Impaired theta phase-resetting underlying auditory N1 suppression in chronic alcoholism

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It has been suggested that chronic alcoholism may lead to altered neural mechanisms related to inhibitory processes. Here, we studied auditory N1 suppression phenomena (i.e. amplitude reduction with repetitive stimuli) in chronic alcoholic patients as an early-stage information-processing brain function involving inhibition by the analysis of the N1 event-related potential and time-frequency computation (spectral power and phase-resetting). Our results showed enhanced neural θ oscillatory phase-resetting underlying N1 generation in suppressed N1 event-related potential. The present findings suggest that chronic alcoholism alters neural oscillatory synchrony dynamics at very early stages of information processing. *NeuroReport* 20:337–342 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

NeuroReport 2009, **20:**337–342

Keywords: alcoholism, auditory N1, gating, phase-resetting, theta

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Received 27 September 2008 **accepted** 19 November 2008

Introduction

Abnormal inhibitory processes, possibly resulting from an increased nervous system hyperexcitability, have been proposed to underlie functional brain deficits in chronic alcoholism [1]. For instance, earlier studies have shown that chronic alcoholics [2] display an altered amplitude of the auditory N1-evoked potential elicited to repeated stimulus presentation, suggesting abnormal automatic sensory gating/suppression in this group as a consequence of a increased state of neural excitement that lacks a recovery capacity after repeating stimulus input [3]. Indeed, auditory N1 suppression (i.e. gating), consisting of a reduction of the N1 amplitude to the repeated auditory presentation of identical auditory stimuli has been argued to reflect active inhibitory mechanisms on its neural generator populations [4,5], thus providing an index of the capacity of brain inhibitory mechanisms to automatically gate irrelevant stimulation from the environment at very early stages of auditory processing [6].

Although the auditory N1 suppression provides an index of early-stage inhibitory-related brain processes, the specific underlying neural mechanisms are difficult to disentangle based only on the given event-related potential (ERP)-based amplitude and latency measures. In fact, recent electrophysiological studies have put forward the relevance of the oscillatory neural activity underlying stimulus-locked brain responses obtained from the scalp magnetoencephalography/electroencephalogram (M/EEG) [7,8] and also with intracranial recordings [9], thus providing powerful information on how neural activity is coordinated in large-scale neural networks giving rise to a particular ERP [10]. Through the analysis of the trial-by-trial oscillatory activity, it has been stated that stimulus-locked brain responses may arise from changes in spectral power and/or event-locked phase shifts (phase alignment) of the underlying spontaneous activity [10]. Furthermore, recent oscillatory studies have suggested that auditory N1 suppression may arise from a differential contribution of spectral power and phase realignment parameters [11], as well as the involvement of different brain cortical sources in these parameters [12], all in all suggesting that inhibitory mechanisms underlying N1 gating phenomena are subserved by distinct neural synchronization patterns.

In this study, we hypothesized that the disturbances suggested in inhibitory-related mechanisms in alcoholic patients should also be observed in early sensory gating mechanisms uncovered in the auditory N1 ERP. To test this hypothesis, we investigated N1 suppression mechanisms in chronic alcoholism by the study of three relevant stimulus-locked dimensions: ERPs, spectral power, and phase-resetting. Furthermore, the study of the oscillatory neural activity would shed some light into the specific neural mechanisms involved in the hypothesized inhibitory deficit presented in these patients.

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Methods

Participants

Seventeen outpatient chronic alcoholics (men, mean age 42 ± 9 years) and 17 age-matched healthy participants (men, mean age 39 ± 11 years) with no history of psychiatric disorders were included in the study, which was conducted according to the principles of the Declaration of Helsinki and approved by the ethics committee of University of Barcelona. Alcoholic patients were diagnosed according the *Diagnostic and Statistical Manual for Mental Disorders-IV* criteria for alcohol dependency. All patients had a history of alcoholism of at least 4 years (11 ± 7 years) and were studied after alcohol withdrawal lasting for at least 4 weeks (10 ± 6 weeks) (Table 1).

Participants with a previous history of severe organic disease, neurologic or psychiatric disorders or any other substance abuse (except tobacco) (Diagnostic and Statistical Manual for Mental Disorders-VI) were excluded from the study. To control drug-free status during the treatment, periodic follow-up interviews with their clinicians and recurrent urine drug screen analyses were performed. Earlier to the neurophysiological study, participants underwent a breath analyzer test to ensure that they were free of alcohol. All participants were free of medication, including disulfiram, for 72 h before the experimental session. After complete description of the study to the participants, written informed consent was obtained from all participants.

Stimuli

Trains of three pure sine tones of 700 Hz and 85 dB sound pressure level were presented binaurally through headphones according to a protocol described elsewhere [13] and successfully applied previously to chronic alcoholism [14]. The first of the three tones of a train was a standard tone with duration of 75 ms ($P = 0.5$) (S1) or a deviant tone with a shorter duration of 25 ms ($P = 0.5$), whereas the other two tones were standard (namely, S2 and S3, respectively). Intertone interval was 300 ms while the intertrain interval was 4 s. Only the trains containing three standard tones (S1, S2 and S3) were analysed in this study.

Event-related potentials and time-frequency analysis

The EEG (bandpass 0.1–70 Hz; 50 Hz notch-filtered) was recorded at 500 Hz sampling rate by a Synamps amplifier (Neuroscan Inc., El Paso, Texas, USA) from 30 electrodes attached at the following 10–20 scalp locations: Fp1/2, Fz, F3/4, F7/8, Cz, C3/4, T3/4, Pz, P3/P4, T5/6, Oz, and from 10 additional electrodes (FC1/2, FT3/4, M1/2, IM1/2, TP3/4, CP1/2). The electrooculogram was recorded from two electrodes placed at the outer canthus and below the right eye.

Table 1 Demographic and clinical data of alcoholic and control participants

Participants	Age (years)	Education (years)	Alcohol per week (mg)	Evolution (years)	Abstinence (weeks)
Healthy	39.6 ± 11.2	11.7 ± 2.4	85 ± 64	–	–
Alcoholics	42.4 ± 8.7	8.7 ± 3.3	933 ± 550	14 ± 8	10 ± 6

ERPs were obtained offline by averaging of EEG epochs lasting 2000 ms, which included a 1000-ms prestimulus baseline and the responses to S1, S2 and S3. Epochs exceeding ± 100 μV in any EEG or electrooculogram channel were excluded automatically from analysis. No further digital off-line bandpass filter was applied after averaging for ERP analysis. The auditory N1 was identified as the largest negative peak between the 80 and 180 ms latency window of the ERPs elicited to each of the three standard tones in the epoch. In each case, the baseline-to-peak value was taken as the magnitude (μV) of the response. N1 amplitude (μV) and peak latency (ms) at central frontal (Fz) and central (Cz) electrodes were analyzed by means of repeated measures analysis of variance including stimulus repetition (S1, S2 and S3) as a within-subject factor. A between-subject factor (controls and alcoholics) was also included to elucidate statistical differences across groups. *P* values were calculated by using the Greenhouse–Geisser correction when appropriate.

Single-trial time-frequency analysis was performed by applying a continuous wavelet transformation to EEG epochs as defined above (i.e. 2000 ms epoch length) by using a complex Morlet wavelet to each participant separately under Matlab 7 (The Mathworks, Inc., Natick, Massachusetts, USA). Complex Morlet wavelet was defined as (1):

$$w(f,t) = (2\pi\sigma_t^2)^{-1/2} e^{\frac{-t^2}{2\sigma_t^2}} e^{2i\pi f_0 t} \quad (1)$$

where the relation f_0/σ_f [where $\sigma_f = 1/(2\pi\sigma_t)$] was set to 7. The time-frequency representation of the signal s(t), at trial k, frequency f and time t was computed as (2):

$$F_k(f,t) = w(t,f) \times s_k(t) \quad (2)$$

29 Wavelet transformation components were extracted [with a time resolution of 2 ms (t)] covering a frequency range of 2–30 Hz [with a resolution of 1 Hz (f)].

Event-related spectral power changes were then computed by the event-related spectral perturbation (ERSP) index (3):

$$ERSP(f,t) = \frac{1}{n}\sum_{k=1}^{n} [F_k(f,t)]^2 \quad (3)$$

where, for n trials, F_k (f, t) is the spectral estimate of trial k at frequency f and time t. ERSP shows mean time-frequency points across the input epochs, where high or

low spectral power differs from mean power during the 1000 ms prestimulus baseline period of the same epochs. Event-locked phase concentration was computed by the event-related intertrail coherence (ITC) index [10] (4), analogous to the 'phase-locking index' [15]:

$$ITC(f,t) = \frac{1}{n}\left|\sum_{k=1}^{n}\frac{F_k(f,t)}{|F_k(f,t)|}\right| \qquad (4)$$

where $\|$ represents the complex norm. ITC measures the consistency across trials of EEG spectral phase at each frequency and its values range from 0 to 1, with values near to 1 implying almost perfect phase coincidence across trials.

Any differences in power spectral band arising between the averaged poststimulus (S1, S2 and S3 time windows) and over the mean baseline period indexed event-related spectral power modulation [16]. Alcoholics' and controls' significant δ, θ, α and β band ERSP and ITC at N1 latency range ($\pm$ 10 ms) after S1, S2 and S3 ($P < 0.05$) was based on a repeated measures Student's t-test comparison between the poststimuli time interval and baseline period (– 1000 ms) preceding S1 entrance [17].

Those ERSP and ITC spectral band measures that resulted significant ($P < 0.05$) when compared with baseline period were used for further analysis. In contrast, it was computed within-group ERSP and ITC modulations among S1, S2 and S3 and, finally, it was compared ERSP and ITC results between alcoholics and controls by means of a Student's t-test.

Results

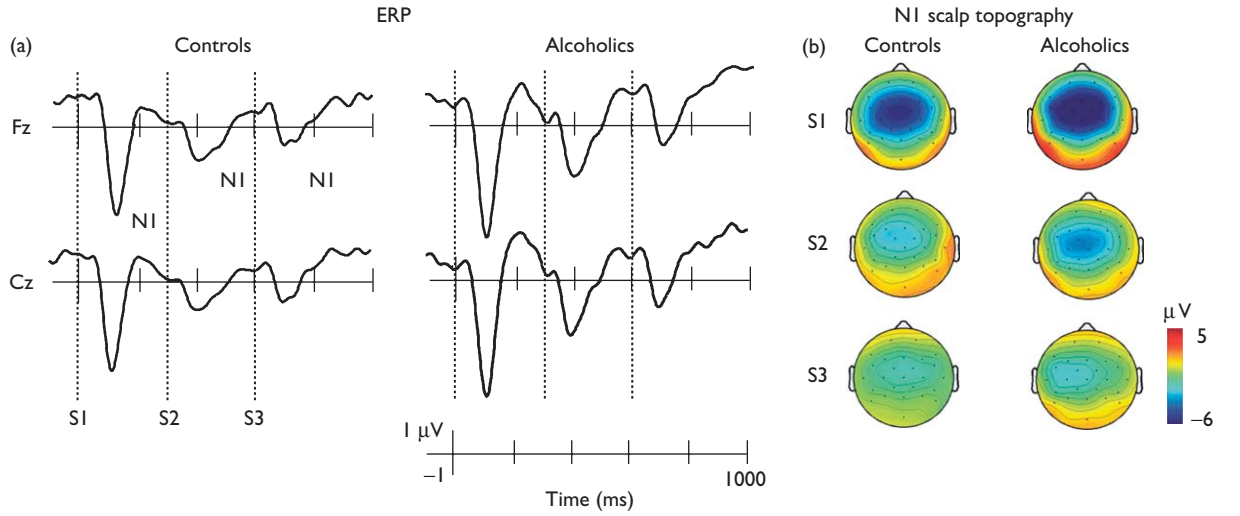
Averaged event-related potentials (N1)

All tones (S1, S2 and S3) elicited significant N1 responses at the Fz and Cz electrode location ($P < 0.05$). Figure 1 depicts the grand average waveforms to the three-stimulus train at the Fz and Cz electrodes (Fig. 1a) and the corresponding N1 scalp distribution at its peak latency (Fig. 1b) for the control and alcoholic groups. Analysis of variance yielded a main N1 effect of repetition on N1 amplitude [Fz: $F(2,48) = 23.26$, $P < 0.005$ and Cz: $F(2,48) = 31.24$, $P < 0.005$] and latency [Fz: $F(2,48) = 7.32$, $P < 0.05$ and Cz: $F(2,48) = 10.61$, $P < 0.05$]. However, no significant interaction between alcoholic and control participants was observed for either N1 amplitude [Fz: $F(2,48) = 5.31$, $P > 0.05$ and Cz: $F(2,48) = 5.31$, $P > 0.05$] or latency [Fz: $F(2,48) = 2.82$, $P > 0.05$ and Cz: $F(2,48) = 1.13$, $P > 0.05$].

Spectral power modulation and event-locked phase-resetting

Both alcoholic and control participants showed significant ERSP to S1 on frequencies ranging from 2 to 20 Hz ($P < 0.05$ in all cases) at the Cz electrode (Fig. 2a and b). No significant ERSP appeared after S2 and S3 to any group and at any frequency range ($P < 0.05$). Repeated measures Student's t-test on the band-to-band comparisons at N1 peak latency across stimuli indicated a decrease in ERSP after S2 when compared with the S1 response ($P < 0.05$), whereas no modulation was observed when the ERSP after S2 was compared with the S3 response (all, $P > 0.05$), this for the two groups and at all the frequency ranges of the study [i.e. δ (2–3 Hz),

Fig. 1

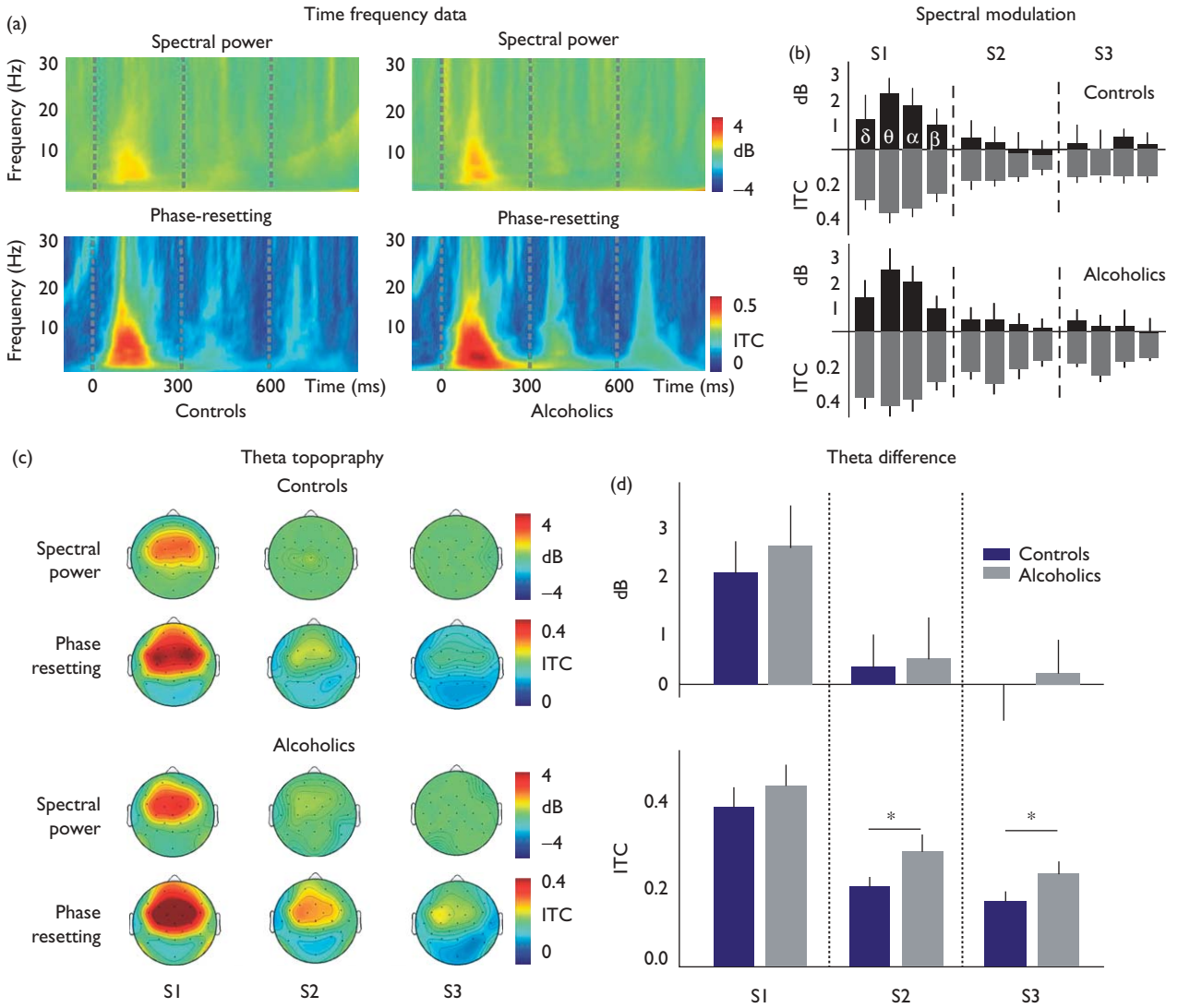


(a) Grand-average event-related potentials (ERPs) elicited to S1, S2 and S3 stimuli in alcoholic and control participants at Fz and Cz. For ERP plot purposes, baseline data are displayed from – 100 ms S1 stimulus onset, although ERP amplitude normalization was based on – 1000 to 0 ms. (b) Isovoltage map of the corresponding three stimulus responses for controls and alcoholics at the N1 latency peak.

θ (4–7 Hz), α (8–12 Hz) and low β (13–20 Hz)]. All ERSP and ITC comparisons were Bonferroni corrected.

All above-mentioned frequencies showed significant ITC ($P < 0.05$) after S1 in both groups at the Cz electrode (Fig. 2a and b). Repeated measures Student's t-test revealed that ITC was reduced after S2 in all 2–20 Hz frequency ranges ($P < 0.05$), and then remained unchanged for S3 in the two groups (all, $P > 0.05$). However, ITC remained significant ($P < 0.05$) after S2 and S3 for frequencies involved in the S1 response in alcoholic and control participants, although the S2 and S3 ITC values at the θ band were smaller for control than alcoholic participants (approximately 0.1–0.2 ITC) (Fig. 2c). Thus, when ITC θ values were compared between groups, a significant θ ITC enhancement was observed for alcoholic over control participants after S2 and S3 $t(12) = -2.4$; $P < 0.05$ for ITC at S2 and $t(12) = -2.3$; $P < 0.05$ for ITC at S3, but not after S1 ERSP: $t(12) = -0.8$; $P > 0.05$ and ITC: $t(12) = -1.4$;

Fig. 2



(a) Grand-average (across individuals) spectral power (event-related spectral perturbation, ERSP, measured in dB) and phase-resetting intertrail coherence (ITC) after S1, S2 and S3 stimuli for alcoholics and controls participants at Cz electrode. Notice that although ITC was evidenced after each stimulus, ERSP was only observable after S1. (b) Spectral ERSP and ITC band (δ, θ, α and β) modulations after S1, S2 and S3 entrance at N1 latency range (±10 ms) for control and alcoholic group compared with each frequency band values in baseline period (−1000 ms). Standard error of the mean was added to each ERSP and ITC frequency band. (c) Spectral power (ERSP) and phase-resetting (ITC) scalp representation after S1, S2 and S3 at the corresponding N1 latency range for control and alcoholic participants. (d) ERSP and ITC Student's t-test comparison between controls and alcoholics' modulations at Cz electrode after each stimuli entrance. *Significant difference ($P < 0.05$).

$P > 0.05$. Alpha and low β bands showed no significant differences between groups (all $P > 0.05$). Similar results were found at Fz electrode (data not shown).

Oscillatory neural responses and clinical measures

Following θ differences on repeated stimulus presentation between control and alcoholic participants, a Pearson's correlation analysis was performed between S1 and S2 ERSP and ITC measures and clinical data obtained from alcoholic patients. Furthermore, a correlation analysis was also computed by using the S1 minus S1 θ ERSP and ITC values. This difference was implemented as an objective measure of suppression, as it is usually computed in sensory-gating studies based on earlier auditory ERP components (i.e. P50) [18]. Significant correlation coefficients were obtained only between ITC measures and two clinical variables. First, it was observed that extended alcoholism evolution ('evolution') resulted in higher ITC θ responses after a repeated stimulus input (S2) ($r = 0.66$; $P < 0.01$). In the second place, alcoholic individuals who had consumed higher doses of alcohol ('alcohol per week') showed reduced suppression capacity, as measured by the difference between S2 and S1 responses reflected in the θ ITC ($r = -0.60$; $P < 0.05$).

Discussion

By using ERPs and single-trial time-frequency analysis we showed that, although no differences could be observed on the N1 amplitude and latency measures, chronic abstinent alcoholics suffered impairment on the neural mechanisms that underlie auditory N1 suppression. Specifically, our results indicated that these alterations arose from an increased phase-resetting response on the θ EEG rhythm while spectral power remained unaffected. Furthermore, we showed that higher θ synchronization underlying N1 suppression in alcoholism was related with clinical measures such as the amount of alcohol consumption.

This findings evidenced no auditory N1 ERP measures of amplitude and latency differences between chronic alcoholism and control participants at all the stimuli responses analysed, that is to initial stimuli entry (S1) and to a repeated stimuli sequence (S2 and S3) (Fig. 1). Several studies reported no differences when auditory N1 ERP was studied in a similar clinical population [19] or in first-relative alcoholic patients [3]. Further, Cohen *et al.* [3] found no differences in N1 amplitude with high-risk and low-risk alcoholic relatives when the interstimulus interval was between 0.5 and 1 s. These authors argued that the lack of significance might be explained by the fact that when S2 is presented in a short interval, many of the neurons would be under the excitability influence of the initial tone entrance (S1). This approach fits well with the one described in the studies of Loveless *et al.* [4] and McEvoy *et al.* [5], where N1 attenuation involved an active inhibitory mechanism of those neural populations that respond to N1. In this line, Sable *et al.* [20] posited that the first tone in each train would cause transient excitation of the N1 generators, resulting in a large N1, and that, later, these activations would spread to neurons that feedback on the N1 generators to inhibit them, which would be accomplished by lateral connections in nonprimary auditory cortex [21].

In agreement with recent findings [11], our results put forward that the inhibited response observed on the N1 suppression phenomena (after S2 and S3 in our case) involved no spectral power modulation but an increase phase-resetting of θ, α and low β EEG bands. The study of neural oscillatory activity underlying specific brain responses in alcoholism has revealed disturbances involved in inhibitory functions [22]. These alterations have been focused in low EEG rhythms such as δ (1–3 Hz) and θ (4–8 Hz). The inability to accurately respond in inhibitory tasks follows the proposal that alcoholics would be engaged in an increased central nervous system hyperexcitability, thus resulting from a reduction in inhibitory-related brain processes [1]. Our results add further support to this view as alcoholic alterations were only observed in brain states where neural inhibition might play an important role, such as in our case of sensory gating. Hence, we argue that differences observed in θ phase-resetting might be well explained by mechanisms of augmented neural excitability in alcoholics as compared with healthy population, thus giving further support to the hypothesis of alcohol-related increased nervous system hyperexcitability [1]. However, our correlation analysis also put forward higher alterations as a function of greater alcohol consumption and therefore not allowing disentangling whether the present alterations could constitute a possible trait-marker of alcoholism as suggested with other θ-related disfunctions [22] or whether this deficit rises up as a consequence of alcohol-related effects on neural activity.

Importantly, the role of oscillatory phase-resetting in brain processing remains unresolved. Evidence from several experiments, however, argues that θ phase-resetting might define excitability windows of phase-locked neurons, which could be used for directing information flow and maintaining activity within neuronal networks [23]. In a similar manner, Klimesch *et al.* [24] suggested that (i) phase-resetting might control the timing of the activation of task-relevant brain areas and (ii) θ oscillations might reflect the excitatory state of task-related brain areas at the time of processing. The enhanced θ phase-resetting responses found in alcoholics' N1 suppression could be well described in terms of excessive information processing within a process that the brain should gather irrelevant information entry. It is interesting to note that David *et al.* [25] showed that phase-resetting could arise from a saturation state of related neural circuitry, supporting high levels of neural activity might be reflected in the scalp in

the form of phase-resetting. Therefore, the increase of phase-resetting in alcoholics compared with control group suggests the neural networks involved in the N1 generation are closer to the saturation/nonlinear domain, showing an abnormal processing behaviour.

Conclusion

The present results indicate that chronic abstinent alcoholics showed alterations on filtering out irrelevant information from the environment at very early stages of information processing. Our results evidenced no differences in ERP measures (i.e. amplitude and latency) between healthy and alcoholics groups, but revealed significant differences in neural synchronization mechanisms underlying N1 generation, specifically at the θ EEG range (4–8 Hz). An interesting approach derived from the present results would be on clear cutting the effects of such synchrony alterations into the neural structures involved in N1 production and its suppression (e.g. [12]).

Acknowledgements

This research was supported by grants of the Generalitat de Catalunya to C.G., A.G., J.M.P., L.F. (SGR2005-00831 and 2004XT-00097) and to C.E. (SGR2005-00953) and the Spanish Government (SEJ2006-13998) to C.G., J.M.P. and L.F.

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