ELSEVIER

Clinical Neurophysiology 114 (2003) 134–146

www.elsevier.com/locate/clinph

Electrophysiological evidence of abnormal activation of the cerebral network of involuntary attention in alcoholism

Maria Dolores Polo[a,b], Carles Escera[a,*], Elena Yago[a], Kimmo Alho[c], Antoni Gual[d], Carles Grau[a]

[a]*Neurodynamics Laboratory, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, P. Vall d'Hebron 171, 08035 Barcelona, Spain*
[b]*The Burden Neurological Institute, Frenchay Park Road, Bristol BS16 1JB, UK*
[c]*Cognitive Brain Research Unit and General Psychology Division, Department of Psychology, University of Helsinki, Helsinki, Finland*
[d]*Alcoholism Unit of the Generalitat de Catalunya, Hospital Clinic de Barcelona, Barcelona, Spain*

Accepted 15 October 2002

Abstract

Objective: Increased distractibility is a common impairment in alcoholism, but objective evidence has remained elusive. Here, a task designed to investigate with event-related brain potentials (ERPs) the neural mechanism underlying distraction was used to show abnormal involuntary orienting of attention in chronic alcoholism.

Methods: Fifteen alcoholics and 17 matched healthy controls were instructed to ignore auditory stimuli while concentrating in the discrimination of immediately following visual stimuli. The auditory sequences contained repetitive standard tones occasionally replaced by deviant tones of slightly higher frequency, or by complex novel sounds.

Results: Deviant tones and novel sounds distracted visual performance, i.e. increased reaction time to visual stimuli, similarly in patients and controls. Compared to controls, however, alcoholics showed ERP abnormalities, i.e. enhanced P3a amplitudes over the left frontal region, and a positive posterior deflection instead of the frontally distributed reorienting negativity (RON).

Conclusions: The enhanced P3a to novelty and subsequent positive wave instead of RON in alcoholics suggests encoding into working memory of task-irrelevant auditory events and provides neurophysiological markers of impaired involuntary attention mechanisms in chronic alcoholism.

Keywords: Alcoholism; Event-related brain potential; Involuntary attention switching; Mismatch negativity; P3a; Reorienting negativity

1. Introduction

Chronic alcohol abuse has been related to structural (Carlen et al., 1981; Gurling et al., 1986; Jernigan et al., 1991; Pfefferbaum et al., 1997), functional (Gilman et al., 1990; Nicolás et al., 1993; Adams et al., 1993; Dao-Castellana et al., 1998), and cognitive brain damage. Moreover, most of these alcohol-related effects have been found consistently in the frontal lobes, suggesting that this brain region is particularly susceptible to the toxic effects of ethanol (Gurling et al., 1986; Gilman et al., 1990; Nicolás et al., 1993; Adams et al., 1993; Kril et al., 1997; Pfefferbaum et al., 1997; Dao-Castellana et al., 1998). Neuropsychological results also support this notion, as poor performance in tasks thought to be served by the frontal cortex, such as planning, categorizing, flexible thinking and inhibitory control, has been found in abstinent chronic alcoholics (Nicolás et al., 1993; Adams et al., 1993; Dao-Castellana et al., 1998).

Event-related brain potential (ERP) studies in chronic alcoholics have provided evidence that the effects of alcohol on the central nervous system (CNS) may extend from controlled (Patterson et al., 1987; Porjesz et al., 1988; Pfefferbaum et al., 1991; Cadaveira et al., 1991; Realmuto et al., 1993) to preattentive stages of information processing. Among them, the mismatch negativity (MMN) component of the ERPs reflects an automatic stimulus-change detector mechanism, which is activated when a stream of repetitive sounds is interrupted by a deviant sound even when attention is directed elsewhere (Näätänen et al., 1978; Sams et al., 1985; Paavilainen et al., 1989; Sharma et al., 1993; Sasaki et al., 2000; see also Cheour et al., 2000), during sleep (Loewy et al., 1996; Atienza et al., 2001) and in comatose patients (Kane et al., 1993). Previous studies investigating the MMN in chronic alcoholics (Kathmann et al., 1995; Pekkonen et al., 1998; Ahveninen et al., 1999; Polo et al., 1999; Grau et al., 2001) have led to partially inconsistent results, likely because of methodological differences (Polo et al., 1999; see also Ahveninen et al., 2000a for a review).

* Corresponding author. Tel.: +34-93-312-5048; fax: +34-93-403-4424.
E-mail address: cescera@psi.ub.es (C. Escera).

1388-2457/02/$ - see front matter
PII: S1388-2457(02)00336-X

CLINPH 1067

For example, Kathmann et al. (1995) reported a delay in the latency of MMN in chronic alcoholics, whereas Pekkonen et al. (1998) found similar amplitudes and latencies of the magnetic counterpart of MMN (MMNm) in alcoholic and their respective control subjects. Consistently, our recent work showed similar amplitudes (Polo et al., 1999; Grau et al., 2001) and latencies (Polo et al., 1999) of MMN in middle-aged chronic alcoholics and in their age-matched controls. Taken together, these results suggest preserved automatic stimulus-change detection, as indexed by the MMN, in middle-aged abstinent chronic alcoholics. Other studies, however, have shown a significant enhancement (Ahveninen et al., 1999, 2000b) and acceleration (Ahveninen et al., 1999) of MMN in abstinent alcoholics, possibly due, as stated by these authors, to the CNS hyperexcitability associated with alcohol withdrawal, as their alcoholics had been abstinent for a relatively short period (1–6 weeks).

MMN is mainly generated in the supratemporal auditory cortices (Csépe et al., 1987, 1992; Javitt et al., 1992; Halgren et al., 1995; see Alho, 1995; Escera et al., 2000a for reviews), and it is partially contributed by an additional frontal source (Giard et al., 1990; Molnár et al., 1995; Deouell et al., 1998; Rinne et al., 2000; Yago et al., 2001), which may reflect a signal to trigger a shift of attention towards the initially unattended stimuli (Näätänen, 1992). This is supported by recent studies showing increased reaction times and number of errors to imperative stimuli of a discrimination task linked to MMN-eliciting stimuli (Schröger, 1996; Alho et al., 1997; Escera et al., 1998, 2001, 2002; Ahveninen et al., 2000b; Yago et al., 2001; see Escera et al., 2000a for a review). The functional role of MMN in involuntary orienting of attention is also supported by the fact that P3a, an ERP component associated with the orienting response (Courchesne et al., 1975; Squires et al., 1975; Knight, 1984; Knight and Scabini, 1998; Woods et al., 1992; Katayama and Polich, 1996; Escera et al., 1998, 2000a), often appears following the MMN (Näätänen, 1992; Sasaki et al., 2000). Contributions to P3a arise from a widely distributed cerebral network, including the auditory (Halgren et al., 1995; Alho et al., 1998), prefrontal (Knight, 1984; Yamaguchi and Knight, 1991) and parietal cortices (Halgren et al., 1995), and the hippocampus (Knight, 1996). Recent evidence indicates that P3a in response to widely deviant novel sounds is a composite response with at least two different subcomponents: an early one (circa 230 ms) of centro-parietal scalp distribution (eP3a), and a later one (circa 315 ms) with a more frontal scalp distribution (lP3a) (Escera et al., 1998, 2000a, 2001). To date, reduced amplitudes (Realmuto et al., 1993; Rodríguez-Holguín et al., 1999; Hada et al., 2000) and delayed latencies (Biggins et al., 1995) of P3a have been found in alcoholics with respect to matched controls. These studies suggest an alcohol-induced dysfunction of the involuntary orienting of attention mechanisms indexed by P3a, though the results are not conclusive.

As important as orienting of attention involuntarily towards change and novelty can be, task performance requires reorienting of attention back to the original activity after temporary distraction. Recent studies suggest that this reorienting of the attention is reflected in a late negative ERP component, the reorienting negativity (RON), appearing after the P3a (Schröger and Wolff, 1998). RON is generated over frontocentral scalp areas at approximately 400–600 ms after irrelevant stimulus changes leading to distraction (Schröger and Wolff, 1998; Schröger et al., 2000; Berti and Schröger, 2001; Escera et al., 2001). Recently, impaired reorienting of attention has been proposed to explain the increased number of errors showed by a group of alcoholics, with respect to their matched-controls, in their responses to auditory stimuli of a forced-choice RT task that were linked to MMN-eliciting stimuli (Ahveninen et al., 2000b). However, this study failed to demonstrate a statistically significant attenuation of the RON in the alcoholic subjects.

In summary, MMN, P3a, and RON appear as promising tools to ascertain the neurophysiological basis of involuntary attention and distraction, and to evaluate their functional integrity in clinical populations. With this purpose, we recorded MMN and P3a to unexpected task-irrelevant auditory changes, and P3a and RON to novel sounds preceding visual stimuli requiring a motor response, in a group of abstinent chronic alcoholics and their aged-matched controls. The distracting effect of the irrelevant auditory events over the visual task was also assessed by means of reaction times (RT) and performance accuracy measures (Escera et al., 1998, 2000a, 2001). Our hypothesis was that if the neural mechanisms involved in the detection and orienting of attention towards unexpected changes in the unattended acoustic environment were impaired by chronic alcohol abuse, then alcoholic patients should display abnormal MMN, P3a, and/or RON. As a result, poorer performance on the visual task would be also expected in the patients, as a behavioural measure of increased distractibility in chronic alcoholism.

2. Materials and methods

2.1. Subjects

Table 1 summarizes demographic and clinical characteristics of participants. Fifteen chronic alcoholics and 17 healthy age-matched controls who drank less than 210 g/week of alcohol signed an informed consent and were rewarded for their participation. The study was conducted with the approval of the Ethical Committee of the University of Barcelona and of the Alcoholism Unit of the *Generalitat de Catalunya*'s authorities, where the alcoholic subjects were outpatients undergoing treatment for alcohol dependence (DSM-IV). All subjects were right-handed (Edinburgh Handedness Inventory, Oldfield, 1971) males with auditory hearing thresholds below 60 dB SPL (at 700

Table 1
Mean, standard deviation (SD), and range for demographic and clinical information

Variable	Alcoholics ($n = 15$)			Controls ($n = 17$)		
	Mean	(SD)	Range	Mean	(SD)	Range
Age (years)	42.0	(9.2)	25–56	39.3	(10.8)	20–57
Education (years)[a]	9.5	(2.2)	5–15	11.6	(2.3)	9–16
Drinking onset age (years)	16.6	(2.8)	10–22	16.4	(2.2)	13–21
Drinking per week (g)[a]	1081.3	(659.3)	300–2380	85.0	(59.6)	10–210
Dependence onset age (years)	30.4	(9.2)	18–47	Not applicable		
Dependence length (years)	11.6	(7.2)	4–27	Not applicable		
Withdrawal (weeks)	10.5	(5.7)	4–21	Not applicable		
Number of treatment attempts	1.3	(0.4)	1–2	Not applicable		
Beck Depression Inventory	4.4	(3.2)	0–12	4.1	(3.8)	0–12

[a] $P < 0.05$.

Hz), and normal or corrected-to-normal vision. Previous history of severe organic disease, neurologic or psychiatric disorder, or other substance abuse (except tobacco) (DSM-IV) were exclusion criteria for participation. At the time of examination, alcoholics were in a withdrawal period of at least 4 weeks, and all subjects had been free of medication for the previous 72 h (including disulfiram). To control drug-free status during the treatment, periodic follow-up interviews with their clinician and recurrent (1–5 per week) urine drug (alcohol, cannabis, benzodiazepines, opiates, amphetamines, and cocaine) screen analyses were performed in alcoholics. On the day of testing, all subjects underwent a breathalyzer test (Breathalyzer model RBT IV; Intoximeters Inc., St. Louis, MO, USA) to ensure that they were free of alcohol. Control subjects were recruited among patient friends and with notices posted in the University of Barcelona campus. All subjects were questioned about alcohol and other drugs use, and medical and psychiatric histories for themselves and first- and second-degree relatives in an interview with a trained psychologist. Control subjects had significantly more education than alcoholics ($t(30) = -2.5$, $P < 0.02$, Table 1), but this variable was not significantly correlated with any of the ERP measures. Score in the self-answered Beck Depression Inventory (BDI; Beck et al., 1961) confirmed that the affective mood of the alcoholic and control subjects had been similar in the week previous to the experiment.

2.2. Stimuli and procedure

Subjects sat in an armchair, in a sound-attenuated, dimly illuminated, and electrically shielded room. Ten blocks with 200 stimulus-pairs (trials) each were presented to the subjects. Each trial consisted of an auditory stimulus followed after 300 ms (onset-to-onset) by a visual stimulus. The inter-pair interval (onset-to-onset) was 1.5 s (Fig. 1). The auditory stimuli were standard tones (80%), deviant tones (10%), or novel sounds (10%) delivered in a random order with the constraint that each deviant-tone and novel-sound trial was preceded by at least one standard-tone trial. The standard and deviant stimuli were pure tones of 600 Hz and 514 or 700 Hz (50% each), respectively, and the novel sounds were 60 environmental complex sounds, such as those produced by an electric drill, hammer, telephone ringing, etc. All auditory stimuli were presented binaurally through headphones with a duration of 200 ms (including rise/fall times of 10 ms) and an intensity of 75 dB SPL. Each different novel sound occurred only once within a stimulus block, and was presented no more than twice or 3 times in the whole experiment. The visual stimuli were white capital letters (A, E, J, P, R, S, U, Y) or digits (2–9) displayed during 200 ms, in random order, at the centre of a black PC computer screen located 1.5 m from the subject, with respective vertical and horizontal angles of 1.3° and 0.8°. Subjects were instructed to look at a fixation cross on the centre of the screen, and to use the index and middle fingers of their right hand to press one of two buttons on a response panel according to whether they saw a letter or a digit, as fast and accurately as possible. The order of fingers was counterbalanced, with half of the subjects using the index finger to respond to the letters. Instructions were also given to ignore the auditory stimulation, and to avoid excessive blinking and body movements. Each block lasted 5 min, and short breaks were given between blocks.

Before the recordings, each subject underwent a training session consisting of two blocks with 200 visual stimuli in which the auditory stimulation had been omitted. All subjects included in the statistical analyses reached at least a hit rate of 80% in the training.

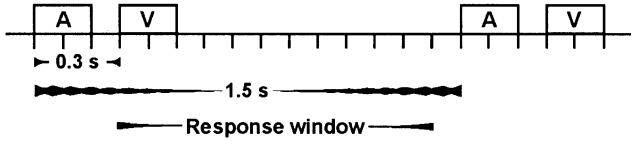

Fig. 1. Experimental design. Pairs of stimuli, consisting of an auditory stimulus (A) followed at 300 ms (onset-to-onset) by a visual stimulus (V), were delivered with an inter-pair interval of 1500 ms. A behavioural response was required within 1100 ms interval after each visual stimuli.

2.3. ERP recording

The electroencephalogram (EEG, bandpass 0.1–100 Hz) was continuously digitized (sampling rate, 500 Hz) by a Synamps amplifier (NeuroScan Inc.), from 18 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, Oz) placed according to the International 10–20 system (Jasper, 1958) and 10 additional electrodes: FC1 (halfway between Cz and F3), FT3 (halfway between F3 and T3), CP1 (halfway between Cz and P3), TP3 (halfway between T3 and P3), IM1 (70% of the distance from the preauricular point to the inion), and the homonymous positions over the right hemisphere, all inserted in a cap (Electrocap Inc.). Activity at the left and right-mastoids (M1 and M2, respectively) was recorded by electrodes placed at a distance of 40% from the left and right pre-auricular points to the inion (Fig. 2A). Horizontal ocular movements and blinks were recorded from electrodes placed at the outer canthus (HEOG) and suborbital ridge (VEOG) of the right eye, respectively. An electrode attached to the tip of the nose served as reference for the EEG and EOG recordings. Impedance remained below 10 KΩ during the whole recording session. Epochs with EEG or EOG changes exceeding ±100 μV, as well as the first 5 epochs of each block, were excluded automatically from averaging. For each subject, ERPs were averaged off-line according to the type of auditory stimulus, and digitally bandpass filtered between 0.5 and 30 Hz. The epoch was 1300 ms, including 100 ms prestimulus baseline. A minimum of 100 responses in the average for each type of auditory stimulus was required for each subject because of signal-to-noise concerns. The ERPs of two alcoholics and one control that did not meet this criterion were excluded from further analysis.

2.4. Data analysis

All ERP amplitudes were measured against the mean amplitude of the 100 ms prestimulus baseline. Latencies were measured from auditory stimulus onset. ERP components detection and measurement were performed automatically at each electrode using the peak detection algorithm of the Scan software package (Neuroscan Inc.). For each subject, the auditory N1 and P2 were identified as the largest negative/positive deflection within 70–150 ms and 150–250 ms latency windows, respectively, and their peak amplitude and latency measured in the ERPs to the standard (N1, P2), deviant (N1), and novel (N1) sounds. The MMN peak was identified as the largest negative deflection within 100–200 ms latency window of the difference waveform obtained by subtracting the ERPs to standard tones from those to deviant tones, and the mean amplitude in this interval was measured for statistical analysis. For the P3a elicited by the deviant tones, the mean amplitude within the 200–250 ms and 250–300 ms latency windows was measured in the deviant minus standard difference waveform. In response to novel sounds, the P3a had two consecutive phases, and therefore the mean amplitude of the early (eP3a) and late (lP3a) phases was measured in the difference waveform obtained by subtracting the ERPs to standard tones from those to novel sounds, in the respective latency windows of 200–300 ms and 300–400 ms. Following the P3a to novel sounds, a frontal negativity, possibly the RON, was observed in the novel minus

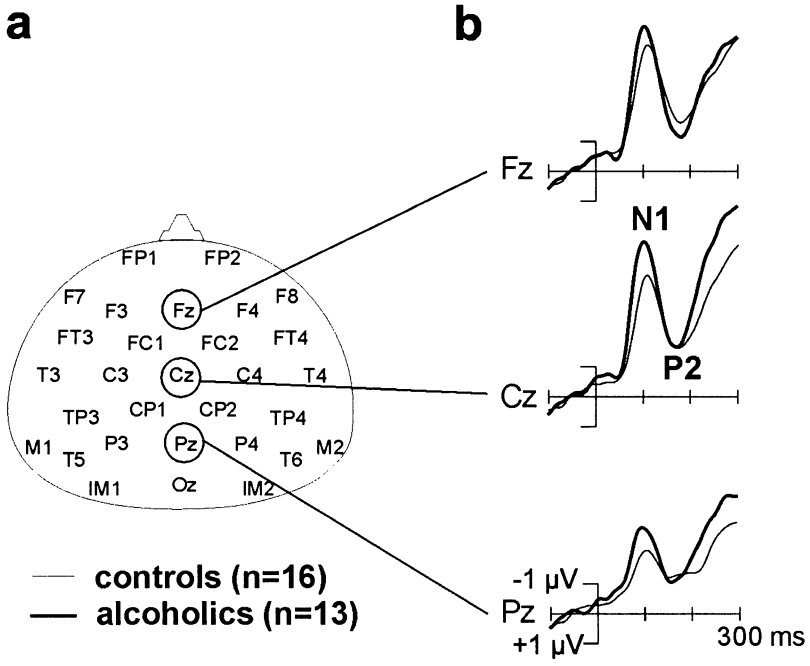

Fig. 2. (A) Distribution over the scalp of the 30 electrodes used in the electroencephalogram (EEG) recordings. (B) Grand-average waveforms of N1 and P2 event-related brain potentials (ERPs) elicited by the standard tones in the control and alcoholic groups at midline electrodes.

standard difference waveform in the control group. In contrast, a late positive peak was found at the concomitant latency range in the alcoholics. To analyse this group difference, the mean amplitude within 500–600 ms latency window in the novel minus standard difference waveform, as well as in the ERP waveform elicited by the standard tone and the novel sounds, was measured.

For the performance analysis, the responses to the visual stimuli were recorded separately according to whether the visual stimulus was preceded by a standard tone, by a deviant tone, or by a novel sound. Pressing the correct button within 1100 ms interval after the visual stimulus onset (Fig. 1) was regarded as a hit, and the average reaction time (RT, in milliseconds) was computed for these trials. An incorrect button press during this interval was classified as an error, and a trial with no response was classified as a miss. Hit, error and miss rates, and mean RT for hits were computed across letters and numbers.

2.5. Statistical analyses

Group comparisons of the demographic and clinical data, the amplitude and latency of N1 and P2 elicited by the standard tones at Cz, the latency of MMN in the deviant minus standard difference waveform at Fz, and all post hoc analyses were performed with paired t tests. Univariate analyses of variance (ANOVA) for repeated measures with group as the between-subject factor and laterality (F3-C3-P3/Fz-Cz-Pz/F4-C4-P4) and frontality (F3-Fz-F4/C3-Cz-C4/P3-Pz-P4) as within-subject factors were performed for MMN and P3a to the deviant tones, and RON to novel sounds. For the RON component, an additional ANOVA including stimulus (standard/novel) as an extra within-subject factor was performed. For the analysis of novel P3a scalp-distributions, a subcomponent (eP3a/lP3a) within-subject factor was added, and the ERP amplitudes were normalized to prevent genuine differences in scalp distribution from being washed out by amplitude differences among electrodes. This normalization was done by dividing the amplitude at each electrode by the square root of the sum of the squared amplitudes at the selected electrodes (McCarthy and Wood, 1985). The scalp distribution analysis of the P3a elicited to novel sounds also included the electrodes F7, F8, T3, T4, T5, and T6.

Performance data analyses were carried out by means of ANOVAs with group as the between-subject factor and stimulus (standard/deviant/novel) as the within-subject factor. For all statistical analysis, and when appropriate, Greenhouse-Geisser corrections were applied, and the corrected P values along with the original degrees of freedom (df1 and df2) and the epsilon factor (ε) are reported.

Pearson correlations were performed to examine the relationship between ERPs and education in each group, and dependence length and withdrawal from alcohol in the patient group. For all analyses, differences and correlations were considered significant only if they exceeded the level of $P < 0.05$.

3. Results

3.1. Performance data

Table 2 shows reaction time (RT) to hits, and hit, error, and miss rates in the performance of the visual task for the control and the alcoholic groups. No statistical group differences were found in RT and accuracy of performance in the visual discrimination task. A significant stimulus effect was observed in the analysis of the RT ($F(2,60) = 52.6$, $P < 0.0001$, $\varepsilon = 0.7$). In both groups, hit RT was significantly delayed by deviant tones (by 6 ms in controls, $t(16) = -2.3$, $P < 0.03$; and by 5 ms in alcoholics, $t(14) = -2.5$, $P < 0.03$) and novel sounds (by 21 ms in controls, $t(16) = -5.4$, $P < 0.0002$; and by 28 ms in alcoholics, $t(14) = -6.5$, $P < 0.0001$), in comparison with RT to visual stimuli preceded by standard tones. In turn, hit RT to novel trials was significantly delayed in comparison with RT to deviant trials (by 15 ms in controls, $t(16) = -4.0$, $P < 0.002$; and by 23 ms in alcoholics, $t(14) = -5.3$, $P < 0.0002$). The stimulus factor failed to reach statistical significance for the hit, error, and miss rates in either group.

3.2. ERP data

The amplitude and latency of the measured ERPs are presented in Table 3. Fig. 2B shows the grand-average ERPs to standard tones in the alcoholic and control subjects. N1 and P2 of similar amplitude and latency were recorded in both groups. A similar enhancement of N1 elicited by the deviant tones and the novel sounds with respect to the standard tones was observed in the control ($t(15) = 4.4$, $P < 0.0006$; and $t(15) = 3.9$, $P < 0.002$, respectively) and alcoholic ($t(12) = 3.5$, $P < 0.005$; and $t(12) = 2.5$,

Table 2
Mean and SD of the reaction time (RT) to hits, and hit, error, and miss rates in the performance of the visual discrimination task for the Alcoholic and Control groups

Performance	Stimulus	Alcoholics ($n = 15$)		Controls ($n = 17$)	
		Mean	(SD)	Mean	(SD)
RT (ms)	Standard	488	(62.0)	501	(64.6)
	Deviant	493	(62.4)	507	(68.9)
	Novel	516	(67.8)	522	(63.6)
Hit rate (%)	Standard	92.4	(5.9)	95.0	(2.9)
	Deviant	91.8	(6.4)	94.4	(3.8)
	Novel	92.4	(5.8)	94.0	(3.6)
Error rate (%)	Standard	4.1	(3.7)	2.8	(1.7)
	Deviant	4.6	(4.2)	2.8	(2.1)
	Novel	4.4	(3.3)	3.2	(2.2)
Miss rate (%)	Standard	3.5	(5.2)	2.2	(2.4)
	Deviant	3.6	(4.9)	2.8	(2.8)
	Novel	3.6	(4.8)	2.8	(2.8)

Table 3
Mean and SD of the amplitude (μV) and latency (ms) of the event-related brain potentials (ERPs) for the Alcoholic and Control groups

ERPs	Waveform	Electrode	Alcoholics ($n = 13$)		Controls ($n = 16$)	
			Mean	(SD)	Mean	(SD)
N1						
Amplitude	Standard ERP	Cz	−5.5	(2.0)	−4.3	(1.7)
	Deviant ERP		−6.8	(2.5)	−5.7	(2.1)
	Novel ERP		−6.8	(2.9)	−5.8	(2.4)
Latency	Standard ERP		101	(10)	110	(11)
P2						
Amplitude	Standard ERP	Cz	−1.4	(2.0)	−1.4	(1.5)
Latency			171	(13)	176	(18)
MMN						
Amplitude	Difference wave	Fz	−2.9	(1.6)	−2.6	(0.9)
Latency	(deviant-standard)		160	(36)	167	(36)
P3a to deviant tones[a]						
Mean amplitude	Difference wave	F3	0.2	(1.1)	−0.4	(1.0)
	(deviant-standard)	Cz	0.7	(1.2)	0.0	(1.1)
P3a to novel sounds[a]						
eP3a						
Mean amplitude	Difference wave	Fz	3.3	(2.0)	3.1	(2.5)
	(novel-standard)	Cz	5.5	(2.7)	4.7	(3.6)
lP3a						
Mean amplitude	Difference wave	F3	4.8	(2.7)	3.5	(2.2)
	(novel-standard)	Fz	5.1	(2.7)	4.3	(2.4)
		F4	4.1	(2.1)	3.8	(2.2)
		Cz	6.1	(3.2)	5.3	(2.8)
RON to novel sounds[a]						
Mean amplitude	Difference wave	Fz	0.2	(1.5)	−1.3	(1.7)
	(novel-standard)	Cz	1.0	(1.8)	−0.7	(2.2)
		Pz	1.6	(1.8)	0.2	(2.2)

[a] $P < 0.05$.

$P < 0.03$, respectively) groups. This additional negativity to the distracting events may be explained by a genuine enhancement of N1 and its overlap with the MMN (Alho et al., 1994, 1998; Escera et al., 1998).

Deviant tones elicited MMNs of similar amplitude and latency in the alcoholic and control groups (Table 3 and Fig. 3). However, as shown in Fig. 3, alcoholics showed a larger P3a than controls at the left frontal region, an effect which was statistically significant when measured as the mean amplitude of the 250–300 ms latency window of the deviant minus standard difference waveform (group × frontality × laterality interaction: $F(4, 108) = 2.9$, $P < 0.05$, $\varepsilon = 0.6$, see also Table 3).

As seen in Fig. 4A, P3a to novel sounds had a double peak over the frontal and central locations, suggesting two different phases. This hypothesis was confirmed by a significant main effect of the subcomponent factor in the ANOVA carried out on the normalized mean amplitudes for this component ($F(1, 27) = 6.8$, $P < 0.02$). Moreover, in both groups, the earlier part of the P3a was smaller than its later part over the frontal locations (subcomponent × frontality interaction: $F(2, 54) = 10.9$, $P < 0.002$, $\varepsilon = 0.6$; see Table 3), and showed a right predominant scalp distribution compared to the bilateral distribution of the late P3a (subcomponent × frontality × laterality: $F(8, 216) = 12.6$, $P < 0.0001$, $\varepsilon = 0.5$). These interactions indicate that, indeed, the P3a response to novel sounds was composed of two different phases of distinct underlying neural generators, as shown in previous studies (Escera et al., 1998, 2001). The ANOVA also revealed group differences in the scalp distribution of the late P3a. Indeed, compared to controls, alcoholic subjects had a significantly larger activation of the late phase of the P3a over the left frontal region (group × subcomponent × frontality × laterality interaction: $F(8, 216) = 2.6$, $P < 0.05$, $\varepsilon = 0.5$, see Table 3 and Fig. 4A,B).

Following the P3a to novel sounds, a frontal negativity, possibly the RON, was observed in the control group. The alcoholic subjects, however, showed at this latency a small positive peak (Fig. 4A,C). This group difference was confirmed by the ANOVA run on the mean amplitude within the 500–600 ms interval of the novel minus standard

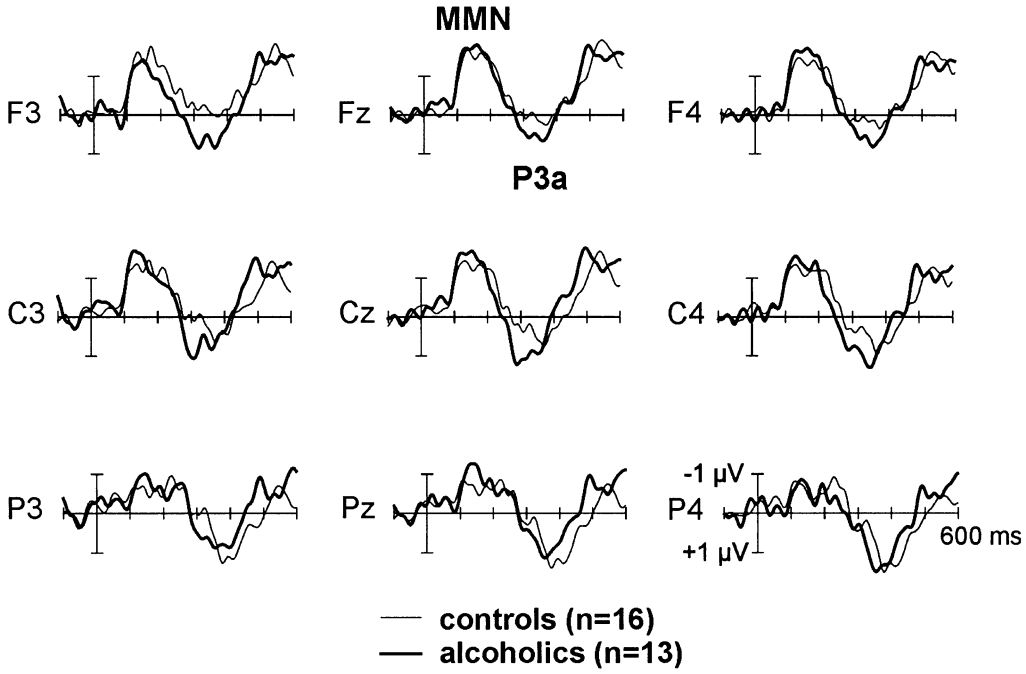

Fig. 3. Grand-average of the difference waveforms obtained by subtracting the event-related brain potentials (ERPs) elicited by the standard tones from those elicited by the deviant tones, for control and alcoholic groups, at the electrodes included in the statistical analysis carried out for mismatch negativity (MMN) and P3a to the deviant tones.

difference waveform ($F(1,27) = 6.1$, $P < 0.03$). A significant main effect of the frontality factor ($F(2,54) = 21.8$, $P < 0.0001$, $\varepsilon = 0.7$) confirmed a frontal maximum for the negativity wave elicited in the control group and a parietal maximum for the positive peak showed by the alcoholic group (Table 3 and Fig. 4A,C). The main laterality factor and possible interactions in the ANOVA were not significant, suggesting a bilateral scalp distribution of the neural activity underlying these two processes. In order to investigate whether the different electrophysiological pattern shown by the control and alcoholic groups could be explained as the result of an interaction between the distracting effect of the auditory task-irrelevant stimuli and the actual processing of the subsequent visual imperative stimuli, an additional ANOVA was performed on the mean amplitude of the ERPs to the standard tone and the novel sounds within the 500–600 ms latency window. This analysis revealed a significant group X stimulus interaction ($F(1,27) = 6.1$, $P < 0.03$), but neither a main effect of these factors.

Pearson correlation analyses of the ERPs with the variables of alcoholism in the patient group did not reveal significant relationships of interest, but for a negative correlation between withdrawal from alcohol and the late phase of P3a to novel sounds. Indeed, the mean amplitude of lP3a, over the left hemisphere, diminished as the number of weeks of abstinence from alcohol increased, particularly at the frontal area ($r = -0.66$, $P < 0.02$, at F7; $r = -0.50$, $P = 0.08$, at F3; $r = -0.32$, $P = 0.28$, at F4; $r = -0.09$, $P = 0.75$, at F8; and $r = -0.39$, $P = 0.18$, at T3; $r = -0.49$, $P = 0.09$, at C3; $r = -0.34$, $P = 0.24$, at C4; $r = -0.03$, $P = 0.91$, at T4).

4. Discussion

The present study provides further evidence that the occurrence of unexpected stimulus changes or novelty in the acoustic environment engages temporarily subject's attention during visual performance, and support previous findings describing the sequence of neural events underlying involuntary detection and orienting of attention to these events (see Escera et al., 2000a for a review). Both deviant tones and novel sounds resulted in increased RTs to the subsequent imperative visual stimuli, these behavioural effects being paralleled in the ERPs by the MMN/P3a in response to deviant tones, and by an enhanced N1/MMN followed by a prominent biphasic P3a and RON in response to novel sounds. A major finding of the present study was the enhanced amplitude over the left frontal region of the P3a in response to both deviant tones and novel sounds in alcoholics, compared to control subjects, and the elicitation of a subsequent positive posterior deflection in response to the novel sounds, instead of the RON response observed in controls.

The slowed speed of performance observed in the visual discrimination task after the occurrence of a stimulus change or novelty is in accordance with previous studies (Schröger, 1996; Alho et al., 1997; Escera et al., 1998, 2001, 2002). Specifically, we found longer RTs to visual

stimuli preceded by deviant tones and novel sounds with respect to those preceded by standard tones. These distracting effects of deviant tones and novel sounds on visual performance were, however, of similar magnitude in both alcoholic and control subjects.

Deviant tones elicited MMNs of similar amplitudes and latencies in both alcoholic and control subjects. This finding corroborates earlier results reporting a preserved automatic-change detector mechanism as indexed by MMN in middle-aged chronic alcoholics (Pekkonen et al., 1998; Polo et al., 1999; Grau et al., 2001). Following MMN, however, the deviant P3a showed larger amplitude in alcoholics than

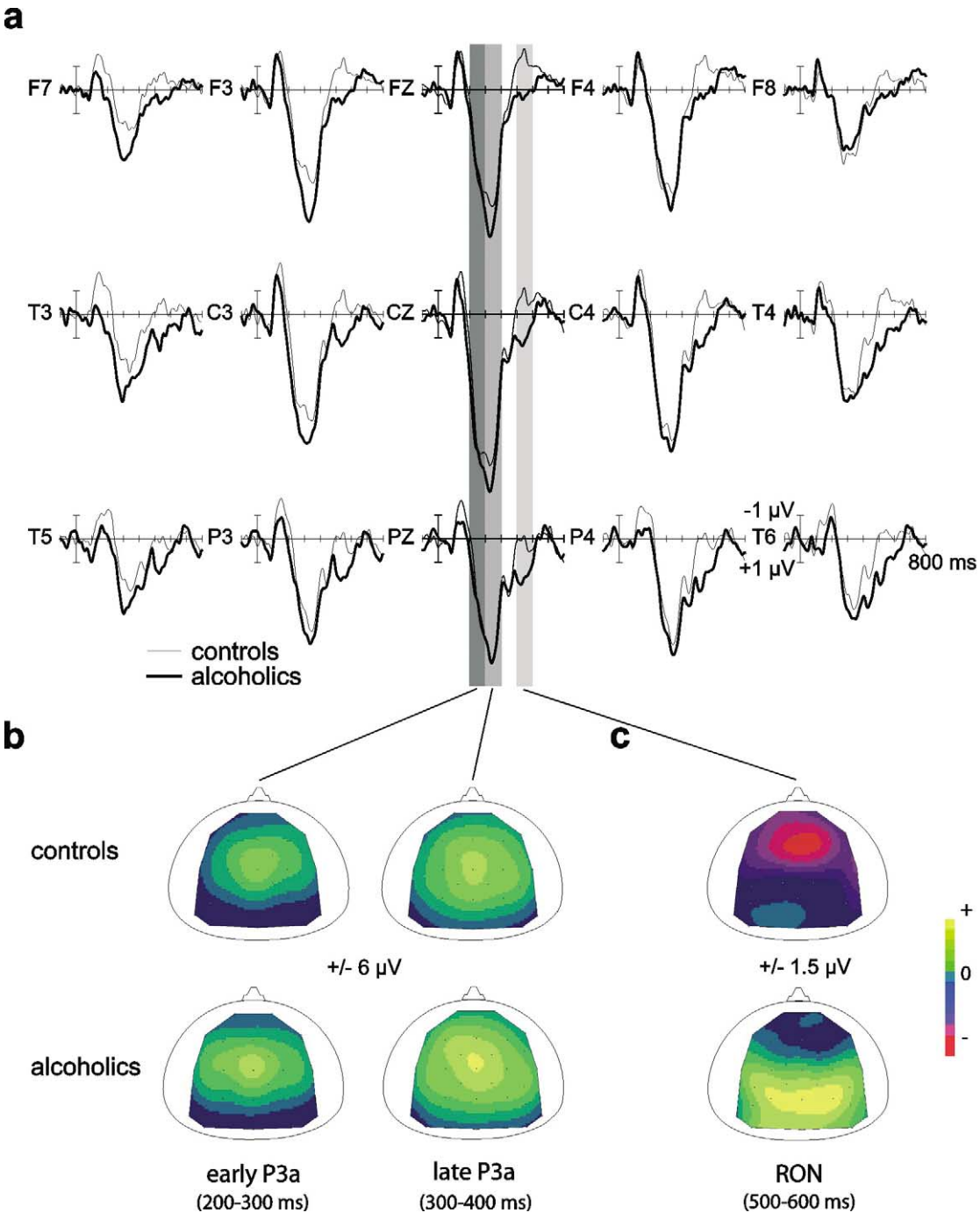

Fig. 4. (A) Grand-average for the difference waveforms obtained by subtracting the event-related brain potentials (ERPs) elicited by the standard tones from those elicited by the novel sounds, in the control and alcoholic groups, at the electrodes included in the statistical analysis carried out for the P3a and the reorienting negativity (RON) to the novel sounds. Grey shadows show the latency intervals used for the statistical analysis of the early (200–300 ms, dark grey) and late (300–400 ms, medium grey) phases of the P3a, and the RON (500–600 ms, light grey). (B) Scalp potential distribution of the two phases of the P3a to novel sounds in the control and alcoholic groups. (C) Scalp potential distribution of the RON to novel sounds in the control group and the concomitant positive peak elicited by the alcoholic group.

controls, particularly over the left frontal scalp, suggesting that deviant tones caused a stronger orienting of the attention among the formers.

In response to novel sounds, chronic alcoholics and control subjects elicited a larger P3a. In both groups, this novelty P3a had two different subcomponents, an early one (eP3a) at 200–300 ms with a central scalp distribution, and a late one (lP3a) appearing at 300–400 ms with a more frontal scalp distribution, in agreement with previous findings (Escera et al., 1998, 2001). However, alcoholic subjects showed a left predominant distribution over the frontal regions of their late P3a, contrasting with the bilateral scalp distribution observed in controls, suggesting an abnormal (augmented) activation of this cerebral region in the generation of the lP3a. Several studies have documented the involvement of the left prefrontal region in the encoding into memory of novel events (Demb et al., 1995), even in the absence of awareness (Berns et al., 1997). Moreover, a recent study has shown increased activity in the left prefrontal cortex of alcoholic subjects, compared to social drinkers, in response to alcohol beverage picture cues exposure (George et al., 2001). This result suggests enhanced attention to alcohol cues in alcoholic subjects, possibly due to the higher emotional relevance of those cues among these subjects. In this framework, the enhancement of the late P3a to novel sounds found in our study suggests that the alcoholics were attributing a greater significance and allocating more attentional resources to the novel, distracting sounds than the control subjects.

Following the P3a to novel sounds, a different pattern of electrophysiological activity was observed in the 500–600 ms latency range between the alcoholics and controls. In the control group, a frontal negative wave, the Reorienting Negativity (RON), was elicited, possibly reflecting the process of returning attention back to task-relevant stimulation after temporary distraction (Schröger and Wolff, 1998; Schröger et al., 2000; Berti and Schröger, 2001; Escera et al., 2001). In contrast, alcoholic subjects showed a small parietal positive response instead, although the absence of a identifiable RON response in alcoholics does not necessarily mean that the process was fully abolished in these subjects, as they did not show any impairment on the visual task performance. This late positivity observed in alcoholics could correspond to the $P3_2$ described by Friedman et al. (1993), and therefore may be reflecting a deeper processing of the novel sounds in alcoholics than in controls. Indeed, Friedman et al. (1993) found a parietally distributed positive deflection appearing at 500–600 ms after irrelevant novel sounds in healthy subjects, and proposed that it may reflect the encoding into working memory of stimuli that, although irrelevant for the current task performance were able to catch the subject's attention (Friedman et al., 1993; Fabiani and Friedman, 1995). In fact, the neural generators of $P3_2$ may correspond to those underlying the generation of P3b (Cycowicz and Friedman, 1997), an ERP signal thought to reflect working memory updating (Donchin and Coles, 1988). The similarities in the latency and scalp distribution of the late positivity elicited in our alcoholics in response to novel sounds, and those of the $P3_2$ described by Friedman and collaborators, lead us to suggest that the two responses may reflect a common neural process. It could be argued that the effects observed at this latency range (500–600 ms post-distractor, i.e. 200–300 post-imperative stimulus), may have arisen from an altered processing of the visual stimuli or from an interaction between the distraction and the actual processing of the visual imperative stimuli. Nevertheless, there are at least two lines of findings that militate against this argument. First, in a previous study, we showed that the scalp distribution of the RON response, obtained in a similar paradigm to that used here, differed from that of the N2 and P3b elicited to the visual target, indicating different underlying processes (Escera et al., 2001). Moreover, in the present study, a statistical comparison of the ERP elicited by the standard tone and the novel sounds within the 500–600 ms latency window did not reveal any group differences, as it would have been expected if the alcoholics had processed the visual stimuli in a different way than the controls. On another hand, as the amount of distraction associated with the novel sounds was larger than that associated to the repetitive tone, a main stimulus effect would be predicted if the ERPs observed at the above interval were the result of an interaction between distraction and the processing of the visual stimuli. However, this prediction was not confirmed by the statistical analysis.

Taken together, these results -i.e. the enhanced left frontal late P3a and the parietal positivity replacing in alcoholics the RON observed in controls, lead us to speculate that our alcoholic subjects were encoding the novel sounds into working memory, possibly as a result of a disinhibition of a frontal executive mechanism. This proposal is based on several arguments. First, post-mortem and neuroimaging studies indicate a profound sensitivity of the frontal lobes to the neurotoxic effects of alcohol (Gurling et al., 1986; Gilman et al., 1990; Nicolás et al., 1993; Adams et al., 1993; Kril et al., 1997; Pfefferbaum et al., 1997; Dao-Castellana et al., 1998). In the second place, it is well known that the frontal lobe plays a crucial role in the control of the attention (Fuster, 1989), exerting a modulatory influence in the inhibition of irrelevant inputs (Knight, 1984). Indeed, the inability to inhibit the frontal neural network activated involuntarily by changes in the acoustic background has been proposed by Ahveninen et al. (2000b) as a possible interpretation for the enhanced frontal MMN subcomponent these authors found in recently detoxified alcoholics. Moreover, specific metabolic abnormalities in the left dorsolateral prefrontal cortex of chronic alcoholics without overt neurological complications have been reported (Dao-Castellana et al., 1998), and abnormal metabolism and cortical atrophy in the frontal lobes have been found to correlate with poor performance in tests of attention and executive functions thought to be served by the frontal brain regions (Nicolás et al., 1993; Adams et al., 1993; Dao-Castellana et

al., 1998). Thereby, it has been suggested that frontal dysfunction may account for some of the alcohol-related neuropsychological and behavioural deficits, even in alcoholics without obvious clinical signs of neurological damage (Dao-Castellana et al., 1998). Neuropsychological assessments of alcoholics very often indicate impairment of 'frontal lobe' skills such as the ability to inhibit inadequate responses, categorize and flexible thinking (Parsons et al., 1972; Tarter, 1976; Nicolás et al., 1993; Dao-Castellana et al., 1998). Therefore, it seems justified to suggest that the abnormal (augmented) activation of the left frontal late P3a in response to irrelevant stimuli during the performance of a discrimination task, which were likely encoded subsequently into working memory, could be a possible explanation for the difficulty shown by chronic alcoholics to inhibit inadequate responses to novel stimuli in everyday life situations.

There is evidence that chronic consumption of alcohol leads to increased number of the excitatory *N*-methyl-D-aspartate (NMDA) glutamate receptor in the frontal cortex (Freund and Anderson, 1996). This up-regulation results in neuronal hyperexcitability during abstinence episodes, and may constitute a primary neurochemical mechanism for chronic alcohol-induced brain damage (Freund and Anderson, 1996; see Fadda and Rossetti, 1998 for a review). Likewise, reduced $GABA_A$-BZD receptor sites in frontal cortex have been reported in chronic alcoholics (Freund and Ballinger, 1988; Gilman et al., 1996), even after 3 months of abstinence (Lingford-Hughes et al., 1998). Thereby, it is feasible to argue that the augmented frontal P3a shown by our alcoholic subjects in response to the novel sounds might have been subserved by an increased neuroexcitability after alcohol withdrawal. Direct evidence of the role that the neurotransmitters glutamate and GABA play in the neural network subserving attentional processes comes from animal research (Montero et al., 2001; Burk and Sarter, 2001). In addition, we found that the amplitude of the late phase of the novelty P3a diminished as the withdrawal period of the alcoholics became longer, this relationship being particularly strong over the left frontal area. This result gives further support to the hypothesis that the abnormal activation of the left frontal area shown by our abstinent chronic alcoholics reflects an alcohol-induced effect and suggests that it might revert with prolonged abstinence.

The enhanced P3a found in the alcoholics in the present study is, nevertheless, in conflict with previous studies showing reduced amplitudes of this ERP component in chronic alcoholism (Realmuto et al., 1993; Rodríguez-Holguín et al., 1999; Hada et al., 2000). The different result between the present and previous studies may have resulted from stimulus and task differences. Indeed, in one of these studies, irrelevant standard and deviant (20%) tones were presented to the subjects while reading a magazine of their choice (Realmuto et al., 1993). In other studies, a visual (Rodríguez-Holguín et al., 1999) or auditory (Hada et al., 2000) 3-stimulus oddball task was used, with the subjects being required to give a motor response to infrequent target stimuli (10%) which were highly similar to standard (80%) stimuli, and to ignore clearly different infrequent non-target stimuli (10%). There is evidence that the degree of attentional orienting to infrequent task-irrelevant stimuli is related to the magnitude of their deviance (Escera et al., 1998; Schröger et al., 2000) and to the stimulus context (Katayama and Polich, 1998; Jeon and Polich, 2001), and that this is reflected in P3a amplitude. Moreover, it has been claimed that the P3a wave elicited by different types of infrequent task-irrelevant stimuli (i.e. infrequent stimuli in a passive condition, physically novel stimuli, or infrequent-nontarget stimuli in a 3-item or more oddball task) may not necessarily reflect an identical and unique processing operation (see Katayama and Polich, 1998). Therefore, methodological differences between these studies make difficult the comparison of results.

The enhanced P3a observed in the alcoholics gives support to the study's hypothesis predicting an abnormal orienting of attention to unexpected changes in the unattended acoustic environment as result of chronic exposure of the brain to alcohol. However, the neurophysiological findings were not paralleled by the behavioural data. It has been suggested that some patients with physiological impairment may compensate for this by increasing mental effort to maintain 'normal' performance during limited time periods (Veltman et al., 1996), particularly in challenging situations, like in an experimental setting. Thus, they may perform normally in neuropsychological or behavioural tasks, but suffer remarkable attention difficulties in everyday life. Therefore, P3a and the other ERP responses examined in the present study may provide a more direct index for assessing distractibility than neuropsychological and behavioural measures, and a sensitive marker of alcohol-related effects on frontal cortex function. If that, ERPs might provide an additional tool for the diagnosis and monitoring of attentional difficulties, since they have been found to be rather stable (Pekkonen et al., 1995; Escera and Grau, 1996; Escera et al., 2000b; Joutsiniemi et al., 1997; Fabiani et al., 1998; Tervaniemi et al., 1999; Schröger et al., 2000). Nevertheless, more research aimed to assess the individual replicability and variability of these measures is needed before they can be introduced in routine clinical practice.

Acknowledgements

This study was supported by BIOMED-2 contract BMH4-CT96-0819-COBRAIN of the European Union, grant UE96-0038 from the Spanish Ministry of Science and Technology, and grants SGR1999-00264 and 1998XT-00046/2000XT-00021 from the *Generalitat de Catalunya*. The authors thank Intoximeter Inc. and Rasfer S.A. for lending us the RBT IV breathalyzer model used, and Maria Jose Corral for her assistance in the subject's recruitment and the preparation of the paper illustrations.

References

Adams KM, Gilman S, Koeppe RA, Kluin KJ, Brunberg JA, Dede D, Berent S, Kroll PD. Neuropsychological deficits are correlated with frontal hypometabolism in positron emission tomography studies of older alcoholic patients. Alcohol Clin Exp Res 1993;17:205–210.

Ahveninen J, Jääskeläinen IP, Pekkonen E, Hallberg A, Hietanen M, Mäkelä R, Näätänen R, Sillanaukee P. Suppression of mismatch negativity by backward masking predicts impaired working-memory performance in alcoholics. Alcohol Clin Exp Res 1999;23:1507–1514.

Ahveninen J, Escera C, Polo MD, Grau C, Jääskeläinen IP. Acute and chronic effects of alcohol on preattentive auditory processing as reflected by mismatch negativity. Audiol Neurootol 2000a;5:303–311.

Ahveninen J, Jääskeläinen IP, Pekkonen E, Hallberg A, Hietanen M, Näätänen R, Schröger E, Sillanaukee P. Increased distractibility by task-irrelevant sound changes in abstinent alcoholics. Alcohol Clin Exp Res 2000b;24:1850–1854.

Alho K. Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. Ear Hear 1995;16:38–51.

Alho K, Woods DL, Algazi A, Knight RT, Näätänen R. Lesions of frontal cortex diminish the auditory mismatch negativity. Electroenceph clin Neurophysiol 1994;91:353–362.

Alho K, Escera C, Díaz R, Yago E, Serra JM. Effects of involuntary auditory attention on visual task performance and brain activity. Neuroreport 1997;8:3233–3237.

Alho K, Winkler I, Escera C, Huotilainen M, Virtanen J, Jääskeläinen IP, Pekkonen E, Ilmoniemi RJ. Processing of novel sounds and frequency changes in the human auditory cortex: magnetoencephalographic recordings. Psychophysiology 1998;35:211–224.

Atienza M, Cantero JL, Escera C. Auditory information processing during human sleep as revealed by event-related brain potentials. Clin Neurophysiol 2001;112:2031–2045.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiat 1961;4:561–571.

Berns GS, Cohen JD, Mintun MA. Brain regions responsive to novelty in the absence of awareness. Science 1997;276:1272–1275.

Berti S, Schröger E. A comparison of auditory and visual distraction effects: behavioural and event-related indices. Cogn Brain Res 2001;10:265–273.

Biggins CA, MacKay S, Poole N, Fein G. Delayed P3a in abstinent elderly male chronic alcoholics. Alcohol Clin Exp Res 1995;19:1032–1042.

Burk JA, Sarter M. Dissociation between the attentional functions mediated via basal forebrain cholinergic and gabaergic neurons. Neuroscience 2001;105:899–909.

Cadaveira F, Grau C, Roso M, Sánchez-Turet M. Multimodality exploration of event-related potentials in chronic alcoholics. Alcohol Clin Exp Res 1991;15:607–611.

Carlen PL, Wilkinson DA, Wortzman G, Holgate R, Cordingley J, Lee MA, Huszar L, Moddel G, Singh R, Kiraly L, Rankin JG. Cerebral atrophy and functional deficits in alcoholics without clinically apparent liver disease. Neurology 1981;31:377–385.

Cheour M, Leppänen PHT, Kraus N. Mismatch negativity (MMN) as a tool for investigating auditory discrimination and sensory memory in infants and children. Clin Neurophysiol 2000;111:4–16.

Courchesne E, Hillyard SA, Galambos R. Stimulus novelty, task relevance and the visual evoked potential in man. Electroenceph clin Neurophysiol 1975;39:131–143.

Csépe V, Karmos G, Molnár M. Evoked potential correlates of stimulus deviance during wakefulness and sleep in cat: animal model of mismatch negativity. Electroenceph clin Neurophysiol 1987;66:571–578.

Csépe V, Pantev C, Hoke M, Hampson S, Ross B. Evoked magnetic responses of the human auditory cortex to minor pitch changes: localization of the mismatch field. Electroenceph clin Neurophysiol 1992;84:538–548.

Cycowicz YM, Friedman D. A developmental study of the effect of temporal order on the ERPs elicited by novel environmental sounds. Electroenceph clin Neurophysiol 1997;103:304–318.

Dao-Castellana MH, Samson T, Legault F, Martinot JL, Aubin HJ, Crouzel C, Feldman L, Barrucand D, Rancurel G, Feline A, Syrota A. Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings. Psychol Med 1998;28:1039–1048.

Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JD. Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. J Neurosci 1995;15:5870–5878.

Deouell LY, Bentin S, Giard MH. Mismatch negativity in dichotic listening: evidence for interhemispheric differences and multiple generators. Psychophysiology 1998;35:355–365.

Donchin E, Coles MGH. Is the P300 component a manifestation of context updating? Behav Brain Sci 1988;11:357–374.

Escera C, Grau C. Short-term replicability of the mismatch negativity. Electroenceph clin Neurophysiol 1996;100:549–554.

Escera C, Alho K, Winkler I, Näätänen R. Neural mechanisms of involuntary attention to acoustic novelty and change. J Cogn Neurosci 1998;10:590–604.

Escera C, Alho K, Schröger E, Winkler I. Involuntary attention and distractibility as evaluated with event-related brain potentials. Audiol Neurootol 2000a;5:151–166.

Escera C, Yago E, Polo MD, Grau C. The individual replicability of mismatch negativity at short and long inter-stimulus intervals. Clin Neurophysiol 2000b;111:546–551.

Escera C, Yago E, Alho K. Electric responses reveal the temporal dynamics of brain events during involuntary attention switching. Eur J Neurosci 2001;14:877–883.

Escera C, Corral MJ, Yago E. An electrophysiological and behavioral investigation of involuntary attention towards auditory frequency, duration and intensity changes. Cogn Brain Res 2002;14:325–332.

Fabiani M, Friedman D. Changes in brain activity patterns in aging: the novelty oddball. Psychophysiology 1995;32:579–594.

Fabiani M, Friedman D, Cheng JC. Individual differences in P3 scalp distribution in older adults, and their relationship to frontal lobe function. Psychophysiology 1998;35:698–708.

Fadda F, Rossetti ZL. Chronic ethanol consumption: from neuroadaptation to neurodegeneration. Prog Neurobiol 1998;56:385–431.

Freund G, Anderson KJ. Glutamate receptors in the frontal cortex of alcoholics. Alcohol Clin Exp Res 1996;20:1165–1172.

Freund G, Ballinger WE. Decrease of benzodiazepine receptors in frontal cortex of alcoholics. Alcohol 1988;5:275–282.

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

Fuster J. The prefrontal cortex: anatomy, physiology, and neuropsychology of the frontal lobe, New York: Raven, 1989.

George MA, Anton RF, Bloomer C, Teneback C, Drobes DJ, Lorberbaum JP, Nahas Z, Vincent DJ. Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. Arch Gen Psychiat 2001;58:345–352.

Giard MH, Perrin F, Pernier J, Bouchet P. Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. Psychophysiology 1990;27:627–640.

Gilman S, Adams K, Koeppe RA, Berent S, Kluin KJ, Modell JG, Kroll P, Brunberg JA. Cerebellar and frontal hypometabolism in alcoholic cerebellar degeneration studied with positron emission tomography. Ann Neurol 1990;28:775–785.

Gilman S, Koeppe RA, Adams K, Johnson-Greene D, Junck L, Kluin KJ, Brunberg J, Martorello S, Lohman M. Positron emission tomographic studies of cerebral benzodiazepine-receptor binding in chronic alcoholics. Ann Neurol 1996;40:163–171.

Grau C, Polo MD, Yago E, Gual A, Escera C. Auditory sensory memory as

indicated by mismatch negativity in chronic alcoholism. Clin Neurophysiol 2001;112:728–731.
Gurling HMD, Murray RM, Ron MA. Increased brain radiodensity in alcoholism. A co-twin control study. Arch Gen Psychiatry 1986;43:764–767.
Hada M, Porjesz B, Begleiter H, Polich J. Auditory P3a assessment of male alcoholics. Biol Psychiatry 2000;48:276–286.
Halgren E, Baudena P, Clarke JM, Heit G, Liégeois C, Chauvel P, Musolino A. Intracerebral potentials to rare target and distractors auditory and visual stimuli. I. Superior temporal plane and parietal lobe. Electroenceph clin Neurophysiol 1995;94:191–220.
Jasper HH. The ten-twenty electrode system of the International Federation. Electroenceph clin Neurophysiol 1958;10:371–375.
Javitt DC, Shroeder CE, Steinschneider M, Arezzo JC, Vaughan Jr HG. Demonstration of mismatch negativity in the monkey. Electroenceph clin Neurophysiol 1992;83:87–90.
Jeon YW, Polich J. P3a from a passive visual stimulus task. Clin Neurophysiol 2001;112:2202–2208.
Jernigan TL, Butters N, Di Traglia G, Schafer K, Smith T, Irwin M, Grant I, Schuckit M, Cermak LS. Reduced cerebral grey matter observed in alcoholics using magnetic resonance imaging. Alcohol Clin Exp Res 1991;15:418–427.
Joutsiniemi SL, Ilvonen T, Sinkkonen J, Huotilainen M, Tervaniemi M, Lehtokoski A, Rinne T, Näätänen R. The mismatch negativity for duration decrement of auditory stimuli in healthy subjects. Electroenceph clin Neurophysiol 1997;108:154–159.
Kane NM, Curry SH, Butler SR, Cummins BH. Electrophysiological indicators of awakening from coma. Lancet 1993;341:688.
Kathmann N, Wagner M, Rendtorff N, Engel R. Delayed peak latency of the mismatch negativity in schizophrenics and alcoholics. Biol Psychiatry 1995;37:754–757.
Katayama J, Polich J. P300, probability, and the three-tone paradigm. Electroenceph clin Neurophysiol 1996;100:555–562.
Katayama J, Polich J. Stimulus context determines P3a and P3b. Psychophysiology 1998;35:23–33.
Knight RT. Decreased response to novel stimuli after prefrontal lesions in man. Electroenceph clin Neurophysiol 1984;59:9–20.
Knight RT. Contribution of human hippocampal region to novelty detection. Nature 1996;383:256–259.
Knight RT, Scabini D. Anatomic bases of event-related potentials and their relationship to novelty detection in humans. Electroenceph clin Neurophysiol 1998;15:3–13.
Kril JJ, Halliday GM, Svoboda MD, Cartwright H. The cerebral cortex is damaged in chronic alcoholics. Neuroscience 1997;79:983–998.
Lingford-Hughes AR, Acton PD, Gacinovic S, Suckling J, Busatto GF, Boddington SJ, Bullmore E, Woodruff PW, Costa DC, Pilowsky LS, Ell PJ, Marshall EJ, Kerwin RW. Reduced level of GABA-benzodiazepine receptor in alcohol dependency in the absence of grey matter atrophy. Br J Psychiatry 1998;173:116–122.
Loewy DH, Campbell KB, Bastien C. The mismatch negativity to frequency deviant stimuli during natural sleep. Electroenceph clin Neurophysiol 1996;98:493–501.
McCarthy G, Wood CC. Scalp-distributions of event-related potentials: an ambiguity associated with analysis of variance models. Electroenceph clin Neurophysiol 1985;62:203–208.
Molnár M, Skinner JE, Csépe V, Winkler I, Karmos G. Correlation dimension changes accompanying the occurrence of mismatch negativity and the P3a event-related potential component. Electroenceph clin Neurophysiol 1995;95:118–126.
Montero VM, Wright LS, Siegel F. Increased glutamate, GABA and glutamine in lateral geniculate nucleus but not in medial geniculate nucleus caused by visual attention to novelty. Brain Res 2001;916:152–158.
Näätänen R. Attention and brain function, Hillsdale, NJ: Lawrence Erlbaum, 1992.
Näätänen R, Gaillard AWK, Mäntysalo S. Early selective-attention effect on evoked potential reinterpreted. Acta Psychol 1978;42:313–329.
Nicolás JM, Catafau AM, Estruch R, Lomeña FJ, Salamero M, Herranz R, Monforte R, Cardenal C, Urbano-Márquez A. Regional cerebral blood flow-SPECT in chronic alcoholism: relation to neuropsychological testing. J Nucl Med 1993;34:1452–1459.
Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 1971;9:97–113.
Paavilainen P, Karlsson ML, Reinikainen K, Näätänen R. Mismatch negativity to change in spatial location of an auditory stimulus. Electroenceph clin Neurophysiol 1989;78:464–479.
Parsons OA, Tarter RE, Edelberg R. Altered motor control in chronic alcoholics. J Abnorm Psychol 1972;80:308–314.
Patterson BW, Williams HL, McLean GA, Smith LT, Schaeffer KW. Alcoholism and family history of alcoholism: effects on visual and auditory event-related potentials. Alcohol 1987;4:265–274.
Pekkonen E, Rinne T, Näätänen R. Variability and replicability of the mismatch negativity. Electroenceph clin Neurophysiol 1995;87:321–325.
Pekkonen E, Ahveninen J, Jääskeläinen IP, Seppä K, Näätänen R, Sillanaukee P. Selective acceleration of auditory processing in chronic alcoholics during abstinence. Alcohol Clin Exp Res 1998;22:605–609.
Pfefferbaum A, Lim KO, Zipursky RB, Mathalon D. Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. Alcohol Clin Exp Res 1991;15:39–50.
Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO. Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. Alcohol Clin Exp Res 1997;21:521–529.
Polo MD, Escera C, Gual A, Grau C. Mismatch negativity and auditory sensory memory in chronic alcoholics. Alcohol Clin Exp Res 1999;23:1744–1750.
Porjesz B, Begleiter H, Rawlings R, Eckardt M. Auditory recovery function and P3 in abstinent alcoholics. Alcohol Alcohol 1988;23:A41.
Realmuto G, Begleiter H, Odencratz J, Porjesz B. Event-related potential evidence of dysfunction in autonomic processing in abstinent alcoholics. Biol Psychiatry 1993;33:594–601.
Rinne T, Alho K, Ilmoniemi RJ, Virtanen J, Näätänen R. Separate time behaviors of the temporal and frontal mismatch negativity sources. Neuroimage 2000;12:14–19.
Rodríguez-Holguín S, Porjesz B, Chorlian DB, Polich J, Begleiter H. Visual P3a in male alcoholics and controls. Alcohol Clin Exp Res 1999;23:582–591.
Sams M, Paavilainen P, Alho K, Näätänen R. Auditory frequency discrimination and event-related potentials. Electroenceph clin Neurophysiol 1985;62:437–448.
Sasaki T, Campbell KB, Bazana PG, Stelmack RM. Individual differences in mismatch negativity measures of involuntary attention shift. Clin Neurophysiol 2000;111:1553–1560.
Schröger E. A neural mechanism for involuntary attention shifts to changes in auditory stimulation. J Cogn Neurosci 1996;8:527–539.
Schröger E, Wolff C. Attentional orienting and reorienting is indicated by human event-related brain potentials. Neuroreport 1998;9:3355–3358.
Schröger E, Giard MH, Wolff C. Auditory distraction: event-related potential and behavioral indices. Clin Neurophysiol 2000;111:1450–1460.
Sharma A, Kraus N, McGee T, Carrell T, Nicol T. Acoustic versus phonetic representation of speech as reflected by the mismatch negativity event-related potential. Electroenceph clin Neurophysiol 1993;88:64–71.
Squires NK, Squires KC, Hillyard SA. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli. Electroenceph clin Neurophysiol 1975;38:387–401.
Tarter RE. Neuropsychological investigations of alcoholism. In: Goldstein G, Neuringer C, editors. Empirical studies of alcoholism, Cambridge, MA: Ballinger, 1976. p. 231.
Tervaniemi M, Lehtokoski A, Sinkkonen J, Virtanen J, Ilmoniemi R, Näätänen R. Test-retest reliability of mismatch negativity for duration, frequency and intensity changes. Clin Neurophysiol 1999;110:1388–1393.
Veltman JC, Brouwer WH, Van Zomeren AH, Van Wolffelaar PC. Central executive aspects of attention in subacute severe and very severe closed

head injury patients: planning, inhibition, flexibility, and divided attention. Neuropsychology 1996;10:357–367.

Woods DL, Alho K, Algazi A. Intermodal selective attention/I/Effects on event-related potentials to lateralized auditory and visual stimuli. Electroenceph clin Neurophysiol 1992;82:341–355.

Yago E, Escera C, Alho K, Giard MH. Cerebral mechanisms underlying orienting of attention towards auditory frequency changes. Neuroreport 2001;12:2583–2587.

Yamaguchi S, Knight RT. P300 generation by novel somatosensory stimuli. Electroenceph clin Neurophysiol 1991;78:50–55.