

ORIGINAL PAPER

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Auditory and visual event-related potentials in alcoholics: abnormalities of components and brain electrical field

Received: 2 July 1999 / Accepted: 14 April 2000

Abstract Alterations of ERPs recorded over midline scalp sites have frequently been reported in alcoholics. To assess the P3 and other ERP components topographically, auditory and visual ERPs were recorded from 33 scalp electrodes in abstinent alcoholics and healthy controls using an oddball paradigm. At the Cz electrode the alcoholics showed decreased visual N1 and increased auditory N2 amplitudes. Topographically, the negative centroids of the visual N1 and P3 and the auditory N2 differed between groups, and the positive centroid of the visual P3 was displaced toward the right hemisphere. While no valid diagnostic classification could be obtained by using the traditional ERP component P3 recorded from Pz, the combination of visual N1 and auditory N2 amplitudes at Cz with centroid parameters amounted to 51 % explained variance and 92 % correct discrimination of alcoholics from controls. Abnormalities of N1 amplitude and P3 topography similar to the current findings in alcoholics have previously been described for schizophrenics.

Key words Alcoholism · Event-related potentials · Evoked potential diagnosis · Brain mapping · Spatial analysis

Introduction

Event-related potentials (ERPs) elicited during information processing tasks are useful for assessment of both normal and abnormal brain functioning, because several of the positive and negative ERP late components relate rather specifically to cognitive processes such as selective atten-

tion and signal analysis (Rugg and Coles 1995). ERP alterations and especially decreased P3 amplitudes have been reported both in adult alcoholics and in unaffected children of alcoholics. The P3 reduction in adult alcoholics, which has been documented by several groups (for a review see Porjesz and Begleiter 1993), was recently found to depend on concomitant comorbid factors rather than to represent an independent marker for chronic alcoholism (Hill et al. 1999c). P3 reduction in children determined to be at high-risk for developing alcoholism (Begleiter et al. 1984; O'Connor et al. 1986; Whipple et al. 1988; Hill et al. 1990) has become an exciting research issue in recent years. Assessing and analyzing longitudinal data in these children has revealed that the reduced P3 represents maturational delay (Hill et al. 1999b). Transmission of P3 in high-risk families most likely follows a polygenic model of inheritance with significant parent-to-offspring transmission (Hill 1999a). Boys studied using ERP paradigms before their first drug exposure (including alcohol) and studied again using a behavioral questionnaire four years later were more likely involved with substance (ab)use at follow-up if their baseline P3 amplitudes had been low (Berman et al. 1993).

ERP findings in chronic alcoholics were often obtained by measurement from the midline recording sites Fz, Cz, and Pz only. Topographical recordings, which can assess the ERP distribution across the whole head, have been performed only rarely in these patients (Pfefferbaum et al. 1991, Cohen et al. 1995), although spatial mapping of brain activity recently received growing attention in basic and clinical neuroscience. In psychiatric research, this approach has previously revealed an asymmetrical distribution of the P3 electrical field in schizophrenics (Morstyn et al. 1983, Strik et al. 1994). This is in line with neuroanatomical and neuropsychological findings of hemispherical asymmetry in this disorder.

Using well-established auditory and visual oddball paradigms, we performed topographical ERP recordings in detoxified alcoholics and control subjects. Our initial focus was on spatial analysis of the P3 field. Unexpectedly, we observed an increased auditory N2 in our patient group,

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and included this component and the visual N1 in our ERP analysis.

Subjects and methods

Twenty-seven alcoholics participated. Thirteen patients had a family history of alcoholism involving siblings or parents (FH+), 14 of them not (FH-). The alcoholics were inpatients from the Psychiatric University Clinic in Freiburg, undergoing detoxification and a rehabilitation program. All alcoholics met the DSM-IV criteria for alcohol dependence and were interviewed using the Addiction Severity Index (McLellan et al. 1992). Exclusion criteria for this study included major medical problems, a history of neurological disease or trauma, major psychiatric disorders, substantial abuse of drugs other than alcohol, or current use of psychoactive drugs. For the alcoholics the mean age was 42.8 ± 7.7 years, the average years of education 9.5 ± 1.6 years, and the average WIP score (a short estimation of the IQ, Dahl 1986) 107.1 ± 6.3 points. At the time of ERP testing they were sober for an average of 22 days (13–34 days).

The controls ($n=15$) were recruited from hospital staff, students and local volunteers. They were screened for major medical problems and history of psychiatric illness, head injury, and drug abuse. None of the controls had a first- or second-degree relative with alcohol dependence. Their mean age (42.8 ± 6.7 years), average years of education (10.0 ± 2.1 years) and average WIP score (110.0 ± 10.0 points) were not significantly different from those of the alcoholics.

ERP testing

Subjects wore earphones and sat upright in an easy chair in a sound attenuated room looking at a CRT screen. ERPs were collected during an auditory and a visual paradigm. In both paradigms, a pseudorandom sequence of target and non-target stimuli was presented, consisting of 400 stimuli with 15 % target probability. The interstimulus interval was randomized between 1 and 2 s. The task was to silently count the target stimuli. The actual target count was varied between 61 and 64 in order to render the counting result less obvious. Subjects were asked for the result at the end of each run. Sequences were generated so that no more than 10 non-target stimuli occurred between two targets in order to avoid unbalanced presentations.

Auditory oddball paradigm. Tone stimuli with 80 dB SPL, 50 ms duration, 1500 Hz (targets) and 800 Hz (non-targets). Counts reported by the controls were on average wrong by 0.4 ± 0.2 , those of the alcoholics by 0.9 ± 0.3 .

Visual oddball paradigm. Presentation of letters “X” (target) and “O” (non-target) on the CRT screen. As in the auditory task, very few counting errors occurred: the mean difference was 0.8 ± 0.3 for the controls and 1.0 ± 0.2 for the alcoholics. Incidentally, in both paradigms, controls only reported values which were either correct or too low, while alcoholics reported too few and too many targets with similar probability.

EEG and EOG recording

The EEG was recorded from 33 scalp electrodes, filtered between 0.15 and 70 Hz and digitized at a rate of 500 Hz. The electrode sites were those of the International 10–20 System with additional electrodes placed in the spaces between 4 neighboring 10–20 sites, effectively doubling the spatial sampling. Recording reference was Cz. Bipolar vertical and horizontal EOG was recorded from above and below the right eye and the outer canthi of the eyes, respectively. Blink artifacts were reduced by an EOG regression technique (Gratton 1983) followed by visual inspection of all single trials for remaining artifacts. Between 22 and 63 artifact-free trials (Alcoholics: 47 ± 2 , Controls: 49 ± 3) were averaged to form an individual ERP trace, which was then computationally rereferenced either to linked (i. e., averaged) mastoids or to common average reference. Potential values for single electrodes were referred to linked mastoids and topographical distribution to common average reference.

ERP data analysis

Spatial analysis of the ERP distributions was performed for the responses to target stimuli and for those components which yielded (near-)significant amplitude differences between alcoholics and controls for our recordings from traditional midline sites Fz, Cz and Pz.

Analyzing ERP scalp distributions based on recordings from 33 electrodes, we used the Global Field Power (GFP) measure introduced by Lehmann and Skrandies (1980). The GFP measure corresponds to the variance of the EEG distribution across electrodes. We used an automatic GFP peak detection step for component latencies, followed by classification using the latency and the polarity at Cz relative to linked mastoids (P or N). The components were then verified by eye. Latency ranges were 65 to 140 ms for the auditory N1, 260 to 500 ms for the auditory P3, 225 to 350 ms for the visual N2 and 280 to 600 ms for the visual P3. The auditory N2 (latency range: 180–300 ms) and visual N1 (140–200 ms) could not be reliably detected in all cases using GFP maxima. In particular, the visual N1 in some alcoholics and the auditory N2 in some controls were so small in amplitude that these components could not reliably be detected in leads far from Cz. Therefore, we used a time window approach to assess the maps: For visual N1 amplitudes we evaluated N1 and P1 latency in the Cz curves to define a time window reaching from N1 latency – $\frac{1}{2}(\text{N1 latency} - \text{P1 latency})$ to N1 latency + $\frac{1}{2}(\text{N1 latency} - \text{P1 latency})$. N1 amplitudes for the 33 electrodes were then obtained by calculating mean amplitudes of ERP curves from these electrodes within this time window. Similarly, auditory N2 amplitudes were calculated using a time window from N2 latency – $\frac{1}{2}(\text{N2 latency} - \text{P2 latency})$ to N2 latency + $\frac{1}{2}(\text{N2 latency} - \text{P2 latency})$.

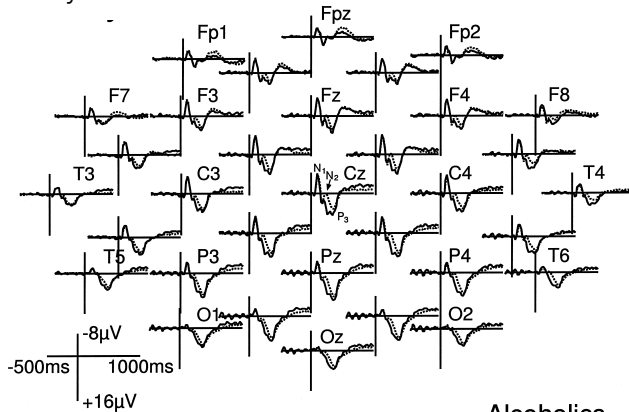
The full ERP scalp distributions were analyzed for group differences using spatial centroid descriptors as described by Lehmann (1987). After subtracting the average potential across all EEG channels for each time point (common average reference), the amplitude-weighted mean x and y coordinates were calculated for the positive and negative parts of each ERP component distribution. The coordinate system used for this calculation extended from –1 to +1 between T3 and T4 (x axis) respectively between Oz and Fpz (y axis), so that the Cz electrode was located at the origin. These center-of-mass or centroid coordinates are by definition independent of the overall ERP amplitude and have been shown to efficiently capture slight but systematic variations in component topography across subject or patient groups. Such variations are statistically difficult to evaluate on the basis of differences in all individual channels, because these differences are usually small and statistical power is lost by parallel testing of a large number of channels.

Results

Figure 1 shows the grand averages of the ERP responses to the target stimuli in the auditory and visual oddball paradigms for alcoholics and controls, referenced to linked mastoids.

As a main issue we compared for each component the amplitudes measured at midline recording sites with spatial parameters with respect to possible differences between alcoholics and controls. Figure 2 shows means and SDs for these variables together with potential maps and Table 1 the results of group comparisons using t-tests. Amplitude data are presented for the lead where the component is usually largest: N1 and N2 for Cz and P3 for Pz. For P3 measurements at Cz, significantly smaller amplitudes were found in alcoholics for the visual ($p = .026$) but not for the auditory task. All components except auditory P3 showed significant ($p < .05$) group differences for one or more centroid coordinates.

Auditory



Visual

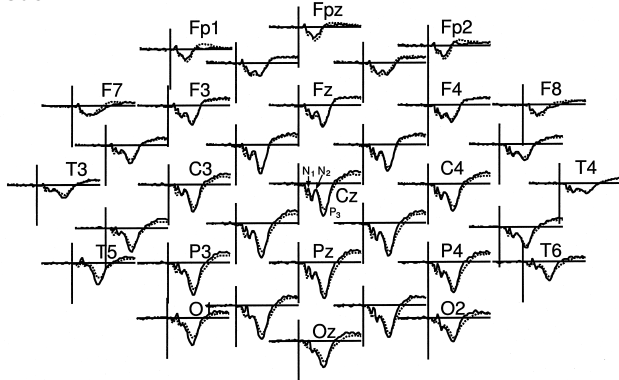


Fig. 1 Grand averages at 33 scalp electrodes for the ERP responses of alcoholics and controls to auditory and visual target stimuli presented in an "oddball" paradigm.

Multiple regression analysis was conducted to assess the effects of age, FH+/FH- status, years of alcoholism, typical drinking occasions over the past six months and mean alcohol intake on a typical drinking occasion on the

Table 1 Comparisons of ERP variables for alcoholics and controls. P-values for t-test. X is the coordinate of left-right and y of posterior-anterior centroid location.

		Amplitude	Positive Centroid		Negative Centroid	
			X	Y	X	Y
Auditory oddball	N ₂	.002	.054	.310	.017	.382
	P ₃	.104	.196	.753	.280	.180
Visual oddball	N ₁	.017	.533	.113	.996	.027
	P ₃	.068	.041	.130	.022	.046

Bold print: $p < 0.05$

8 ERP variables of Table 1, which yielded significant or near-significant (visual P3 amplitude) group effects. Visual P3 amplitude at Pz was significantly influenced by age ($p = .02$) and auditory N2 amplitude at Cz was (near-) significantly influenced by age ($p = .04$) and FH status ($p = .052$).

When conducting stepwise multiple regression analysis, 4 ERP variables were selected into a model significantly predicting the subjects studied as alcoholic or control individual: Auditory N2/Cz amplitude ($t = 3.98$; $p < .001$), visual N1/Cz amplitude ($t = -2.08$; $p = .046$), visual N1/y coordinate of negative centroid ($t = -2.07$; $p = .047$), and auditory N2/x coordinate of negative centroid ($t = -1.87$; $p = .071$).

Table 2 shows the efficacy of visual P3 amplitude (Pz) alone and in combination with the above listed N1 and N2 amplitudes and centroid coordinates in predicting alcoholic/control status. The amount of variance of alcoholic/control status accounted for by the variables was obtained by (multiple) regression and the correct classification of alcoholics or control subjects by discriminant function analysis.

Fig. 2 Alcoholics and controls for auditory N2 and P3 and visual N1 and P3. **A** Means and SDs of the amplitudes recorded from Cz (N1 and N2) and Pz (P3) against linked mastoids reference. **B** Grand average potential maps referred to average reference. The dark area represents positive and the light area negative values. The distance between neighboring isopotential lines is 1 μ V. **C** Means and SEs of the coordinates of the positive and negative centroids. The Cz electrode site is located at the coordinate center (0, 0).

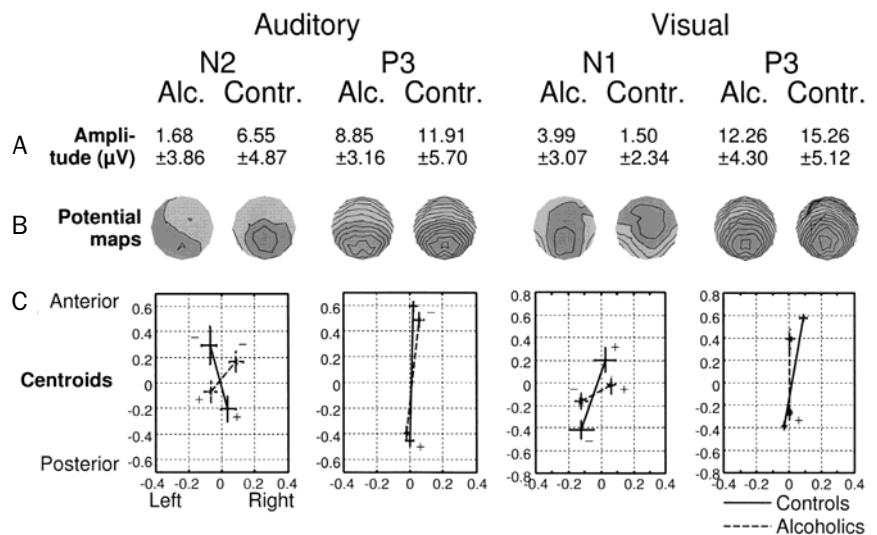


Table 2 Efficacy of P3 amplitude at Pz alone (A), in combination with N1 and N2 amplitudes (B), and with N1 and N2 spatial parameters (C) for the classification of subjects into patients and controls. C-X and C-Y: X and Y coordinates of the negative centroid.

Variables	Explained variance	Classification	
		Correct %	χ^2
A Visual P ₃ (P _z)	9.0 %	60.5 %	3.3
B + Visual N ₁ (C _z) + Auditory N ₂ (C _z)	35.9 %	81.1 %	15.2**
C + Visual N ₁ (C-Y) + Auditory N ₂ (C-X)	50.9 %	91.9 %	26.1***

** p<0.01; *** p<0.001

Discussion

In our study, alcoholics showed diminished visual N1 and increased auditory N2 over midline recording sites and altered electrical fields of visual N1 and P3 and auditory N2. Cz amplitudes and centroid parameters of visual N1 and auditory N2 could be used to discriminate alcoholics and control subjects with high accuracy.

P3 components

Spatial analysis of the P3 field revealed significant group differences for visual P3 showing displacement of the positive centroid to the right and a corresponding shift of negative centroid to the left and to the back. Cohen and coworkers studied regional characteristics of P3 in alcoholics using an auditory oddball paradigm (Cohen et al. 1995) and a visual Go/No Go reaction time paradigm (Cohen et al. 1997) and a recording electrode montage with 31 scalp electrodes. They found that for each of 5 different scalp regions studied – frontal, central, parietal, occipital and temporal – visual and auditory P3 amplitudes were significantly reduced in alcoholics compared to controls. Hemispheric differences of the P3 field were not analyzed. Therefore, our finding of a displacement of the positive centroid to the right in alcoholics, resulting in a more reduced visual P3 over the left compared to right hemisphere, cannot be compared to these studies. Pfefferbaum et al. (1991), recording ERPs with a 19 electrodes montage, found that alcoholics showed a more frontal distribution of the visual but not auditory P3 than controls. A similar trend could be observed in our data (see also Fig. 1).

At Pz, no significant reduction of visual and auditory P3 could be observed in our alcoholics. This is in line with interesting ERP data recently published by Hill et al. (1999c). Contrary to several reports of reduced auditory and especially visual P3 in alcoholics (e.g., Patterson et al. 1987, Pfefferbaum et al. 1991, Porjesz and Begleiter 1993, Glenn et al. 1996), Hill and coworkers could not find significantly diminished auditory and visual P3 in 101 male and female alcoholics compared with healthy controls. The finding that 37 other female alcoholics simulta-

neously suffering from depression did show significant P3 reduction indicated that P3 reduction in alcoholics may occur only in presence of concomitant factors such as comorbid psychopathology. At the central electrode Cz, we found reduced amplitudes of visual but not for auditory P3 in the alcoholics. This probably corresponds to the group difference in P3 topography observed for the visual but not the auditory condition.

Visual N1 and auditory N2

For the auditory N2, a significant dislocation of the negative centroid to the right was found in the alcoholics. Unexpectedly, the N2 amplitude over midline recording sites was found to be increased. Realmuto et al. (1993), using an auditory unattended oddball paradigm, found a *decreased* N2 together with reduced P3a in alcoholics. Among the various N2 kinds of ERP components (Näätänen and Picton 1986), Realmuto et al. probably observed the so-called mismatch negativity, whereas our recordings revealed a component with the characteristics of the N2b. While mismatch negativity and P3a seem to be aspects of the same mental operations and increase or decrease jointly together during information processing, in our recordings an increase of the N2 wave was associated with a reduction of P3a (Fig. 3). Increased N2 amplitudes have not previously been reported in alcoholics, but in children at risk for alcoholism (Hill et al. 1995).

For the visual N1, a displacement of the negative centroid and reduced amplitudes over midline electrode sites were found. Reduced N1 values recorded from traditional midline sites have been reported in several studies in alcoholics and seem to occur more consistently in the visual than in the auditory modality (e.g., Patterson et al. 1987, Glenn et al. 1996).

Family history of alcoholism

Reduction of P3 amplitude has been observed by a number of laboratories in children at high risk for developing

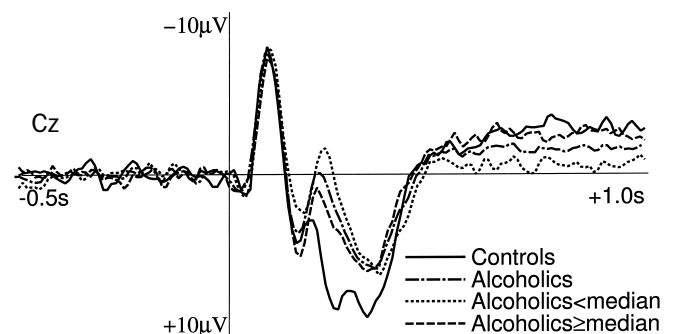


Fig. 3 Auditory ERP responses of controls, alcoholics, and the two subgroups of alcoholics with visuomotor test scores lower respectively higher than the median. Note the disappearance of P3a together with larger and later N2 in alcoholics.

alcoholism compared to those at low risk (cf. the Introduction) suggesting that a small P3 amplitude may be a genetic marker for, and precede the development of, alcoholism. Furthermore, as mentioned above, increased N2 amplitudes have been reported in children at risk for alcoholism. With respect to these findings, we analyzed the effects of FH+/FH- status on those ERP variables for which differences to the control group had been found. Family history of alcoholism had no significant influence. Possibly, the investigation of larger samples including FH+ subjects with high density of alcoholism would be needed to see significant effects (Hill et al. 1990, Cohen et al. 1995). An alternative interpretation would follow the argument recently made by Hill and coworkers (1999b, c) that the genetic vulnerability to alcoholism manifesting in lower P3 amplitude in high-risk children does not persist beyond childhood. If reduced P3 is observed in adult alcoholics, it would not correspond to a P3 abnormality that these subjects may have had in childhood, but rather to other concomitant factors. Our study design did not allow to address this issue specifically. Of the concomitant factors possibly causing ERP alterations in our patients, we could only analyze the severity of alcoholism, which, by multiple regression analysis, showed no effects on ERP variables.

Résumé

The components studied and especially their spatial parameters showed considerable diagnostic accuracy in differentiating alcoholics from healthy individuals. While by P3 amplitude (on the Pz site) alone, the hitherto mostly used ERP marker for alcoholism, valid classification of alcoholic versus control status could not be achieved, a satisfactory hit rate for correct classification was obtained by using visual N1 and auditory N2 amplitudes (at Cz) and centroid topographical descriptors as predictor variables.

The alcoholics showed similar ERP changes described in patients with schizophrenia. Schizophrenics typically show reduced N1 amplitudes over traditional midline recording sites (e. g., Pritchard 1986). In addition, a dislocation of the positive P3 centroid to the right has been observed in schizophrenics resulting in reduced left hemispheric P3 amplitudes (Morstyn et al. 1983; Strik et al. 1994). Instead of representing features specific for a distinct diagnosis, these ERP changes suggest some common cerebral dysfunction in alcoholics and schizophrenics. The N1 component seems to reflect attentional processes and N1 reduction may index deficits in adequately allocating processing resources (e. g., Hillyard 1993). Attention deficits have been described both in schizophrenia and alcoholism especially with a focus on impairment of attentional filtering (Nuechterlein and Dawson 1984; Parsons et al. 1987). There are several reports of deficits of working memory and especially of the "central executive" component in both disorders (e. g., Rosenberg et al. 1990; Stone et al. 1998). Alterations of working memory processing may manifest in P3 electrical field changes, as well of the

kind discussed above (Gevins and Cuttillo 1993; Gevins et al. 1996).

Acknowledgments This study was supported by the Bundesminister für Bildung und Forschung (FKZ 01 EB 9413).

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