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Auditory sensory gating deficit in abstinent chronic alcoholics

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Abstract

P50 event-related potential was studied in abstinent chronic alcoholics to determine whether they had normal sensory gating. Repeated tones were presented to 17 recently detoxified chronic alcoholic patients and 17 healthy subjects while EEG was recorded. Low-resolution tomography (LORETA) was performed to obtain cerebral sources of P50. Abstinent chronic alcoholics showed reduced P50 sensory gating. Present results suggest an inhibitory deficit in early pre-attentive auditory sensory processing in chronic alcoholism.
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The P50 sensory gating effect refers to the amplitude reduction of the P50 event-related potential to the second stimulus of a pair of identical stimuli delivered in a short inter-stimulus interval [1]. P50 gating is one of the early measurable brain sensory processing stages reflecting screening-out and filtering mechanisms of redundant incoming information, and it is attributed to a neuronal inhibitory process [9]. Sensory gating deficit has been repeatedly found in schizophrenic patients [1,17] and genetically linked to a cholinergic receptor's α7 nicotinic subunit [7]. Several other brain disorders also show decreased P50 gating, such as bipolar disorder [6], cocaine dependency [3,5] and Alzheimer's disease [15]. Though acute ingestion of low doses of alcohol reduced P50 amplitude and sensory gating response [8], there is no clear evidence in the literature of disturbed P50 and P50 gating in chronic alcoholism. In this study we investigated P50 sensory gating in abstinent chronic alcoholic patients. We applied low-resolution tomography (LORETA) [19] to the brain's electrical activity data to search for possible differences in neural substrates involved in P50 sensory gating.

Seventeen outpatients chronic alcoholics (male, mean age 42 ± 9 years) and seventeen age-matched healthy subjects (male, mean age 39 ± 11 years) with no history of psychiatric disorders were studied. Patients suffering from chronic alcoholism were diagnosed through the DSM-IV for alcohol dependency. They all 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). Subjects with previous history of severe organic disease, neurologic or psychiatric disorder or other substance abuse (except tobacco) (DSM-IV) were excluded. To control drug free status during the treatment, periodic follow-up interviews with their clinicians and recurrent urine drug screen analyses were performed. Previous to the neurophysiological study, subjects underwent a breathanalyzer test to ensure that they were free of alcohol. All subjects were free of medication, including disulfiram, for 72 h before the experimental session. After complete description of the study to the subjects, their written informed consent was obtained. There were no differences in age of the two groups ($t_{32} = 0.74$; $p > 0.4$), but there were significant differences in years of education ($t_{32} = 2.94$; $p < 0.01$).

Stimuli and EEG recording characteristics, as in a previous study [11], consisted of groups of three pure sine tones of 700 Hz and 85 dB SPL, administered binaurally through headphones. The first of the three tones of a group was a standard tone with duration of 75 ms ($p = 0.5$) or a deviant

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Table 1
Demographic and clinical data of subjects

Subjects	Age (years)	Education (years)	Maximum alcohol per day (mg)	Alcohol per week (mg)	Abstinence (weeks)
Control	39.6 ± 11.2	11.7 ± 2.4	26 ± 12	85 ± 64	–
Patients	42.4 ± 8.7	8.7 ± 3.3	220 ± 120	1040 ± 640	11 ± 6

tone with duration of 25 ms ($p = 0.5$), whereas the other two tones were standard. The intra-group stimuli interval was 300 ms and the interval between groups was 5 s. A total of 400 trials were administered. Only the two initial stimuli (S1 and S2) of series consisting of standard tones were analyzed. An electroencephalogram (EEG, bandpass 0.1–100 Hz) was recorded at 500 Hz sampling rate by a Synamps amplifier (Neuroscan Inc.) from 30 electrodes on the scalp, following the 10–20 position system (FP1, OZ, FP2, F7, F3, FZ, F4, F8, T3, C3, CZ, C4, T4, T5, P3, PZ, P4, T6) with ten additional electrodes (FC1, FC2, FT3, FT4, M1, M2, IM1, IM2, TP3, TP4, CP1 and CP2). An electro-oculogram was recorded from two electrodes placed at the outer canthus and below the right eye. Epochs exceeding ± 100 μV were automatically rejected. The remaining trials were digitally band-pass filtered (0.1–30 Hz), and corrected for baseline. Results of mismatch negativity event related potential (ERP) with the same subjects and paradigm were described in a previous study [12].

Event-related potentials were obtained by separate averaging of S1 and S2 trials, from 100 ms pre-stimulus to 100 ms post-stimulus. P50 was defined in CZ as the most prominent positive peak between 30 and 70 ms after stimulus presentation. P50 amplitude was determined by the difference in microvolt between the peak and the preceding valley, as described by Adler et al. [1]. One alcoholic patient and one control were removed from the study because no P50 waves were identifiable. P50 amplitudes were compared between groups (control versus alcoholic) and conditions (S1 versus S2) using one-way ANOVA. To obtain sources of activation of ERPs, Low-resolution tomography was applied to the data. LORETA is an EEG tomography method that has proved to be useful in several neurophysiologic and psychiatric studies [18]. LORETA was applied for 10 ms around the P50 peak of each subject. Sources found by LORETA were analyzed statistically using the non-parametric analysis, as in Holmes et al. [14], corrected through multiple comparisons. Sources showing $p < 0.05$ between conditions (S1 versus S2) were accepted as being different in the two stimuli. Three analyses were performed on P50 data, including P50 amplitudes, S2/S1 ratio of P50 amplitude, and source current density values.

In controls, P50 amplitude to S2 was reduced respective to S1 ($F = 4.62$, $p < 0.05$), whereas no significant difference was encountered in the alcoholic group ($F = 0.05$, $p > 0.8$), which reflected disturbed sensory gating responses in patients (see Fig. 1, Tables 2 and 3). When the P50 amplitude elicited by S1 in controls and in alcoholics was compared, there was no difference ($F = 0.47$, $p = 0.50$), although there was a significant difference between the two groups for the P50 elicited by S2 ($F = 10.49$, $p < 0.005$). No differences in latencies of the P50 peak were found between P50 elicited by S1 and by S2 ($F(1,30) = 1.12$, $p > 0.2$ for controls; $F(1,30) = 0.12$, $p > 0.5$ for alcoholics); or between the control and alcoholics groups ($F(1,30) = 1.02$, $p > 0.2$ for S1; $F(1,30) = 2.1$, $p > 0.15$ for S2).

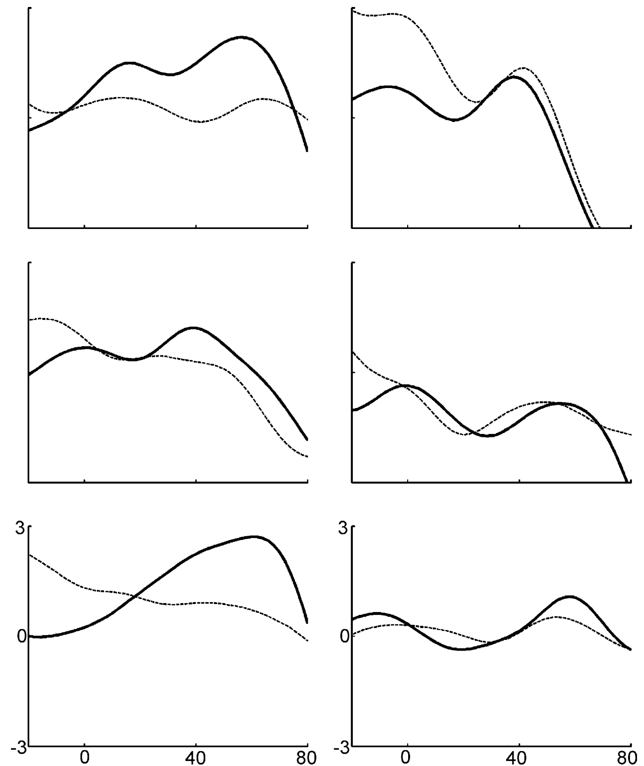

Fig. 1. P50 responses at CZ to S1 (solid and thick) and S2 (dashed and thin) for three control subjects (left) and three alcoholic patients (right). Units of vertical axis are microvolts (μV) and units of horizontal axis are milliseconds (ms).

P50 amplitude ratio (S2/S1) showed a significant difference between controls and alcoholics ($F(1,30) = 4.95$, $p < 0.05$), which reflected reduced sensory gating response

Table 2
P50 amplitudes (μV) and latencies (ms) at CZ electrode

	S1 amplitude	S2 amplitude	Amplitude difference S1 − S2	Amplitude ratio S2/S1	S1 latency	S2 latency
Control	0.68 ± 0.20	0.20 ± 0.10	0.48 ± 0.22	0.30 ± 0.11	54.1 ± 3.1	59.9 ± 4.5
Alcoholic	0.85 ± 0.14	0.80 ± 0.16	0.05 ± 0.12	0.94 ± 0.26	49.6 ± 3.2	51.4 ± 3.8

Table 3
P50 amplitude and latency (comparison between S1 and S2 responses and between control and alcoholic groups)

	F	p
P50 amplitude		
Control	4.62	0.04
Alcoholic	0.05	0.82
Control–alcoholic amplitude comparison		
S1	0.47	0.50
S2	10.49	0.003
P50 latency		
Control	1.12	0.30
Alcoholic	0.12	0.73
Control–alcoholic latency comparison		
S1	1.02	0.32
S2	2.1	0.16

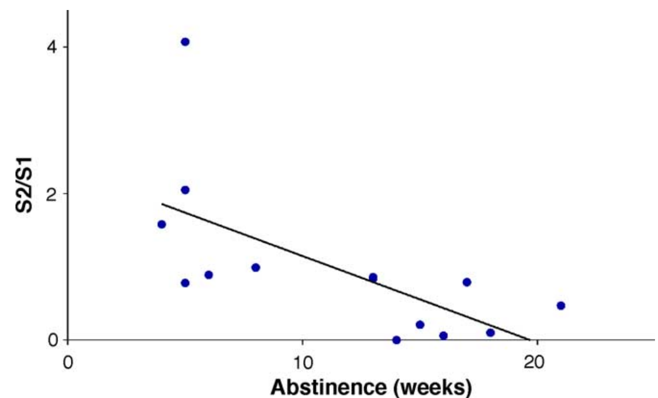

Fig. 3. Correlation between S2/S1 factor and weeks of abstinence of alcoholism for 14 alcoholic subjects ($r = -0.6433$, $p < 0.05$). If subject presenting S2/S1 = 4.07 is considered as an outsider, correlation is enhanced ($r = -0.726$, $p < 0.01$).

in patients. When the S2/S1 ratio was related to clinical and demographic data, auditory sensory gating deficit in alcoholics showed a recovery negatively correlated with the duration of abstinence ($r = -0.6433$, $p < 0.05$, Fig. 3). No other demographic or clinical characteristic of patients (age, years of education, alcohol consumption per week, tobacco consumption per week and previous to experimental session) showed any relation with the P50 parameters.

LORETA showed that sources of P50 to S1 were located in left and right supratemporal areas in both alcoholic and control groups ($p < 0.05$), with an additional contribution of left inferior parietal ($p < 0.05$) in controls. P50 to S2 showed significant sources on both supratemporal areas ($p < 0.05$) and in right inferior frontal in alcoholics, while no activation was found in controls.

P50 source current density activations had significant differences between S1 and S2 in the control group (reduced response to S2) in both temporal and left parietal areas ($p < 0.05$ in all cases) (Fig. 2). In the alcoholic group there was no significant difference for sources of P50 between S1 and S2.

Present P50 amplitude and current density results revealed clear sensory gating in the control group, but not in the alcoholic group. To our knowledge, this is the first study to describe a sensory gating deficit in abstinent chronic alcoholics. Moreover, latency and amplitude of the P50 to S1 seem to be preserved in alcoholics, whereas P50 gating is altered. This suggests that the brain mechanisms underlying these two phenomena are differentially affected in alcoholism.

Our control group results showed P50 sources on temporal and left parietal areas and the involvement of these structures in P50 gating, as suggested in [13]. In alcoholics, we found a common lack of normal reduced response to the second stimulus in reported P50 source areas, suggesting that decreased P50 sensory gating is better explained by a widespread disturbed inhibition phenomenon than by differential effects affecting any of these structures.

An interesting finding in P50 gating research is the heritability of this phenomenon [16,20]. This leads to speculation on the function of genetic factors in the etiology of brain diseases in which P50 gating was disturbed. We cannot be sure whether deficit in P50 sensory gating found in alcoholism antedates the onset of the illness or is due to brain damage related to its evolution. If it antedates the illness, this would add support the hypothesis of an inherited deficit of inhibition in the central nervous system in alcoholics [2]. However, our findings showing partial P50 sensory gating recovery with abstinence suggest that the alteration is, at least to some degree, related to the active course of the disease. In this case,

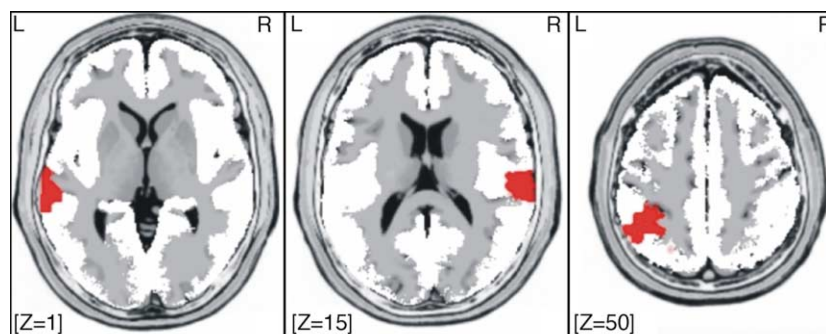

Fig. 2. Source current density for activated structures ($p < 0.05$) in S1 as compared to S2 in control group in axial slices of the Talairach human brain atlas. R: right, L: left. No differences were found between activation by S1 and S2 in the alcoholic group.

P50 sensory gating could be explained by an alcohol induced decrease of $GABA_A$ activity [4] and/or direct interaction with α-7 nicotinic receptor of interneurons [21] that has been argued to mediate the P50 suppression [10].

In summary, present study proposes that there is a deficit in auditory sensory gating in abstinent chronic alcoholics that could be interpreted as a deficit in inhibition sensory processing. Future studies will be necessary to determine the precise neuronal processes underlying this deficit and its consequences for the study of alcoholism.

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