences between alcoholics and controls at posterior sites become less pronounced anteriorly. However, the exaggerating effect of age does not rule out the intrinsic effect of alcoholism on the differences in the P3 topographic distribution, since neither a 3-way nor 2-way interaction between age and group nor frontal-central-parietal-occipital effect was statistically significant. The sources in the CSD maps of alcoholics seem weaker than those of controls and appeared to describe a modality-specific pattern: alcoholics manifested weaker current density sources mainly in the

frontal region in the auditory modality and mainly in the parietal-occipital region in the visual modality (Fig. 8).

In summary, this study of auditory and visual P3 in alcoholics has both confirmed previous findings and documented new and interesting results. For example, the decreased P3 response over widespread cortical regions has been reported in other studies. However, the results also indicate that the decrease was neither modality nor task specific and suggest that neither factor strongly influenced the deficit. Furthermore, whereas other studies have demonstrated that P3 amplitude is a function of age, this investigation has demonstrated that the relationship differs between alcoholics and controls. Moreover, the difference was not manifested consistently in group comparisons of P3 responses in each region; rather, it appeared to be localized to the frontal region and was not modality specific.

The analyses of CSD revealed that sources in alcoholics were generally weaker and manifested greater hemispheric asymmetries than those in controls. Thus, it is of interest to determine whether the findings regarding the P3 generators are, in fact, associated with the left-worse-than-right (LWTR) distribution of the P3 deficit. In several previous studies, the LWTR designation has been applied to the topography of the P3 deficit that characterized schizophrenic subjects. Interestingly, there is evidence that, in schizophrenics, the topography of the amplitude decrease may have a structural basis; imaging studies have described anatomic deficits in the left temporal lobe and associated structures. The present investigation is one of very few that has documented the LWTR pattern in a population of alcoholic individuals. Further, the real extent of the deficit was greater than that which had been reported previously. However, in contrast to the findings in schizophrenics, anatomic and/or imaging studies in alcoholics have not yet described well-localized structural deficits that could contribute to both the P3 decrease as well as its topography. It is possible that the present sample of alcoholics comprises an alcoholic subtype defined, in part, by the topography of the P3 deficit. It remains for imaging and related studies to determine whether this subject group is also characterized by specific structural deficits (Desmedt and Chalklin, 1989; Pfefferbaum et al., 1998).

ACKNOWLEDGMENTS

The authors thank Arthur Stimus, Brian Beckrich, Vladimir Kotlyarevsky, Elisabeth Iskander, Marty Krakowsky, and Sergio Valentini for their valuable technical assistance.

REFERENCES

Anderer P, Semlitsch HV, Saletu B (1996) Multichannel auditory event-related brain potentials: effects of normal aging on the scalp distribution of N1, P2, N2 and P300 latencies and amplitudes. Electroencephalogr Clin Neurophysiol 99:458–472.

Bashore TR, van der Molen MW (1991) Discovery of the P300: a tribute. [Review] Biol Psychol 32:155–171.

Begleiter H, Porjesz B, Bihari B, Kissin B (1984) Event-related potentials in boys at risk for alcoholism. Science 225:1493–1496.

Begleiter H, Porjesz B, Rawlings R, Eckardt M (1987) Auditory recovery function and P3 in boys at high risk for alcoholism. Alcohol 4:315–321.

Begleiter H, Reich T, Hesselbrook VM, Porjesz B, Li TK, Schuckit MA, Edenberg HJ, Rice JP (1995) The Collaborative Study on the Genetics of Alcoholism. Alcohol Health Res World 19:228–236.

Benegal V, Jain S, Subbukrishna DK, Channabasavanna SM (1995) P300 amplitudes vary inversely with continuum of risk in first degree male relatives of alcoholics. Psychiatr Genet 5:149–156.

Biggins CA, MacKay S, Poole N, Fein G (1995) Delayed P3A in abstinent elderly male chronic alcoholics. Alcohol Clin Exp Res 19:1032–1042.

Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI, Reich T, Schmidt I, Schuckit MA (1994) A new semi-structured psychiatric interview for use in genetic linkage studies: a report of the reliability of the SSAGA. J Stud Alcohol 55:149–158.

Ciesielski KT, Madden JS, Bligh JG, Schopflocher D (1985) Long-term brain impairment in chronic alcoholics: N2-P3 cognitive potentials in a template-matching memory task. Alcohol Alcohol 20:403–408.

Cohen HL, Porjesz B, Begleiter H, Wang W (1997) Neurophysiological correlates of response production and inhibition in alcoholics. Alcohol Clin Exp Res 21:1398–1406.

Cohen HL, Wang W, Porjesz B, Begleiter H (1995) Auditory P300 in young alcoholics: regional response characteristics. Alcohol Clin Exp Res 19:469–475.

Emmerson RY, Dustman RE, Shearer DE, Chamberlin HM (1987) visually evoked and event related potentials in young abstinent alcoholics. Alcohol 4:241–248.

Friedman D, Simpson G Hamberger M (1993) Age-related changes in scalp topography to novel and target stimuli. Psychophysiology 30:383–396.

Glenn SW, Oscar A, Sinha R (1994) Assessment of recovery of electrophysiological and neuropsychological functions in chronic alcoholics. Biol Psychiatry 36:443–452.

Glenn SW, Parsons OA, Smith, LT (1996) ERP responses to target and nontarget visual stimuli in alcoholics from VA and community treatment programs. Alcohol 13:85–92.

Glenn SW, Sinha R, Parsons OA (1993) Electrophysiological indices predict resumption of drinking in sober alcoholics. Alcohol 10:89–95.

Hada M, Porjesz B, Begleiter H, Polich J Auditory (2000) P3a assessment of male alcoholics. Biol Psychiatry 48:276–286.

Halpern DF (1992) *Sex differences in Cognitive abilities.* Lawrence Earlbaum Associates, Hillsdale, NJ.

Hamon JF, Camara PA (1994) Effects of an acute dose of palm alcohol on normal brain functioning: an auditory, event-related potential study. Ann Trop Med Parasitol 88:561–568.

Hill SY, Steinhauer SR (1993) Event-related potentials in women at risk for alcoholism. Alcohol 10:349–354.

Hill SY, Steinhauer S, Lowers L, Locke J (1995) Eight-year longitudinal follow-up of P300 and clinical outcome in children from high-risk for alcoholism families. Biol Psychiatry 37:823–827.

Hill Sy; Locke J, Steinhauer SR (1999) Absence of visual and auditory P300 reduction in nondepressed male and female alcoholics. Biol J Psychiatry 46:982–989.

Hirayasu Y, McCarley RW, Salisbury DF, Tanaka S, Kwon JS, Frumin M, Snyderman D, Yurgelun TD, Jolesz FA, Shenton ME (2000) Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic resonance imaging study of first-episode patients. Arch Gen Psychiatry 57:692–699.

Holguin SR, Porjesz B, Chorlian D, Polich J, Begleiter H (1999) Visual P3a in male alcoholics and controls. Alcohol Clin Exp Res 23:582–591.

Ji J, Porjesz B, Begleiter H, Chorlian D (1999) P300: the similarities and differences in the scalp distribution on visual and auditory modality. Brain Topogr 11:315–327.

Ji J, Porjesz B, Chorlian D, Begleiter H (1998) Event-related potentials during digit recognition tasks. Brain Res Cogn Brain Res 7:179–190.

Johnson R Jr (1993) On the neural generators of the P300 component of the event-related potential. Psychophysiology 30:90–97.

Kaseda Y, Miyazato Y, Ogura C, Nakamoto H, Uema T, Yamamoto K, Ohta I (1994) correlation between event-related potentials and MR measurements in chronic alcoholic patients. Jpn J Psychiatry Neurol 48:23–32.

Kathmann N, Soyka M, Bickel R, Engel RR (1996) ERP changes in alcoholics with and without alcohol psychosis. Biol Psychiatry 39:873–881.

Knight RT (1997) Distributed cortical network for visual attention. J Cogn Neurosci 9:75–91.

Kwon JS, McCarley RW, Hirayasu Y, Anderson JE, Fisher IA, Kikinis R, Jolesz FA, Shenton ME (1999) Left planum temporale volume reduction in schizophrenia. Arch Gen Psychiatry 56:142–148.

McCarthy G, Wood CC (1985) Scalp Distributions of Event-Related Potentials: An ambiguity associated with analysis of variance models. Electroencephalogr Clin Neurophysiol 62:203–208.

Miyazato Y, Ogura C (1993) Abnormalities in event-related potentials: N100, N200, and P300 topography in alcoholics. Jpn J Psychiatry Neurol 47:853–862.

Naatanen R, Picton T (1987) The N1 wave of the human electric and magnetic response to sound: a review and analysis of the component structure. Psychophysiology 24:375–386.

Naumann E, Huber C, Maier S, Plihal W, Wustmans A, Diedirch O, Bartussek D (1992) The scalp topography of P300 in the visual and auditory modalities: a comparison of three normalization methods and the control of statistical type II error. Electroencephalogr Clin Neurophysiol 83:254–264.

Niznikiewicz MA, Donnino R, McCarley RW, Nestor PG, Iosifescu DV, O'Donnell B, Levitt J, Shenton ME (2000) Abnormal angular gyrus asymmetry in schizophrenia. Am J Psychiatry 157:428–437.

Oades RD, Zerbin D, Dittmann-Balcar A (1995) The topography of event-related potentials in passive and active conditions of a 3-tone auditory oddball test. Int J Neurosci 81:249–264.

O'Donnell BF, McCarley RW, Potts GF, Salisbury DF, Nestor PG, Hirayasu Y, Niznikiewicz MA, Barnard J, Shen ZJ, Weinstein DM, Bookstein FL, Shenton ME (1999) Identification of neural circuits underlying P300 abnormalities in schizophrenia. Psychophysiology 36:388–398.

Oscar-Berman M (1987) Alcohol-related ERP changes in cognition. Alcohol 4:289–292.

Parsons OA (1994) Neuropsychological measures and event-related potentials in alcoholics: interrelationships, long-term reliabilities, and prediction of resumption of drinking. J Clin Psychol 50:37–46.

Parsons OA, Sinha R, Williams HL (1990) Relationships between neuropsychological test performance and event-related potentials in alcoholic and nonalcoholic samples. Alcohol Clin Exp Res 14:746–755.

Patterson BW, Williams HL, McLean GA, Smith LT, Schaeffer KW (1987) Alcoholism and family history of alcoholism: effects on visual and auditory event-related potentials. Alcohol 4:265–274.

Perrault N, Picton TW (1984) Event-related potentials recorded from the scalp and nasopharynx. I. N1 and P2. Electroencephalogr Clin Neurophysiol 59:177–194.

Perrin F, Pernier J, Bertrand O, Echallier JF (1989) Spherical splines for scalp potential and current density mapping. Electroencephalogr Clin Neurophysiol 72:184–187.

Pfefferbaum A, Ford JM, White PM, Mathalon D (1991) Event-related potential in alcoholic men: p3 amplitude reflects family history but not alcohol consumption. Alcohol Clin Exp Res 15:839–850.

Pfefferbaum A, Horvath TB, Roth WT, Clifford SW, Kopell BS (1979) Event-related potential changes in chronic alcoholics. Electroencephalogr Clin Neurophysiol 47:637–747.

Pfefferbaum A, Margaret R, Ford JM (1987) Late event-related potential changes in alcoholics. Alcohol 4:275–281.

Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon DH, Lim KO (1998) A controlled study of cortical gray matter and ventricular changes in alcohol men over a 5-year interval. Arch Gen Psychiatry 55:905–912.

Picton T, Stuss DT, Champagne SC, Nelson RF (1984) The Effects of age on human event-related potentials. Psychophysiology 21:312–325.

Polich J, Pollock VE, Bloom FE (1994) Meta-analysis of P300 amplitude from males at risk for alcoholism. Psychol Bull 115:55–73.

Porjesz B, Begleiter H, Garozzo R (1980) Visual evoked potential correlates of information processing deficits in chronic alcoholics. *Biological Effects of Alcohol* (Begleiter, ed), pp 603–623. Plenum, New York.

Porjesz B, Begleiter H (1983) Brain dysfunction and alcohol, in *The Biology of Alcoholism: The pathogenesis of Alcoholism: Biological Factors* (Kissin B, Begleiter H eds), pp 415–483. Plenum Press, New York.

Porjesz B, Begleiter (1985) Human brain electrophysiology and alcoholism. *Alcohol and the Brain* (Tarter R, Thiel DV, eds), pp 139–182, Plenum, New York.

Porjesz B, Begleiter H (1987) Evoked Brain Potentials and Alcoholism, in *Neuropsychology of Alcoholism* (Parsons OA, Butters N, Nathan P eds), pp 45–63. Guilford Press, New York.

Porjesz B, Begleiter H (1996) Effects of alcohol on electrophysiological activity of the brain, in *The Pharmacology of Alcohol and Alcohol Dependence, Alcohol Alcohol, Vol 2* (Begleiter H, Kissin B eds), pp 207–247. Oxford University Press, New York.

Porjesz B, Begleiter H (1998) Genetic basis of the event-related potentials and their relationship to alcoholism and alcohol use. J Clin Neurophysiol 15:44–57.

Porjesz B, Begleiter H, Bihari B, Kissin B (1987) The N2 component of the event-related brain potential in abstinent alcoholics. Electroencephalogr Clin Neurophysiol 66:121–131.

Porjesz B, Begleiter H, Garozzo R (1980) Visual evoked potential correlates of information processing deficits in chronic alcoholics, in *Biological effects of Alcohol* (Begleiter H ed), pp 603–623. Plenum Press, New York.

Potts G, Hirayasu Y, O'Donnell BF, Shenton ME, McCarley RW (1998) High-density recording and topographic analysis of the auditory oddball event-related potential in patients with schizophrenia. Biol Psychiatry 44:982–989.

Realmuto G, Begleiter H, Odencrantz J, Porjesz B (1993) Event-related potential evidence of dysfunction in automatic processing in abstinent alcoholics. Biol Psychiatry 33:594–601.

Ritter W, Ford JM, Gaillard AW, Harter MR, Kutas M, Naatanen R, Polich J, Renault B, Rohrbaugh J (1984) Cognition and event-related potentials. I. The relation of negative potentials and cognitive processes. Ann N Y Acad Sci 425:24–38.

Romani A, Cosi V (1989) Event-related potentials in chronic alcoholics during withdrawal and abstinence. Neurophysiol Clin 19:373–384.

Salisbury DF, Shenton ME, McCauley RW (1999) P300 topography differs in schizophrenia and manic psychosis. Biol Psychiatry 45:98–106.

Sinha R, Bernardy N, Parsons OA (1992) Long-term test-retest reliability of event-related potentials in normals and alcoholics. Biol Psychiatry 32:992–1003.

Srebro R (1996) A bootstrap method to compare the shapes of two scalp fields. Electroencephalogr Clin Neurophysiol 100:25–32.

Steinhauer SR, Hill SY, Zubin J (1987) Event-related potentials in alcoholics and their first-degree relatives. Alcohol 4:307–314.

Sullivan E, Mathalon DH, Lim KO, Marsh L, Pfefferbaum A (1998) Patterns cortical dysmorphology distinguishing schizophrenia and chronic alcoholism. Biol Psychiatry 43:118–131.

Wang WY, Begleiter H, Porjesz B (1994) Surface energy, its density and distance: new measures with application to human cerebral potentials. Brain Topogr 6:193–202.