0145-6008/99/2304-0582$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 23, No. 4
April 1999

Visual P3a in Male Alcoholics and Controls

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The goal of this study was to assess the P3a component of event-related potentials in a population of abstinent, chronic alcoholics. A three-stimulus visual oddball paradigm was used to elicit robust P3a components in a large group of well-characterized male alcoholics (n = 44) and controls (n = 28). The task required subjects to make a difficult perceptual discrimination between randomly presented, frequently occurring vertical lines (.80) and infrequent target lines that were tilted 2° to the right of vertical (.10) by only responding with a button press to the target stimuli. A nontarget infrequent horizontal line occurred (.10) randomly to which no response was made. The target stimulus elicited robust late P3b components with a parietal maximum amplitude, and the nontarget stimulus elicited reliable P3a components with a fronto-central maximum amplitude distribution. Group differences in P3a were assessed using repeated measures ANCOVA analyses in five scalp regions. Alcoholic subjects produced smaller P3a amplitudes over the central, parietal, temporal, and occipital areas compared with controls. Current source density analyses supported these findings with extension of the differences between the groups to the frontal region. The results suggest that the P3a may be important in the evaluation of alcoholism and its heritability. Theoretical implications are discussed.

Key Words: Alcoholism, Visual Event-Related Potentials (ERPs), P300, P3a, Current Source Density (CSD).

IN THE PAST two decades, event-related potentials (ERPs) have been demonstrated to be sensitive to the neurotoxic effects of both acute and chronic ethanol. Alterations in the time and voltage parameters of several components of the sensory evoked potentials (brainstem auditory evoked potentials, visual P100), and of the event-related potentials recorded during cognitive processes (N1, N2, Nd, MMN, P3, N400, CNV, visual memory potentials) have been identified in relation with alcohol intoxication, tolerance, withdrawal, and chronic alcoholism (Porjesz and Begleiter, 1996). The most studied ERP component in alcoholism has been P300 (P3b), which has been used extensively for assessing disorders involving cognitive function. Typically elicited by infrequent relevant stimuli during discrimination tasks, P3b is a positive-going wave, with a maximum centroparietal peak occurring between 300 and 600 ms after the stimulus. Its appearance and characteristics are related to the significance of the stimulus (subjective probability, stimulus meaning, and information transmission) more than to its physical properties (Donchin et al., 1986; Johnson, 1986).

ERPs and Alcoholism

The most frequently reported anomaly in ERPs among alcoholic subjects is a decreased P3b amplitude, especially in the visual modality where amplitude reductions have been found using oddball tasks (Porjesz et al., 1980; Patterson et al., 1987; Porjesz et al., 1987b; Pfefferbaum et al., 1991; Glenn et al., 1996) and other visual paradigms (Ciesielski et al., 1985; Pfefferbaum et al., 1987; Porjesz et al., 1987a; Whipple et al., 1988; Cohen et al., 1997). Although P3b reductions in the auditory modality have also been reported (Patterson et al., 1987; Pfefferbaum et al., 1991; Cohen et al., 1995), results are less consistent, and some reports have not found differences in amplitudes between alcoholics and controls (Pfefferbaum et al., 1979; Steinhauer et al., 1987; Cadaveira et al., 1991; Hill et al., 1995). A few studies have also reported delayed latencies in auditory P3b among alcoholics compared with controls (Pfefferbaum et al., 1991; Pfefferbaum et al., 1979; Cadaveira et al., 1991).

Although the consistency of results from different laboratories is high (especially in the visual modality), the importance of P3b in assessing alcoholism was encouraged by the finding that the abnormal values persist after long periods of abstinence (Porjesz and Begleiter, 1985; Glenn et al., 1993; Parsons, 1994). Other ERP components pro-

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Received for publication September 22, 1998; accepted January 9, 1999.

This work was supported by NIH Grants AA 08401 and AA08403; and the Galician Government Research Authority (DOG 8/26/1997).

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gressively attain the normal range with sustained abstinence (Porjesz and Begleiter, 1985; Emmerson et al., 1987; Cadaveira et al., 1994), whereas the P3b component remains altered after several months, and even years of abstinence (Porjesz and Begleiter, 1985; Glenn et al., 1993; Parson, 1994). This evidence, in conjunction with the genetic influence on the amplitude of P3b (Eischen and Polich, 1994; Polich and Burns, 1987; O'Connor et al., 1994; Van Beijsterveldt and Boomsma, 1994; Katsanis et al., 1997; Almasy et al., in press) has lead to the hypothesis that the anomalies in P3b may be genetically determined, and precede the development of alcoholism. Under this hypothesis, reduced P3b has been assessed as a phenotypic marker of a genetic predisposition to alcoholism (Begleiter and Porjesz, 1995; Polich et al., 1994).

The P3b voltage decrease in alcoholism suggests the inability to use available information to reduce uncertainty about the relevance of the stimulus, so that each stimulus in the task is evaluated anew. This cognitive dysfunction would have its electrophysiological manifestation as the undifferentiated response to the target stimulus, which suggests deficits in electrophysiological inhibition (Porjesz and Begleiter, 1996). Positive-going ERP waves have been related to inhibition of cortical neuronal networks (Birbaumer et al., 1990). This inhibitor disfacilitation of surrounding regions may be necessary to limit cortical excitation to task specific areas (Woodward et al., 1991; Rockstroh et al., 1992; Schupp et al., 1994; Rockstroh et al., 1996). Thus, the P3b reduction of amplitudes in alcoholics suggests a deficit in the electrophysiological inhibition necessary for the efficient processing of the stimulus (Porjesz and Begleiter, 1998).

Neurophysiological Basis for Alcoholic ERP Deficits

P3b reductions have also been demonstrated to be larger in alcoholics with cortical atrophy than in alcoholics without structural damage (Begleiter et al., 1980). Several different areas have been proposed as contributors to P3b. Depth electrode recordings in humans initially suggested that at least some portion of the P3b is generated in the hippocampal areas of the medial temporal lobe (Halgren et al., 1980; McCarthy et al., 1989). However, ERPs recorded at the scalp are unlikely to reflect activity in the hippocampus (Lutzenberger et al., 1987); subsequent studies of individuals who have undergone temporal lobectomy (Johnson, 1988; Smith and Halgren, 1989), or stroke patients (Onofrj et al., 1992; Polich and Squire, 1993), and monkeys (Paller et al., 1988; Paller et al., 1992) have indicated that the hippocampal formation influences P3b only indirectly (Molnár, 1994). Other reports have implicated the temporal-parietal junction in P3b generation (Knight et al., 1989; Yamaguchi and Knight, 1992; Verleger et al., 1994), and there are some findings that imply that P300-related activity recorded at the scalp is primarily a cortical process (Scherg and Picton, 1991; Johnson, 1993).

An important theoretical point is that the P300 component also reflects intrusive or "novel" stimuli (e.g., dog barks, abstract color forms, etc.). Such stimuli have been found to produce an earlier, positive potential called "P3a" that sometimes is confused with the later P300 or P3b peak (Squires et al., 1975). P3a is typically larger in amplitude than the P3b over the frontal and central electrode sites and is thought to reflect an alerting process that originates in the frontal cortex (Courchesne et al., 1975; Knight, 1984). Recent evidence, however, indicates that P3a generation depends on the stimulus context in which "novel" or even typical stimuli are presented (Comerchero et al., 1997; Katayama and Polich, 1998). Thus, the P3a is observed when infrequently presented deviant stimuli interrupt attentional mechanisms engaged in performance of the primary task.

One of the main hypotheses attempting to explain the cognitive deficits in alcoholism proposes that the impairments found in chronic alcoholics are related to frontal lobe dysfunction (Ryan and Butter, 1983). Alcoholic subjects have demonstrated poor performance on tasks related to frontal lobe functioning (Adams et al., 1993; Nicolás et al., 1993; Ciesielski et al., 1995), and neuroimaging techniques have shown decreased local cerebral metabolic rates for glucose (Adams et al., 1993), and cerebral blood flow ratio (Nicolás et al., 1993), as well as deficits in gray and white matter (Pfefferbaum et al., 1997) in the frontal lobes of alcoholic patients. The deficits in frontal lobe function have even been proposed as partially preceding the onset of alcoholism (Ciesielski et al., 1995). Given this perspective, assessment of P3a in alcoholics can be used to ascertain the neurophysiological and cognitive dysfunctions involved in alcoholism, especially because of the relation established between this component and frontal lobe activity (Knight, 1984; Katayama and Polich, 1998; Knight, 1997).

P3a in Alcoholism

Only a few studies have assessed the more automatic P3a in alcoholics. When auditory oddball paradigms have been used, P3a amplitude to the infrequent nontarget tones was smaller in the alcoholics (Realmuto et al., 1993), although significant group differences have not always been found (Pfefferbaum et al., 1991). A recent study assessed the P3a in elderly alcoholics and controls with visual and auditory three-stimulus paradigms; they found no group differences for P3b or P3a amplitudes but reported latency delays for the visual and auditory P3a and for the visual P3b (Biggins et al., 1995). Another study of cocaine dependent and alcohol and cocaine co-dependent subjects found both latency delays and amplitude reductions

of P3a in the twogroups of dependent subjects (Biggins et al., 1997). Thus, P3a evaluations of alcoholic and related subject groups have produced mixed results to date.

These differences may have resulted from using paradigms in which robust P3a components are not well elicited. Several recent studies have begun to characterize the task parameters in which the P3a and P3b components can be elicited reliably with a three-stimulus paradigm. In these paradigms, a task-relevant target stimulus produces a parietal P300 (P3b), which is the same in one-, two-, and three-stimulus tasks (Katayama and Polich, 1996a) with amplitude and latency values that are not influenced by the probability of the infrequent nontarget stimulus (Katayama and Polich, 1996b) or by the infrequent nontarget/standard stimulus discriminability (Katayama and Polich, 1998). Indeed, the infrequent nontarget stimulus elicits a P300 component, the morphological characteristics of which vary systematically as a function of the stimulus context. When the target/standard perceptual discrimination is easy, the infrequent nontarget produces a parietal P3b, smaller and longer than the target P3b but with similar topography. When the target/standard perceptual discrimination is difficult, a well-differentiated infrequent nontarget elicits a clear P3a, which is larger in amplitude and shorter in latency than P3b with a more anterior distribution and similar in morphology to the P3a elicited by novel stimuli (Courchesne et al., 1975). In this framework, the stimulus context defined by the difficult target/standard discrimination leads to an attentional redirection to the nontarget because of frontal lobe activation (Comerchero et al., 1997; Katayama and Polich, 1998). Thus, a three-stimulus paradigm with perceptually similar target/standard stimuli and a distinct infrequent nontarget stimulus generates a parietal P3b from the target and a more anterior P3a from the infrequent nontarget stimulus.

Present Study

The present study used a visual three-stimulus paradigm to assess the P3a component in a population of abstinent, chronic alcoholics and a control group. Similar target and standard stimuli, and well-differentiated (but not "novel") infrequent nontarget stimuli, were used to separate the P3a and P3b components. To specify the neural loci of the resulting ERP components, amplitude and latency measures and current source density (CSD) topographic maps were assessed. CSD analysis provides an accurate measure of the sources and sinks of current under the scalp that contribute to the ERP cortical generators. It is based on the spline Laplacian method, and constitutes a reference-free measure of the electrical activity in the brain, independent of any physical conductive head models (Nunez and Pilgreen, 1991).

METHODS AND MATERIALS

Subjects

The subjects were 72 adult males ranging from, 19 to 50 years of age. Control individuals (n = 28, mean = 27.7, SD = 7.8 yrs) were recruited through newspaper ads or notices posted in the Health Science Center. The initial screening procedure required each subject to complete a questionnaire detailing alcohol and drug use history and the medical and 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 control candidate's first-or second-degree relatives were diagnosed as alcoholic. The alcoholic group (n = 44, mean = 37.0, SD = 6.8 yrs) consisted of individuals undergoing alcohol treatment in hospital alcoholism treatment programs. The alcoholic patients were significantly older than the controls ($p < .00005$), manifested an early onset of drinking (mean = 17.4 yrs), and had a positive family history of alcoholism (mean = 2.4 alcoholic relatives).

Alcoholic patients participated in a mandatory regimen that included vitamin and nutritional therapy, and were monitored closely for any signs of drug and/or alcohol abuse. Participants were typically tested on their 28th day in the program or as close as possible to their release, provided informed consent, and were paid for their participation. For the alcoholic group, exclusionary criteria included a history of intravenous drug use, treatment medication (e.g., antabuse, psychoactive drugs, or other drugs with CNS effects), seizures unrelated to withdrawal, retardation, hearing, or visual impairments, and liver damage. Exclusionary criteria for both the alcoholic and control groups included major medical problems, a current CNS medication, or a history of psychiatric illness and/or drug abuse (a degree of drug abuse was permitted if secondary to alcoholism). Each subject underwent a detailed psychiatric interview focusing on questions of drug histories for both himself and his first- and second-degree relatives. All subjects were asked to abstain from alcohol for 48 hr before testing, and each was interviewed using the SemiStructured Assessment for the Genetics of Alcoholism (SSAGA), which uses both DSM-III-R alcohol dependence and Feighner definite criteria for the determination of alcoholism (Bucholz et al., 1994). All subjects were randomly distributed across variables known to affect P300 measures, such as ERP assessment time (hr of the day, month), recency of food ingestion, handedness, etc. (Polich and Kok, 1995). The main demographic characteristics of the sample are summarized in Table 1.

Experimental Design

A 31 lead electrode cap (Electro-Cap International, Inc) was used to obtain the entire, 10–20 International montage, with an additional, 12 sites also assayed: AF1, AF2, FC1, FC2, FC5, FC6, CP1, CP2, CP5, CP6, PO1 and PO2 [Standard Electrode Position Nomenclature (American Electroencephalographic Society, 1991)]. All scalp electrodes were referred to the nose, and a forehead electrode served as ground. EEG activity was amplified, 10K by using a band-pass 0.02–50 Hz (Sensorium EPA-2 Electrophysiology Amplifier), and was sampled at a rate of 256 Hz, with a 125 ms prestimulus baseline and an epoch length of 1375 ms. Both vertical and horizontal eye movements were monitored with electrodes that were placed supraorbitally and at the outer canthus of the right eye. Trials with excessive eye and body movements (> 73.3 μV) were rejected

Table 1. Demographic Characteristics of Control and Alcoholic Groups

	Controls (n = 28)		Alcoholics (n = 44)	
	Mean	SD	Mean	SD
Age (years)	27.7	7.8	37.0	6.8
Education (years)	15.9	2.3	12.9	1.8
Age of onset of drinking (years)	na	na	17.4	4.0
Drinking days/month	3.4	4.1	19.0	7.6
Drinks/occasion	2.1	1.6	12.0	7.1

na: not applicable.

on-line. Digital filtering was performed off-line using a 16 Hz low pass filter.

Stimuli were three white lines presented on a black background, one vertical, one 2° off vertical, and one horizontal. They were presented at the center of a computer monitor with 45 ms duration. The interstimulus interval was 1.6 sec, and the stimuli were approximately 8.5 cm length. The vertical line was presented with a probability of 0.80 and was designated as the standard stimulus; the 2° off vertical line (0.10) was the target, whereas the horizontal line (0.10) was the infrequent nontarget stimulus.

Subjects were seated comfortably in a dimly lighted, temperature-regulated, sound-attenuated chamber, and fixated on a centrally displayed point located 1 m from their eyes on a computer monitor. A brief training sample was run to ensure accurate identification of the target line and acceptable task performance. Subjects were instructed to press a button as quickly as possible after seeing the line 2° tilted from vertical. Response speed was emphasized, but not at the cost of accuracy. Response hand side was alternated across subjects, and trials with response time >1000 ms were automatically excluded from all analyses. The subjects received a maximum of 350 trials, but the experiment could be terminated when 200 artifact-free trials were acquired (25 target, 25 infrequent nontarget, and 150 of the standard stimuli). ERPs from artifact-free trials were averaged according to stimulus type. Because the major purpose of the present study was to evaluate P3a differences between the subject groups, only ERP data from the infrequent nontarget (P3a) are presented here.

Data Analysis

The average ERPs were analyzed with a semiautomatic peak detection program. The P3a component was selected as the largest amplitude peak within a time window from 325–550 ms for the infrequent nontarget ERPs. Both amplitudes (μV) and latencies (ms) were obtained at each of the 31 electrodes from all subjects.

Component measurements were organized into five regional groupings: frontal (FP1, FP2, AF1, AF2, Fz, F3, F4, F7, F8), central (FC1, FC2, FC5, FC6, Cz, C3, C4), parietal, (CP1, CP2, Pz, P3, P4), temporal (T7, T8, CP5, CP6, P7, P8), and occipital (PO1, PO2, O1, O2). As there were differences in age between the two groups, preliminary Group by Age analyses were performed to determine the inclusion of the Age variable in the design. There were no significant interactions between Group and Age either in the repeated measures ANOVAs in each scalp region or in the individual ANOVAs at each electrode site, which indicated that effects of age over P3a amplitude and latency were not different in the two groups. Hence, the Age variable was included as a covariate. ANCOVAs with group as a between-subjects factor and electrode as a within-subject factor using age as a covariate were performed to assess group differences in P3a amplitudes and latencies in each of the regions. Greenhouse-Geisser adjustments to the degrees of freedom were used where appropriate to correct for violations of sphericity. ANCOVAs were also used to analyze differences in the ERP measurements for individual electrodes between the two groups. The behavioral data (response time, correct responses, omissions, and false alarms) were assessed using similar ANCOVAs. Bonferroni corrected probabilities were used for all the comparisons.

CSD topographic maps were calculated at the time point of the maximum global field power corresponding to the P3a component in each group (controls = 414 ms, alcoholics = 417 ms). The positive values represent sources of current—i.e., a source region where a local radial current is flowing through the skull into the scalp. These procedures have demonstrated considerable success previously at isolating critical neural loci (Nunez and Pilgreen, 1991; Gevins et al., 1991; Chorlian et al., 1995; Zhang et al., 1997). The activity in the two groups was compared according to the method of Srebro (1996), using the t test statistic for both global and regional (frontal, central, parietal, left temporal, right temporal, and occipital) comparisons.

Table 2. Behavioral Data for Control and Alcoholic Groups

	Controls (n = 28)		Alcoholics (n = 44)	
	Mean	SD	Mean	SD
Response time (ms)	585	116.4	542	97.1
% Correct	70.9	14.5	83.2	13.7
% False alarms	4.6	7.1	6.4	8.2

RESULTS

Behavioral Performance

Table 2 summarizes the behavioral data for each group. No significant differences between the groups were obtained for response time, percentage of correct responses, and percentage of false alarms ($p > .05$).

P3a Amplitude

Fig. 1 illustrates the grand mean waveforms of the ERPs for the control and alcoholic groups. The descriptive data are summarized in Table 3.

The mixed-model ANCOVA analyses of the P3a characteristics for the infrequent nontarget condition demonstrated significant differences between the two groups in the central [$F(1,69) = 6.81, p < .0111$], parietal [$F(1,69) = 8.21, p < .0055$], temporal [$F(1,69) = 8.21, p < .0055$], and occipital [$F(1,69) = 5.08, p < .0274$]regions, but not in the frontal region [$F(1,69) = 3.58, p > .0626$]. ANCOVA analyses of each individual lead yielded significant reductions in the P3a amplitude in the alcoholic group for six central, five parietal, six temporal, and two occipital leads (see Table 3). Fig. 2 illustrates the P3a amplitudes at the three midline electrodes Fz, Cz, and Pz.

P3a Latency

There were no significant group effects on any of the regional or individual ANCOVA analyses executed on the latency of P3a ($p > .05$).

CSD Topographic Maps

Fig. 3 illustrates the P3a CSD maps for the control and alcoholic groups. Visual inspection of the maps indicated that the alcoholic group produced smaller current sources than the control group. The differences mainly appeared in the centroparietal and right temporal areas, where the control group presented extended sources of positive activity. Statistical comparison of the two maps (Srebro, 1996) demonstrated a significant overall reduced level of neuroelectric activity in the alcoholic group ($t = 40.1, p < .05$). Regional comparisons showed that the differences were significant for all the regions ($p < .05$).

DISCUSSION

P3a waveforms obtained with the present paradigm closely resemble previous reports when the perceptual discrimination between the target and standard stimuli is difficult, and the infrequent nontarget stimulus is clearly dif-

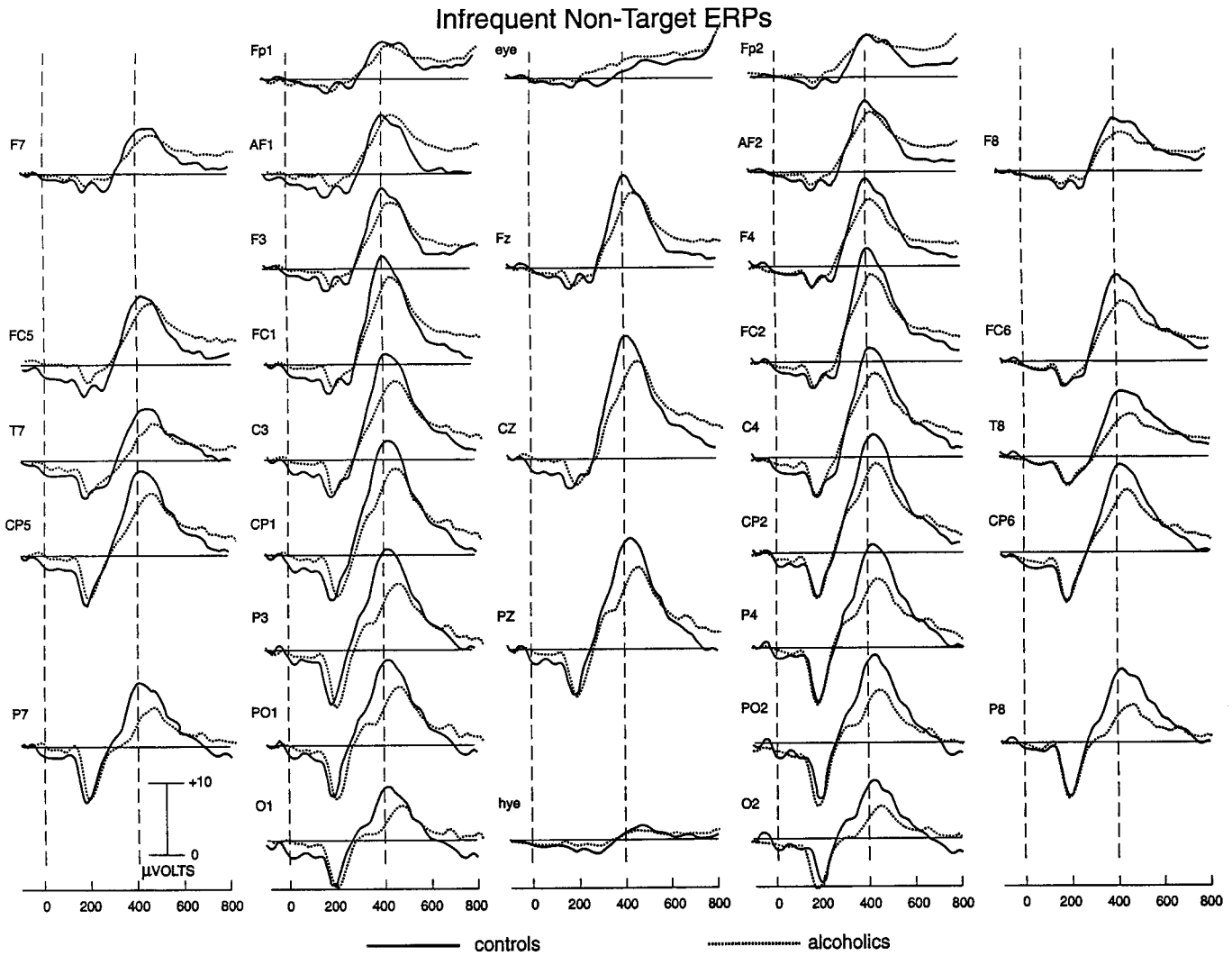

Fig. 1. Grand mean waveforms of the ERPs for the control and alcoholic groups.

ferent (Katayama and Polich, 1998). The rare nontarget stimulus elicited a P3a component that was larger in amplitude and shorter in latency than the P3b elicited by the target stimulus at all electrodes. P3b was later and smaller than those recorded during easy stimulus oddball paradigms (Katayama and Polich, 1996a,b). Furthermore, preliminary repeated measures ANOVAs, comparing both amplitude and latency of the P3 components elicited by the target and the infrequent nontarget in the two groups, statistically differentiated the two components (P3b and P3a) in the present study.

P3a, P3b, and Alcoholism

Differences between alcoholic and control subjects in the visual P3b amplitude have been extensively reported (Porjesz et al., 1980; Patterson et al., 1987; Porjesz et al. 1987b; Pfefferbaum et al. 1991; Glenn et al. 1996; Ciesielski et al. 1985; Pfefferbaum et al. 1987; Porjesz et al., 1987a; Whipple et al., 1988; Cohen et al., 1997). The present study results indicated that there are also strong group differences for the P3a component from the infrequent irrelevant stimuli, which has not been studied extensively. Alcoholics manifested a widespread reduction in the P3a voltage, with smaller amplitudes in 19 of the 22 leads at the central, parietal, temporal, and occipital locations. Thus, the P3a reduction is broadly extended on the scalp, but yielded similar values to the controls over the frontal sites.

The present results are consistent with previous findings of a reduced P3a to infrequent stimuli in unattended oddball paradigms in alcoholics (Realmuto et al., 1993). However, the paradigm used here is more appropriate for assessing the automatic processing of irrelevant infrequent events, because it requires a difficult perceptual discrimination, with the infrequent nontarget stimulus inducing a switch in the attentional focus that generates a strong P3a frontocentral amplitude distribution. The only similar previous report on alcoholics that used a three-stimulus paradigm found delayed P3a latency but not reduced amplitude in the alcoholic group, although diminished amplitudes were found in a group of cocaine and alcohol co-dependent

Table 3. Mean P3a Amplitudes (μV) for the Infrequent Non-Target Stimulus in the Control and Alcoholic Groups

	Controls (n = 28)		Alcoholics (n = 44)			
	Mean	SD	Mean	SD	F	p‡
Fp1	6.61	5.16	6.16	4.21	1.55	ns
Fp2	6.63	4.79	6.33	4.40	0.93	ns
AF1	10.10	5.61	9.46	5.06	1.77	ns
AF2	10.75	6.30	9.46	4.94	2.75	ns
Fz	14.06	6.05	12.06	6.14	3.94	ns
F3	12.44	5.84	10.39	5.55	6.37	.0139*
F4	13.22	5.78	11.04	5.66	4.99	.0287*
F7	7.24	3.94	6.12	4.13	4.73	.0330*
F8	8.48	4.21	7.01	3.64	2.09	ns
FC1	16.91	6.83	13.70	6.60	7.35	.0085
FC2	17.45	7.10	13.95	6.51	5.66	.0201
FC5	11.36	5.08	9.43	5.21	4.96	.0292*
FC6	13.12	5.35	10.04	4.95	5.77	.0190
Cz	19.05	7.26	15.08	7.31	6.75	.0115
C3	16.72	6.18	12.72	6.61	8.11	.0058
C4	17.66	6.05	13.78	6.40	5.73	.0194
CP1	18.39	6.27	13.94	6.99	8.15	.0057
CP2	18.99	6.62	14.25	7.08	8.06	.0060
Pz	17.54	5.78	13.27	6.86	6.11	.0159
P3	15.88	6.04	11.25	6.42	7.56	.0076
P4	16.03	5.39	11.35	5.83	8.74	.0043
T7	9.00	4.62	6.73	4.54	4.80	.0318
T8	10.34	4.47	7.28	4.01	5.28	.0245
CP5	13.76	4.72	9.91	5.84	6.44	.0134
CP6	14.80	4.99	10.81	5.53	6.02	.0166
P7	10.43	5.07	6.62	5.24	6.72	.0116
P8	11.70	4.32	6.84	4.76	11.97	.0009
PO1	13.66	5.91	10.08	6.12	4.85	.0310
PO2	14.20	5.69	9.97	6.13	6.35	.0141
O1	9.58	5.50	6.47	4.91	3.67	ns
O2	9.36	5.24	6.18	4.84	3.74	ns

‡ df (1, 69); * no significant Bonferroni comparison; ns, not significant.

subjects (Biggins et al., 1995, 1997). Although that study used novel nontarget infrequent stimuli to elicit P3a, it used an easy perceptual discrimination task, which elicited P3 components that were very similar for both the target and the infrequent nontarget stimuli (Katayama and Polich, 1998). In addition, the sample used was smaller (n = 11 alcoholics and n = 11 controls) than that in the present report (n = 44 alcoholics and n = 28 controls) and may not have been sufficiently powerful to isolate P3a amplitude effects.

The P3a wave has been interpreted as a marker of frontal lobe attentional activity (Squires et al., 1975; Knight, 1984, 1990) and may reflect activation of an attentional switch between a stimulus presented and a passively formed neuronal trace (Näätänen, 1990). However, the present study, and related previous studies, have demonstrated that the P3a appears when the attentional resources required for a difficult perceptual discrimination task are redirected to an infrequent stimulus. This is not the case when the discrimination is easy, which enables an infrequent but nontarget stimulus to be evaluated without interruption of attentional focus (Katayama and Polich, 1998). This conception of the meaning of the P3a closely agrees with the proposed neural generators of this scalp recorded wave (Knight, 1996).

P3a, Frontal Lobe Function, and Alcoholism

The frontocentral distribution of the P3a component, as well as the frontal lobe neural mechanisms involved in novelty detection, have pointed to the frontal structures as P3a generators, but other cortical association areas are also involved (Knight, 1996, 1997). Unilateral lesions in the dorsolateral prefrontal cortex have been associated with bilateral reduction of P3a to novel stimuli without affecting P3b (Knight, 1997), although it has been proposed that the frontal lobe could act as a modulator of the sensory and limbic input, more than a generator (Knight, 1984). Intracranial recordings have identified a triphasic ERP activity pattern for the N2a/P3a/SW that corresponds with the extracranial P3a and suggests that an anatomically diffuse frontal lobe generator contributes to P3a generation (Baudena et al., 1995). Hence, the frontal lobe may act not only as an inhibitor of posterior structures, but may operate mainly as a novelty detector. Moreover, lesions in the posterior association cortex, including the temporoparietal junction and the lateral parietal lobe, have been found to reduce visual P3a (Knight, 1997). Intracranial N2a/P3a/SW components also have been observed in temporal and parietal locations (Halgren et al., 1995a,b). Finally, the hippocampus and limbic structures, as well as the medial temporal lobe, have been found to be involved in the generation of visual P3 (Verleger et al., 1994; Knight, 1996). Reduced visual P3a amplitudes have been observed in patients with posterior hippocampal lesions (Knight 1996), and intracranial correlates of the scalp P3a, in limbic locations such as the parahippocampal region, the cingulate gyrus, or medial temporal lobe areas (Halgren et al., 1995a,b). These brain areas appear to be involved in P3a generation, are closely interconnected, and have been proposed to form a widespread limbic-cortical network for novelty detection and orientation of attention (Knight, 1997; Mesulam, 1990).

In this context it is important to note that the P3a amplitude reduction for the alcoholic group was significant in all but the frontal areas. Although the P3a is more frontal than the P3b, its amplitude was maximum at the Cz electrode, and was larger at Pz than at Fz for the two groups (see Fig. 2). The P3a amplitude reductions in alcoholics, maximum in the centroparietal leads, resembled the anomalies usually described for the P3b wave. The P3a and P3b components overlap one another when recorded at the scalp, and this view is supported both from intracranial and scalp reports (Baudena et al., 1995; Halgren et al., 1995a,b; Polich, 1988). Therefore, the present findings that P3a abnormalities to the infrequent nontarget stimuli in alcoholics produced similar scalp topography distributions to those previously described for the P3b to target stimuli suggests that a neurophysiological process that is common to the two components differentiates between alcoholic and control groups. The P3a CSD maps confirmed that the diminished electrical activity in the alcoholic group had a

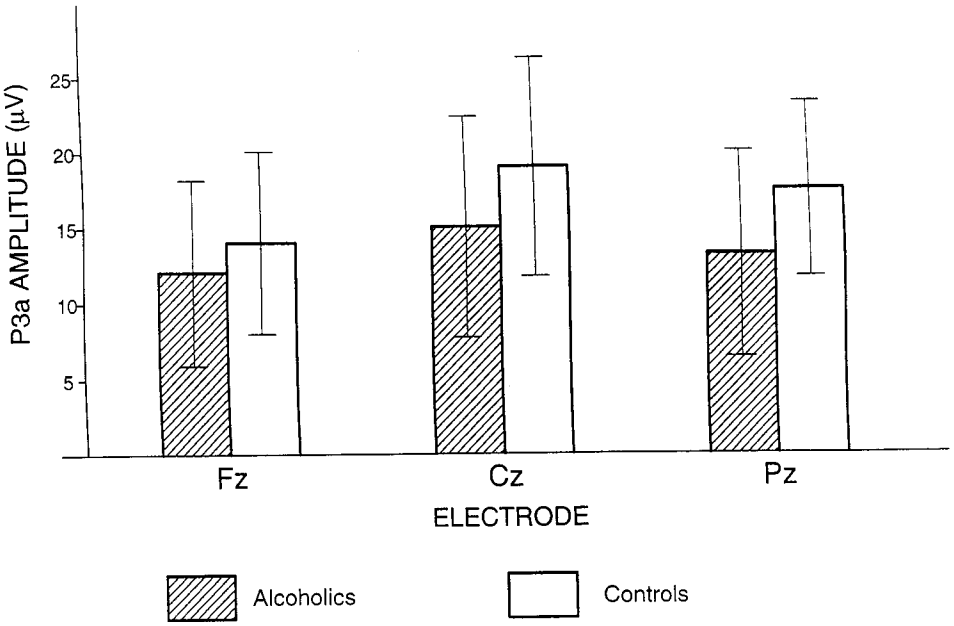

Fig. 2. Means (± 1SD) of P3a amplitudes (μV) at the three midline electrodes for the alcoholic group versus the control group.

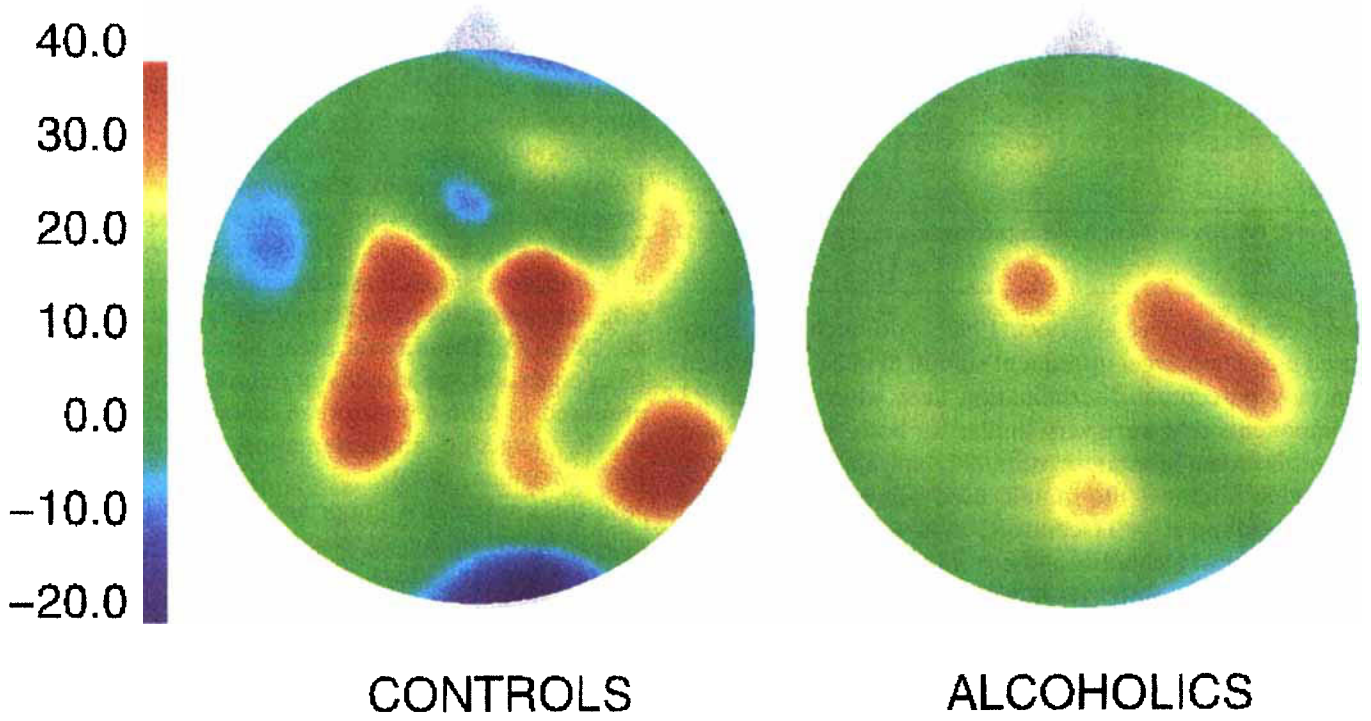

Fig. 3. CSD maps at the P3a peak for control (414 ms), alcoholic (418 ms) groups (the scale uses arbitrary units).

widespread distribution, and the maps of the two groups were statistically different in all the regions, including the frontal area. The control group presented two symmetrical sources in the centroparietal region. However, P3a activity in the alcoholic group was considerably weaker than in the control subjects, especially at the left hemisphere. The right temporal source and the occipital sink in the control group did not appear in the alcoholics. Differences also appeared in the frontal region but were less pronounced, because the control group produced a single activity source in the right hemisphere and a sink in the middle of the region that were absent in the alcoholic group.

Theoretical Interpretation

Positive scalp waves have been interpreted as an index of inhibition of cortical areas during the processing of stimuli (Rockstroh et al., 1992; Schupp et al., 1994; Rockstroh et

al., 1996; Porjesz and Begleiter, 1998). Hence, the diminished ERPs in alcoholics may indicate a deficiency in cortical inhibition and a reduced ability in processing the stimuli (Begleiter et al., 1980). From a behavioral perspective, alcoholism is frequently associated with impulsive and disinhibited behavior that is often associated with a high prevalence of attentional problems which include distractibility and difficulties in sustained attention. These characteristics have been related to deficits of prefrontal functioning and have been proposed to antecede alcohol abuse (Tarter and Edwards, 1988; Peterson and Pihl, 1990), an interpretation consistent with biobehavioral models of alcoholism vulnerability (Peterson and Pihl, 1990; Tarter 1991). The present study provides evidence that a neurophysiological index of processing of distractor stimuli is also impaired, although a selective impairment of the frontal structures is not suggested. Rather, the findings suggest deficits in alcoholics that involve several cortical regions, probably those that participate in a neural network engaged for attention and orientation (Knight 1997; Mesulam 1990), because infrequent events that take attention away from relevant stimuli must be efficiently evaluated and discarded (Katayama and Polich, 1998). The neurophysiological dysfunction evidenced by alcoholic subjects may be related to the impulsivity and distractibility often associated with alcoholism and could contribute to the dysfunction in the processing of the relevant information (Porjesz and Begleiter, 1998).

Finally, even though the target stimulus P3b was not assessed, this component also seemed to be significantly reduced over the parietocentral electrodes in the alcoholic group, which suggests that these subjects processed both the target and the nontarget infrequent stimuli inadequately. If the diminished P3b in this population is due to an impairment in the match/mismatch process necessary for the evaluation of the stimulus, it may be that this impairment affects the evaluation of both relevant and irrelevant infrequent stimuli (Porjesz and Begleiter, 1996, 1998).

CONCLUSION

In summary, ERP deficits in abstinent chronic alcoholics also affect the amplitude of the P3a, although this conclusion awaits replication and extension to the auditory modality. Additional studies should also assay comprehensively the scalp topography signatures of the P3a and P3b distinction in this important psychiatric patient group. Thus, because P3b anomalies in alcoholics seem related to the genetic vulnerability for alcoholism more than the neurotoxic effects of chronic ingestion of ethanol (Pfefferbaum et al., 1991; Cohen et al., 1995), evaluation of P3a in the assessment of nonalcoholic subjects with a family history of alcoholism is highly warranted.

ACKNOWLEDGMENT

We thank Brian Beckrich, Tao Chang, Lisa Iskander, Vladimir Kotlyarevsky, Arthur Stimus, Hanbi Ye, and Sergio Valentini for their invaluable technical assistance.

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