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Mismatch negativity impairment associated with alcohol consumption in chronic alcoholics: A scalp current density study

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Abstract

Previous studies, based on amplitude and latency measurements of auditory event-related brain potentials, yielded inconclusive results about the status of mismatch negativity (MMN) in chronic alcoholics. The present study explores scalp current density (SCD) dynamics during MMN latency range in alcoholics, and correlates electrical SCD results with clinical data of the patients. SCD was computed from 30 electrodes in 16 abstinent chronic alcoholics and 16 healthy control volunteers in a paradigm on MMN elicited by duration changes. Reduced activity was observed in left frontal and right anterior and posterior temporal areas during MMN in alcoholics. Alcohol consumption correlated negatively with SCD intensity in these regions. Delayed activation was observed in the left posterior temporal area in the patients. Alcohol abstinence duration correlated positively with SCD intensity in this region. These results point to an impairment of automatic brain processing mechanisms associated with auditory change detection in chronic alcoholism. The present results suggest a reorganization of the computational neurodynamics of automatic auditory change detection linked to the amount of alcohol consumed in abstinent chronic alcoholics.

Keywords: Chronic alcoholism; Mismatch negativity; Scalp current density

1. Introduction

Chronic alcohol consumption, the metabolites involved and other conditions associated with it (e.g., nutritional deficits) have been shown as adversely affecting the brain of chronic alcoholics. In particular, considerable efforts have been put into the study of event-related brain potentials (ERPs) in alcoholic patients. This technique provides a non-invasive way to study brain computing at the sub-second temporal level, and has uncovered many brain processing abnormalities in chronic alcoholics.

There is evidence that abstinent alcoholic patients, compared to control subjects, have delayed brain-stem auditory evoked potentials (BAEPs) (Begleiter et al., 1981), enhancement of peak-to-peak amplitude of the N1–P2 (Cadaveira et al., 1991), and reduced P300 amplitude (Porjesz et al., 1987, 1998). Other ERP abnormalities in chronic alcoholics include enhanced P3a elicited by novel sounds (Polo et al., 2003), reduced P3a in visual paradigms (Rodriguez-Artalejo et al., 1999) and a reduction in the amplitude of N400 (Nixon et al., 2002) and contingent negative variation (CNV) (Chao et al., 2003).

A component of the auditory ERPs that has received recent attention in the alcoholism literature is the mismatch negativity (MMN). The MMN appears circa 100–200 ms after the occurrence of a deviant auditory event in a repetitive pattern of sounds (Näätänen et al., 1978). The main generators of MMN are located in the supratemporal cortex (see review in Escera et al., 2000). In addition, studies using scalp source current density analysis (SCD) have shown that MMN also has sources located

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in the frontal cortex (Giard et al., 1990; Deouell and Bentin, 1998; Rinne et al., 2000; Yago et al., 2001) and parietal cortex (Levanen et al., 1996).

Studies of MMN in abstinent chronic alcoholics have yielded contradictory results. Enhancement of MMN amplitude has been shown (see review in Ahveninen et al., 2000a), but several studies reported normal MMN in the patients (Polo et al., 1999, 2003; Grau et al., 2001; Fein et al., 2004), leaving the status of MMN in alcoholism as an open question. In addition, Polo et al. (1999) proposed a key role of age in the generation of MMN in chronic alcoholic people, as they showed that alcoholic patients over 40 years had an accelerated attenuation of MMN amplitude, compared to the normal aging effect on MMN in healthy subjects (Pekkonen et al., 1993, 1996).

Recent studies of SCD computed from electrical recordings at multiple scalp electrode sites have shown that several cerebral sources contribute to MMN (Giard et al., 1990; Rinne et al., 2000; Yago et al., 2001; Waberski et al., 2001; Marco-Pallarés et al., 2005), and moreover, that these sources were activated in an orchestrated temporo-spatial pattern of independent contributions from a distributed brain network (Marco-Pallarés et al., 2005). From this perspective, the commonly used MMN peak latency/amplitude may underestimate the complex neurodynamics on the brain computing mechanisms underlying the generation of this ERP. The present study uses SCD – a computation of the second spatial derivative of scalp potentials, giving rise to improved spatial resolution of EEG signals (Nunez, 1995) – analysis to investigate the topography and time course of activations underlying MMN in abstinent chronic alcoholics and control subjects, in order to uncover specific auditory processing deficits in chronic alcoholic patients.

2. Material and methods

2.1. Subjects

Subjects were 16 alcoholic patients (male; mean age = 41.9 years, SD = 8.7), and 16 age-matched (male; mean age = 39.3 years, SD = 10.9) healthy social drinkers, with an intake of alcohol lower than 210 g/week. Patients were recruited from the Unitat d'Alcohologia of the Hospital Clínic i Provincial of Barcelona, and all had a history of alcohol dependence according to DSM-IV criteria (303.90) of at least 5 years (mean = 11.0 years, SD = 6.9), and no other major psychiatric or organic disease. Chronic alcoholics were assessed after alcohol withdrawal lasting at least 4 weeks (mean = 10.2 weeks, SD = 6.0). Before the treatment patients had an intake of alcohol of 1014 ± 600 mg/week. To control drug-free status during the treatment, periodic follow-up interviews with their clinicians and recurrent urine drug screen analyses were performed. Before the neurophysiological recording session, subjects underwent a breathanalyzer test to ensure that they were free of alcohol. All subjects were free of medication (including disulfiram) during the 72 h preceding the experimental session. All subjects were right-handed, and naive to the purpose of the experiment. After a full description of the study, all subjects signed their informed consent to the study, and answered a questionnaire about their clinical history and their habits of alcohol intake. A Spanish version of the Beck Depression Inventory (Beck et al., 1961) was administered to assess the mood state of the subjects. The experiment complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and 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.

2.2. Stimuli and procedure

Auditory stimuli were presented in sequences according to a MMN paradigm described elsewhere (Grau et al., 1998). These sequences consisted of trains of three tones separated by SOA of 300 ms. A total of 400 trains were presented, half of them starting with a standard stimulus, and half of them starting with a deviant stimulus, the other two stimuli within the train being standard tones. The inter-train interval was 400 ms. Pure sine-wave tones of 700 Hz, with a duration of 75 ms (standard) or 25 ms (deviant), including 5 ms of rise/fall times, were delivered through headphones, binaurally, at an intensity of 85 dB SPL. ERP recordings took place in a shielded room, where the subject was instructed to perform an irrelevant visual task, while ignoring the auditory stimuli. Subjects were asked to refrain from moving or blinking.

2.3. Recording

The electroencephalogram (EEG) was continuously recorded, at a sampling rate of 500 Hz from 30 tin scalp electrodes mounted on a cap and referenced to the tip of the nose. The recording sites were based on the 10–20 systems (Fp1, Oz, Fp2, F7, F3, Fz, F4, F8, T3, C3, CZ, C4, T4, T5, P3, Pz, P4, T6) with 12 additions (FC1, FC2, FT3, FT4, M1, M2, IM1, IM2, TP3, TP4, CP1 and CP2). The electro-oculogram was recorded from two additional electrodes, placed at the outer canthus and below the right eye. The epoch spanned 600 ms, including 100 ms of pre-stimulus baseline. Trials with voltages at any scalp electrode or the electro-oculogram exceeding ±100 μV were automatically excluded from averaging. The remaining trials were digitally band-pass filtered (0.1–30 Hz). Data obtained from eight of the electrodes used in this study, with the same subjects and analyzed with a different procedure, were discussed elsewhere (Grau et al., 2001).

2.4. Data analysis

For each subject, electrical responses to deviant and standard tones starting a three-tone train were averaged separately. Difference waves were computed for each electrode and subject by subtracting the ERPs elicited by standard stimuli from those to deviant stimuli. Four alcoholics and four controls did not show any negative deflection between 100 and 200 ms (2 SD over baseline) and were rejected from further analysis. Group comparisons of the amplitude and latency of MMN in the

deviant minus standard difference waves were analyzed with *t*-test.

The goal of the present work was to study the temporal dynamics of different areas contributing to the MMN during its latency window. However it is well-known that the MMN presents a great inter-individual variability in latency (Escera and Grau, 1996). In addition in Marco-Pallarés et al. (2005) we described that the MMN could be composed by at least five statistical independent components, with proper sources and temporal evolution that would underlie the MMN ERP. Hence, MMN could be not a unique phenomenon (or dual, presenting a frontal and a temporal activation), but would present a more complex spatio-temporal pattern. Hence, a procedure to minimize the individual differences in MMN, not only in latency peak, but also in the whole MMN span was developed. For each single subject the averaged MMN waveform was cross-correlated to the MMN grand-averaged envelope — defined as the minimum value among all electrodes for each time frame, of the control group, and the maximum delay value resulting from the cross-correlation was then used to align the individual MMN waveform.

Prior to SCD estimation by mean of a Laplacian operator (Perrin et al., 1989), individual data were interpolated in a spherical scalp model using 1000 pixels by means of a Spherical Harmonics Expansion (Lagerlund et al., 1995), according to the method described by Ruffini et al. (2002). A scalp area was considered activated on the grand-average SCD map if 4 adjacent pixels showed $p<0.05$ relative to pre-stimulus interval during 6 consecutive time frames using the Holmes non-parametric method, that is corrected from multiple comparisons (Holmes et al., 1996). When a group of six pixels met both conditions, it was selected as being a region of interest.

The activated zones for the alcoholic and control groups were also compared using non-parametric tests, as described in Holmes et al. (1996), to reduce type-I error due to multiple comparisons, defining scalp areas where the two groups showed significant differences.

In a further step of the analysis, the time evolution of the surface Laplacian in areas appearing as significant was plotted for alcoholics and controls, to identify possible differences in their temporal dynamics. In addition, the ±10 ms SCD amplitude values around the highest peak of time evolutions of alcoholics in the above scalp areas were correlated with age, years of education, scores in the Beck Depression Inventory, years of alcohol consumption, years of alcohol dependence, age of beginning of alcohol dependence, alcohol and tobacco consumption (maximum alcohol and tobacco consumption in one "typical" day as reported by the patient before starting the treatment), and weeks of abstinence (before ERP exploration).

3. Results

As expected, both groups showed a clear MMN in the 100–200 ms range after the deviant stimulus (Fig. 1). No differences

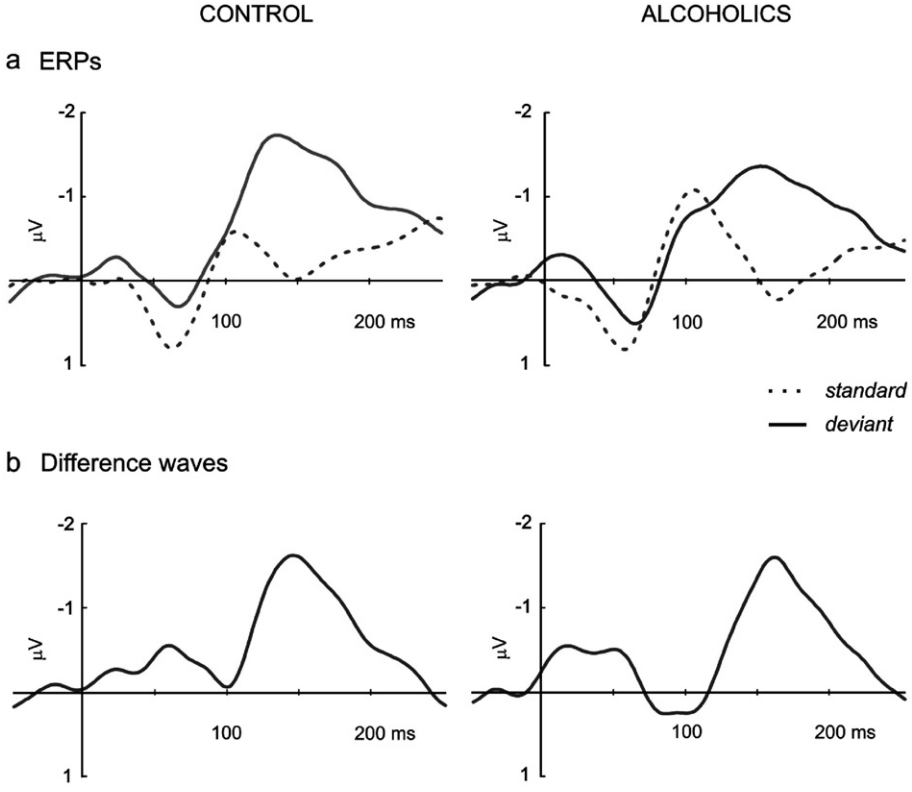

Fig. 1. a) Grand average waveforms for control (left) and alcoholic (right) groups elicited by standard (dashed) and deviant (solid) tones at Fz. b) Grand average difference waveforms obtained by subtracting the ERPs elicited by standard tones from the deviant tones for control (left) and alcoholic (right) groups at Fz.

were found between control and alcoholic groups in the MMN peak amplitude (controls = −1.74 ± 1.1 μV, alcoholics = −1.77 ± 0.92 μV; $t_{22} = 0.0867$, $p = 0.93$) and latency (controls = 145 ± 15 ms, alcoholics = 154 ± 20 ms; $t_{22} = -1.24$, $p = 0.21$).

In control subjects, sequential mapping of time dynamics of scalp SCD activations was characterized by scalp negative sources on right anterior and posterior temporal areas during the 120–200 ms latency window. Left anterior and posterior temporal, and right and left frontal sources were activated 20 ms later and deactivated 20 ms earlier. Similar scalp areas to those that were activated in controls were also activated in the alcoholic group, but in the latter all areas were activated simultaneously and were restricted to the 160–200 ms interval (Fig. 2).

Scalp areas that showed significant differences ($p < 0.05$ using the Holmes non-parametric method) in SCD activation for control and alcoholic groups for at least 10 ms were found in left posterior temporal (including T3, TP3 and T5 electrodes), right anterior temporal (including F8 electrode), right posterior temporal (including T4, TP4 and T5) and left frontal (including Fp1). These regions and the corresponding temporal evolution of their activation for the alcoholic and control groups are shown in Fig. 3. As can be seen, SCD activation in the left posterior temporal area was delayed in the alcoholics. The other three regions (left frontal and right temporals) were activated from 110–120 to 200 ms after stimulus onset in the control group, while these areas were only activated from approximately 150 ms to 200 ms in the alcoholic group.

Pearson correlation analyses carried out between SCD peak amplitude in the above-mentioned areas and clinical data from the alcoholic subjects are summarized in Table 1. The variable 'maximum alcohol consumption per day' showed negative correlations with SCD in left frontal ($r = 0.59$, $p < 0.05$) and right anterior ($r = 0.64$, $p < 0.05$) and posterior ($r = 0.72$, $p < 0.01$) temporal areas, suggesting an alcohol dose-effect related decrease of the activity of these areas; the variable 'alcohol abstinence' showed positive correlation with SCD in the left temporal area ($r = -0.72$, $p < 0.01$), which could be interpreted as an early recovery index; and the age presented significant negative correlations in left frontal ($r = -0.64$, $p < 0.05$) and right ($r = -0.54$, $p < 0.05$) and left ($r = -0.73$, $p < 0.01$) temporal posterior areas, in agreement with previous age related alterations of the MMN described in alcoholics (Polo et al., 1999). No other significant correlations were found between clinical data and SCD values.

4. Discussion

The main original contribution of the present study is that, although there are no differences in the peak latency and amplitude of MMN between chronic alcoholics and control subjects, there are differences between groups in the SCD dynamics of the areas involved in MMN generation. These can be interpreted as being due to reorganization in the dynamics of the cerebral areas involved in the analysis of changes in sound duration.

The topography and time behaviour of SCD during the MMN interval indicate that four areas, all traditionally related to MMN, i.e. three temporal areas (left posterior and right anterior and posterior) and the left frontal area, activate differently in

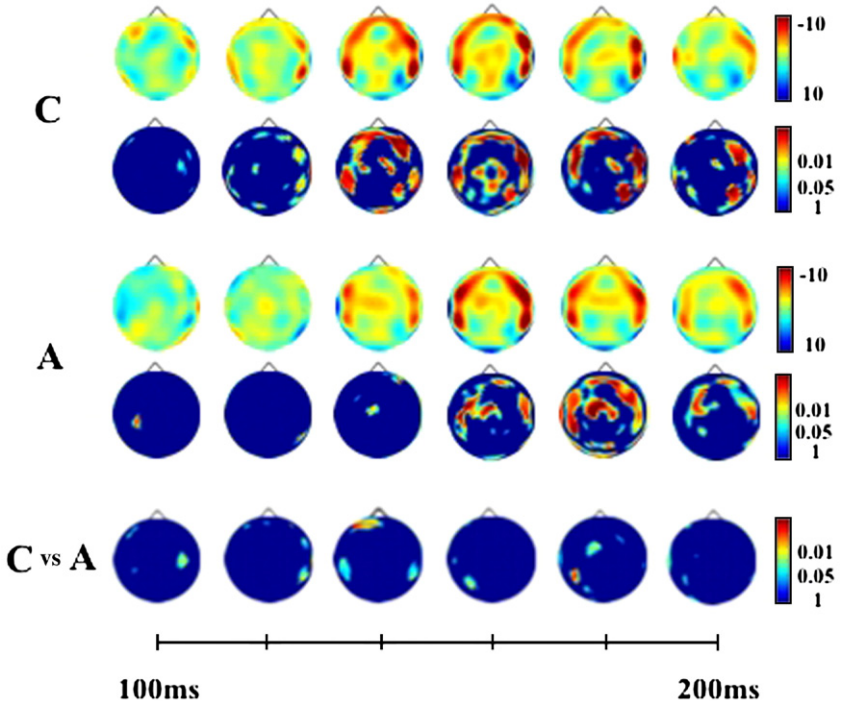

Fig. 2. MMN SCD scalp maps for control (C) and alcoholic (A) subjects from 100 ms to 200 ms after stimuli onset. For each group, upper maps are the SCD values (units proportional to $\mu V/m^2$) and lower maps indicate the comparison level (p) of this time range to 100 ms baseline Pixels with $p < 0.05$ using the Holmes non-parametric test are accepted as being significantly activated. Below: probability values for the comparison between control and alcoholic groups (C vs A).

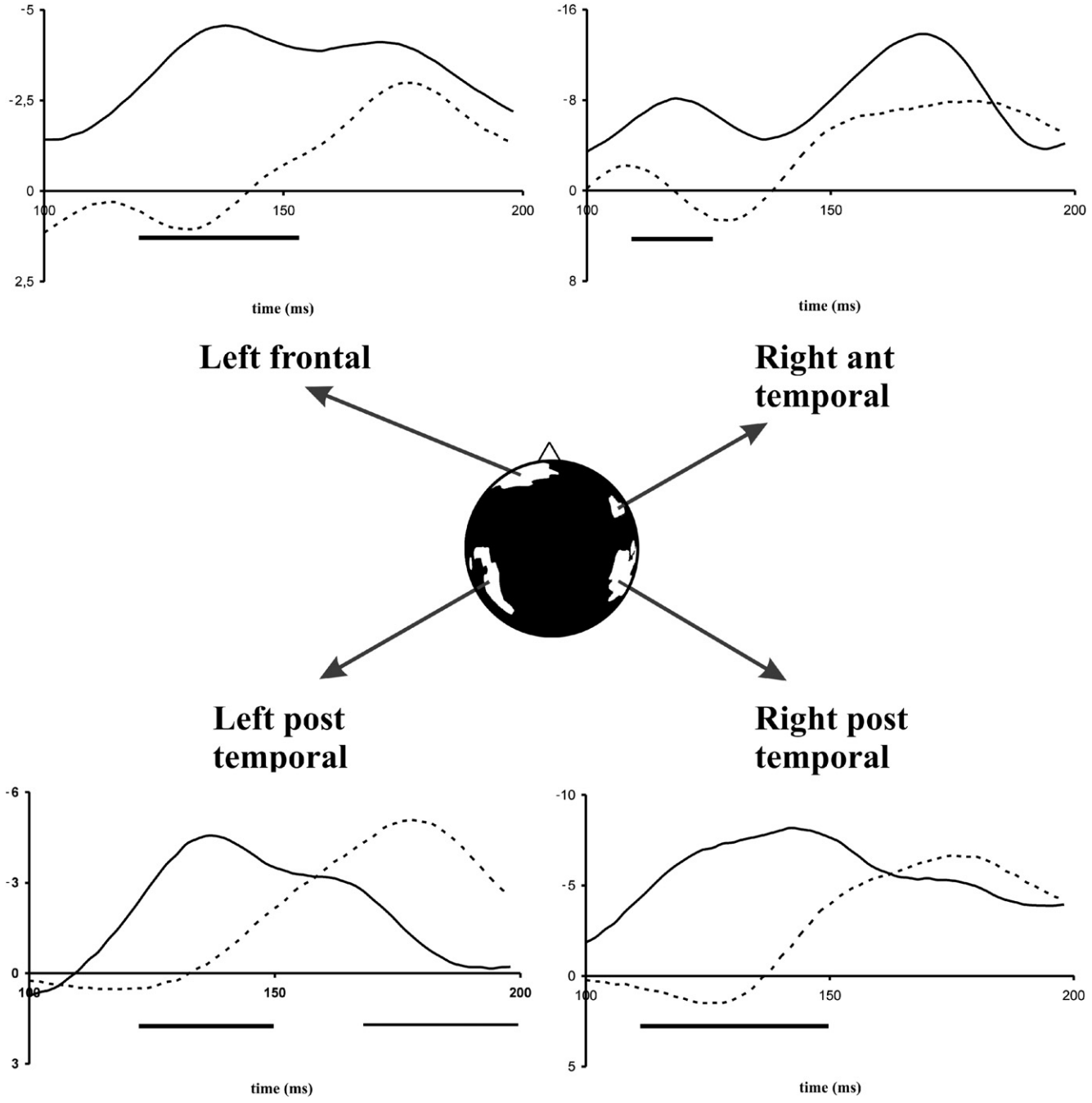

Fig. 3. Areas that show significant differences ($p<0.05$ using the Holmes non-parametric method) in activation for control and alcoholic groups during at least 10 ms, and their corresponding scalp SCD temporal dynamics. Horizontal lines at the bottom of each temporal representation are the intervals at which there are significant differences between control and alcoholic groups.

alcoholics from controls. In patients, the duration of SCD activation was reduced in left frontal and right anterior and posterior areas, and was confined to the second half of MMN latency range, while left posterior temporal activation was delayed and coincided with the others in the same time interval (see Fig. 3).

Nevertheless, the temporal differences between control and alcoholic groups cannot be explained only by a delayed latency of the alcoholic group because: a) there were no significant differences in the latency of the MMN ERP wave between groups; the non-significant 9 ms of difference between control and alcoholic group for the MMN latency (see Results and Fig. 1) cannot explain the differences shown in the temporal evolution of SCD (Fig. 3); b) as can be seen in Fig. 3, only the left posterior temporal area seems to show a 50 ms "latency shift" in the alcoholic group compared to the control group. In the other areas (left frontal and right temporal), there is no latency shift of activation for the alcoholic group, but a lack of activation for this group in the first half of the MMN time window (100–150 ms). Thus,

Table 1

	Maximum alcohol consumption (mg)	Abstinence	Age
Left frontal	0.59*	0.1	−0.64*
Left posterior temporal	0.07	−0.72**	−0.73**
Right posterior temporal	0.72**	−0.24	−0.54*
Right anterior temporal	0.64*	−0.30	−0.47

Correlation coefficients between clinical data (maximum alcohol consumption and weeks of abstinence) and ±10 ms SCD amplitude values around the highest peak of time evolution of alcoholics in the selected areas of Fig. 2 (*$p<0.05$; **$p<0.01$).

alcoholics show a shortening of the time that large neuronal populations underlying the generation of MMN expend in the processing of auditory differences. In addition, all scalp areas were activated synchronously in alcoholics, lacking the more complex spatio-temporal sequence of brain activations underlying MMN in control subjects (see Figs. 2 and 3).

According to the most accepted MMN account (Näätänen et al., 2001), temporal areas are associated with the automatic detection of unexpected changes in the auditory environment, whereas frontal areas are related to the orienting of attention to auditory change. Our results suggest that, in abstinent chronic alcoholics, both neural mechanisms are impaired.

If we assume that frontal SCD activation reflects the activity of a frontal generator, finding less left frontal scalp SCD participation in alcoholics is consistent with a range of neuropsychological (Duka et al., 2003), structural (Mathalon et al., 2003) and functional neuroimaging (Pfefferbaum et al., 2001) studies reporting prefrontal cortex deficits in chronic alcoholics. For instance, several hemodynamic studies reported hypoactivation in frontal areas (for a review see Mosely et al., 2001), which seems to indicate that the frontal lobe is a relevant target of vulnerability for brain damage in alcoholic patients.

Likewise, the SCD deficit found in temporal areas could be a functional counterpart of structural and metabolic impairment previously reported in temporal lobes in magnetic resonance imaging studies (Pfefferbaum et al., 1997), which show that there is a gray matter volume loss in the auditory cortex of alcoholic patients.

Interestingly, the alterations in SCD time course of same areas in the alcoholics and the association between SCD activations in these structures and clinical data are grouped in two different patterns: a) right anterior and posterior temporal and left frontal scalp areas, that show a lack of activation in the first half of the MMN latency window (see Fig. 3), and a negative correlation between alcohol consumption and SCD amplitude; and b) left posterior temporal area, with a delay in SCD activation and a rapid recovery of SCD amplitude with the duration of alcohol abstinence. Moreover, there was a negative correlation between age and SCD amplitude at left frontal and right and left temporal posterior areas, supporting previous findings suggesting a reduction in the amplitude of MMN for alcoholic patients over 40 years old (Polo et al., 1999). However the relatively small number of subjects ($N=12$) does not allow us to make strong inferences about these effects.

Studies of MMN of alcoholic patients using traditional latency/amplitude criteria have yielded contradictory results (Ahveninen et al., 2000b). Our results complement these studies by proposing that the main differences between control and alcoholic groups are in the temporal dynamics of studied areas. The extended information provided by the proposed SCD methodology could be used in other pathologies that have alterations in MMN, such as schizophrenia (Javitt et al., 1995).

Some limitations of this study have to be taken into account. Firstly, the use of the Laplacian operator in ERP data allows improvement of spatial resolution compared to voltage data, but could amplify the noise of the signal (Bradshaw and Wikswo, 2001). Since the main application of SCD in the present experiment is to MMN data, that is, obtained from the subtraction of two ERPs (with a consequent decrease in the signal-to-noise ratio), an increase in SCD noise compared to voltage data could diminish the quality of signals. However, previous studies have shown the power of this method to disentangle the spatio-temporal dynamics of MMN generators (Yago et al., 2001). Second, although some of the present results (mainly the correlation between MMN data and alcohol consumption and abstinence) could be relevant to the understanding of the effects of chronic alcohol consumption on MMN, the relatively small number of subjects in the present study does not allow us to make strong inferences from these results and their consequences. In this sense, it would be interesting to replicate these findings using the same techniques with a larger pool of subjects. In addition, although patients were free of medication 72 h before the experiment, some drugs present longer half life and could have a direct or indirect effect on MMN. However, and due to ethical reasons, we reduced the time without medication to 4 days only. Finally, in the present report we have not studied the P3a wave, although it is a major topic in the study of auditory event-related potentials in alcoholism (Porjesz et al., 2005). Its study under the experimental conditions used here, with inter-stimulus intervals of 300 ms, is inadequate, since the P3a time range is between 185 and 385 ms (Escera et al., 1998; Yago et al., 2003). If it was included, the P3a information might be partially truncated. However, experiments should be designed for studying such a relationship between MMN and P3a, using similar SCD methodology and an appropriate experimental paradigm.

In conclusion, these findings support the view that the brain computation mechanisms to detect auditory differences are reorganized in the brains of alcoholics. Changes in brain computation strategies in chronic alcoholism were previously described (Pfefferbaum et al., 2001) in a working memory paradigm demanding behavioural response. The present study suggests that in an automatic cerebral detection process, as indexed by MMN, brain computation mechanisms are read-apted in a less complex and shorter way, which seems to be related to alcohol consumption.

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