

Middle-latency auditory evoked potentials in children at high risk for alcoholism

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Summary – Purpose. In the course of a high-risk study for alcoholism, the middle-latency auditory evoked potentials (MAEPs) of children of alcoholics were explored. **Material and Methods.** A series of auditory clicks (0.1 ms, 60 dB SL, 1.1/s) were used to record the Pa and Pb peaks of the MAEPs in 15 children of alcoholics with a multigenerational family history of alcoholism, and 17 control subjects, ranging from 10 to 14 years of age. **Results.** The latency of Pb was shorter in the high-risk than in the control group, and there was also a significant risk group by age interaction on Pa latency. The amplitude of Pa was smaller in the children of alcoholics. **Conclusions.** The characteristics of the MAEPs of the high-risk subjects did not match the pattern of abnormalities previously observed in chronic alcoholics, which are supposed to be a consequence of the neurotoxic effects of ethanol. Nonetheless, the results showed significant differences in MAEPs between children of alcoholics and controls, pointing to an anomalous pattern of information transmission from thalamus to cortex that should be further analyzed using larger samples in a broader age range.

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alcoholism / children of alcoholics / event-related potentials / high risk / middle-auditory evoked responses (MAEPs)

Résumé – Potentiels évoqués auditifs de latence moyenne chez les enfants d'alcooliques. Objectifs. Étudier le risque possible d'alcoolisme chez des enfants d'alcooliques par l'enregistrement des potentiels évoqués auditifs de latence moyenne (PEALM). **Matériel et méthodes.** Dans le but d'enregistrer les composantes Pa et Pb, une série de clicks (0.1 ms, 60 dB S.L., 1.1/s) a été délivrée à deux populations d'enfants âgés de 10 à 14 ans : 17 enfants-témoins et 15 enfants faisant partie d'une famille d'alcooliques. **Résultats.** La latence du Pb était raccourcie chez les enfants d'alcooliques. L'amplitude du Pa était plus petite et il y avait une interaction significative âge/groupe sur la latence de ce potentiel chez ces enfants. **Conclusions.** Les PEALM des sujets à haut risque ne présentent pas les mêmes anomalies que celles observées précédemment chez des alcooliques chroniques, qui sont une conséquence des effets neurotoxiques de l'alcool. Cependant, les résultats montrent des différences significatives des PEALM entre les enfants

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d'alcooliques et les enfants contrôles, suggérant une anomalie dans la transmission d'informations du thalamus au cortex. Cette analyse devra être approfondie grâce à des échantillons plus grands et un panel d'âges plus important.
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alcoolisme / enfants d'alcooliques / potentiels évoqués auditifs de latence moyenne (PEALM) / risque

Research into alcoholism has extensively employed psychophysiological and neurophysiological measures with the aim of determining the effects of chronic alcohol abuse on the function of the nervous system and identifying vulnerability markers that could differentiate those subjects liable to develop alcoholism.

The spontaneous EEG activity as well as sensory evoked potentials and cognitive event-related potentials have been used to assess alcoholic patients. In subjects at familial risk for alcoholism, both spontaneous EEG and event-related potentials (mostly P300) have been studied as genetic vulnerability markers, so long as abnormalities observed in abstinent alcoholics are also present in children of alcoholics (for review see [5]). Early evoked potentials (EPs) have been less employed once it was reported that abnormalities affecting auditory brainstem evoked responses in alcoholics were not observable in children of an alcoholic father [6]. The fact that some of the anomalous electrophysiological characteristics first found in chronic alcoholics have been identified in their alcohol-naïve relatives [7, 8, 20, 32, 36] indicates that they are not only a result of the neurotoxic effects of substance abuse, and might be assessed as putative of electrophysiological markers for the development of alcoholism.

Although the EPs' abnormalities have been reported in alcoholics for early [9, 13, 14] and late [13, 15, 31] components in the auditory modality, few studies have assessed the middle-latency auditory evoked potentials (MAEPs) in relation to alcoholism. In a previous study at our laboratory, the Na and Pa components of the MAEPs were assessed in a group of abstinent alcoholics and matched controls [16]. Alcoholics presented shorter latencies of Na and Pa than controls, which were interpreted as the result of a disinhibitory effect of decreased GABAergic activity at the thalamic level, induced by the chronic exposure to alcohol. These results were subsequently confirmed in a study in animals with a long period of chronic ethanol intake [18].

Although the MAEPs' abnormalities were initially attributed to the neurotoxic consequences of alcohol,

both deficits in inhibition and GABAergic function anomalies have been related to genetic vulnerability to alcoholism: deficits in electrophysiological inhibition have been proposed as the cause of abnormalities in other components of event-related potentials, such as P3b and P3a amplitude reductions, both in alcoholics and their children [30, 33]. Autonomic psychophysiological studies also point to problems with inhibition of the information input, indicated by the cardiac hyperreactivity to stressful and novel stimuli [29]. Furthermore, genetic differences in GABA_A receptor function have been proposed as mediating differences in the responsiveness to the sedative and anesthetic effects of alcohol between selective breeding rodents [1, 37]. Then, it was considered of interest to explore these middle-latency responses in children of alcoholic parents when research into high risk for alcoholism was initiated in our group.

To assess the possibility that MAEPs were anomalous in high-risk subjects, the present study assessed a sample of young children of alcoholics with a multigenerational family history of alcoholism and controls.

METHODS AND MATERIALS

Subjects

The subjects were 32 children ranging from 10 to 14 years of age. The high risk (HR) group ($N = 15$, eight females, mean = 12.2 ± 1.5 years) consisted of children of an alcoholic father with a high-density family history of alcoholism. The subjects in the HR group were selected from community treatment centres, where their fathers had been diagnosed and treated. All the alcoholic fathers met DSM-III-R [4] criteria for alcohol dependence (diagnosis made by the staff of the centres was corroborated during the selection interview). Those with a history of psychopathological problems other than secondary to alcoholism (according to the clinical history from the centres and the information collected during the selection interview) were excluded.

The family history of alcoholism was ascertained from fathers and mothers using the family history interview method. Only children of alcoholic fathers who had at least two other first- or second-degree alcoholic relatives were included. The control (CN) group ($N = 17$, ten females, mean = 11.8 ± 1.4 years) consisted of children of non-alcoholic fathers without a family history of alcoholism. To guarantee homogeneity with regard to socio-demographic variables, control subjects were recruited from voluntary families from schools in the region within the same age range and socioeconomic status as those in the HR group. Control families who reported any problems with alcohol in first- or second-degree relatives were excluded.

Other exclusion criteria were similar for the two groups, and included consumption of alcohol or other drugs, a history of psychopathological disorders, prenatal exposure to alcohol, developmental or school retardation, a positive neurological history, major medical problems, current medication, non-corrected sensory deficits, a family history of major mental diseases and problems of alcoholism in the mother. Information about inclusion and exclusion criteria was obtained through detailed semi-structured interviews with both the children and their fathers and mothers. The interviews were a translated and adapted version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), versions for adults, children, adolescents and parents, as well as the Family History Assessment Module, designed by the Collaborative Study on the Genetics of Alcoholism (COGA) [10]. Questions about individual and familial psychopathological problems were based on DSM-III-R criteria and at least one other diagnostic classification system. Information was also obtained during the interviews about demographic data, family relations, school achievement and social activities.

The final sample was well matched on age, socioeconomic status and education (all subjects were enrolled in compulsory schooling and followed the grade according to age) between the groups (*table I*).

Procedure

Families who met requirements for the study were asked to participate; those who agreed signed a consent form, and then received an appointment for the assessment. When children arrived at the laboratory (early in the morning or in the afternoon), the members of staff

Table I. Demographic characteristics of control and high-risk groups.

	<i>Controls</i>	<i>High-Risk</i>	<i>P</i>
	(<i>N</i> = 17)	(<i>N</i> = 15)	
Gender (f/m)	10/7	8/7	
Age (range)	10–14	10–14	
Mean (SD)	11.8 (1.4)	12.2 (1.5)	0.412
Education (years)	6.1 (1.3)	7.0 (1.3)	0.059

f/m : female/male.

showed them the laboratory and explained the contents and procedure of the assessment.

The subjects sat in a comfortable armchair, in an electrically-isolated, sound- and light-attenuated laboratory. They received instructions to avoid moving during the tests and to direct their gaze to a point 1 m in front of their eyes where the stimuli were presented.

The stimuli were 400 rarefaction clicks (0.1 ms duration) generated by the Stim module of a Neuroscan system and presented binaurally at a rate of 1.1/s through earphones, with an intensity 60 dB SL (60 dB above individual perceptual threshold, estimated using the method of ascending and descending limits with variation intervals of 0.75 dB SPL). The experimental paradigm (both stimuli characteristics and recording parameters) was selected to optimize the recordability of both Pa and Pb. Tones are frequently used to obtain the Pb peak, and it has been reported that low-frequency (500 Hz), long-duration (60 ms) tone bursts are optimal to evoke Pb [26]; however, these parameters are not the best for obtaining Pa, due to the long duration of the stimuli, which overlap with the earlier MAEP components. Clicks are the most common stimuli used to record Pa [35]. The inter-stimulus interval was also the result of a trade-off; a higher rate would be adequate to obtain Pa, and it would permit us to use a larger number of stimuli per run; nonetheless, the recordability of Pb would be seriously impaired, due to amplitude decrease with repetition rates higher than 1/s.

Electroencephalographic (EEG) activity was recorded at Cz and Fz (Standard Electrode Position Nomenclature [3, 21]) using tin electrodes, referred to linked earlobes, and with a forehead ground. Additional electrodes were used to monitor eye movements (supraorbital and the outer canthus of the left eye, referred to an infraorbital electrode). EEG activity was filtered (1–300 Hz) and amplified 50 K (Grass Neuro-

data Acquisition System, mod. 12, connected to a Neuro Scan, Inc. system for the analog-to-digital conversion and storage). Impedance values were kept at 5 K Ω or below.

EEG was continuously sampled at a rate of 1500 Hz. The signal was processed off-line: EEG was epoched from 10 ms pre-stimulus to 100 ms post-stimulus, digitally filtered at 10–300 Hz, linear trends were eliminated and the signal was adjusted to 0 mV pre-stimulus baseline and averaged (400 epochs). Moreover, to assess the reproducibility of the waveforms, the first 200 segments were averaged separately from the last 200 segments, and the intra-class correlation between the two traces were performed.

Data analysis

Peak latencies (ms) and amplitudes (μ V) of Pa and Pb at each electrode were measured with a semi-automatic peak detection program. First, a computer algorithm was used to search for the maximum negative peak amplitude for each electrode within the predefined latency window: 25–40 and 50–80 ms for Pa and Pb respectively. Peaks were then verified and adjusted by visual inspection, and those which were doubtful were revised by a second experienced member of the laboratory, blind to the risk status of the subject and the initial peak. Amplitude and latency values were automatically exported to an ASCII file for subsequent analyses.

Preliminary risk group (control, HR) by gender (male, female), and risk group (control, HR) by age (five levels, 10–14 years old) ANOVAs were made for determining the inclusion of gender and age variables in the design. As gender manifested no main effects or interactions in these analyses, both genders were considered jointly. Age showed an interaction with the risk group factor for the Pa latency, then it was considered in the final analysis; this demographic factor had no effects on the other dependent variables, where it was excluded from subsequent analyses.

Then, the data were analyzed using 2×2 mixed-model ANOVAs, with electrode site (Fz, Cz) as a within-subject factor and risk group (control, HR) as between-subjects factor for the amplitudes of Pa and Pb, and the latency of Pb, and using an Electrode (Fz, Cz) by risk group (control, HR) by age (five levels, 10–14-years old) design for the latency of Pa.

RESULTS

Reproducibility of the recordings and peak detectability

The intra-class correlations between the two waveforms obtained from each subject were high both for the control (Cz mean = $.80 \pm .17$, Fz mean = $.87 \pm .12$) and the high risk group (Cz mean = $.82 \pm .17$, Fz mean = $.85 \pm .18$), and similar for the two groups ($t = -0.28$, NS at Cz, and $t = 0.42$, NS at Fz), indicating an adequate similarity between the two segments of the run, and then an adequate reproducibility of the whole waveform.

The rate of detectability of the two main positive MAEP peaks were acceptable in the light of previous reports. Pa was observable in 20 subjects (62.5%, 11 controls and nine HR) and Pb was measurable in 26 subjects (81.2%, 12 controls and 14 HR). Both Pa and Pb jointly were observed in 18 of the 32 subjects (nine controls and nine HR). Four subjects (three controls and one HR) showed a waveform consisting of a broad positive deflection, peaking in the middle between the Pa and the Pb latency windows, and were excluded from the study; this morphology has been described previously [27, 34]. The waveforms recorded from four representative subjects are presented in *figure 1*.

Risk group effects

Figure 2 illustrates the grand averaged EP waveforms for the control and HR subjects where both Pa and Pb were measurable, and the descriptive data are summarized in *table II*. Significant effects affecting the risk group factor were observed for the amplitude of Pa ($F [1, 18] = 9.925$, $P = 0.006$) and the latency of Pb ($F [1, 24] = 4.340$, $P = 0.048$). The amplitude of Pa was smaller and the latency of Pb was shorter in the HR group than in the control group. Risk group and age factors manifested a significant interaction on the latency of Pa ($F [4, 10] = 31.124$, $P = 0.025$), where the age factor also had a significant main effect ($F [4, 10] = 3.652$, $P = 0.044$). This interaction effect is illustrated in *figure 3*, where it can be observed that the latency of Pa tends to diminish with age, and this effect was more prominent in the HR group than in the control group. It must be noted that the regression functions are non-significant, and they are only presented to illustrate the interaction effect. No risk group effects were observed on Pb amplitude. The within-

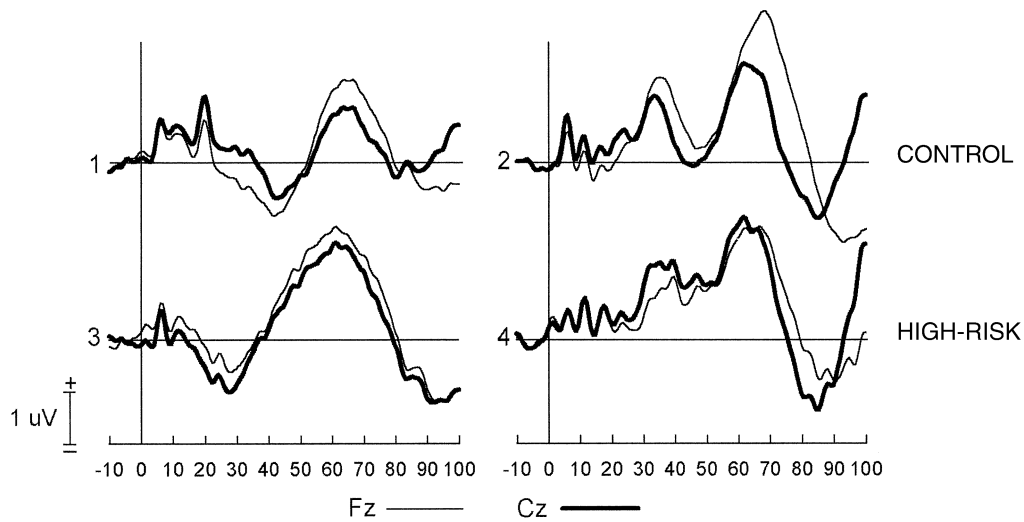


Figure 1. Individual waveforms from four representative subjects, two from the control group (top) and two from the high-risk group (bottom). The left waveforms are representative of those cases where only Pb was identified; the right waveforms represent those cases where both Pa and Pb were identified.

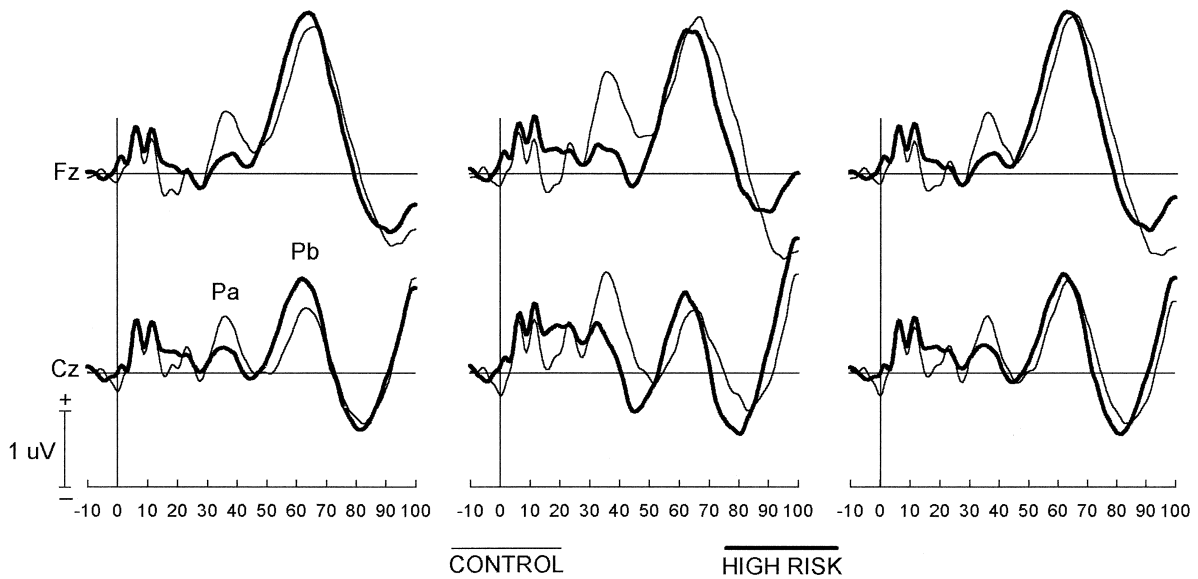


Figure 2. Grand mean waveforms of the MAEPs for the control and the high-risk groups, including the total sample (left), those subjects who entered the Pa ANOVA (center) and those who entered the Pb ANOVA (right).

Table II. Mean (SD) amplitude (μ V) and latency (ms) values for the Pa and Pb peaks at Fz and Cz in the control and high-risk groups.

Control					High-Risk		
		N	Amplitude	Latency	N	Amplitude	Latency
Pa	Fz	11	1.44 (0.53)	36.05 (1.60)	9	0.52 (0.75)	35.31 (3.71)
	Cz	11	1.43 (0.72)	35.67 (1.59)	9	0.65 (0.82)	35.17 (3.78)
Pb	Fz	12	2.36 (0.54)	65.21 (3.83)	14	2.22 (1.41)	62.90 (2.30)
	Cz	12	1.47 (0.63)	65.17 (3.92)	14	1.44 (1.10)	62.36 (2.39)

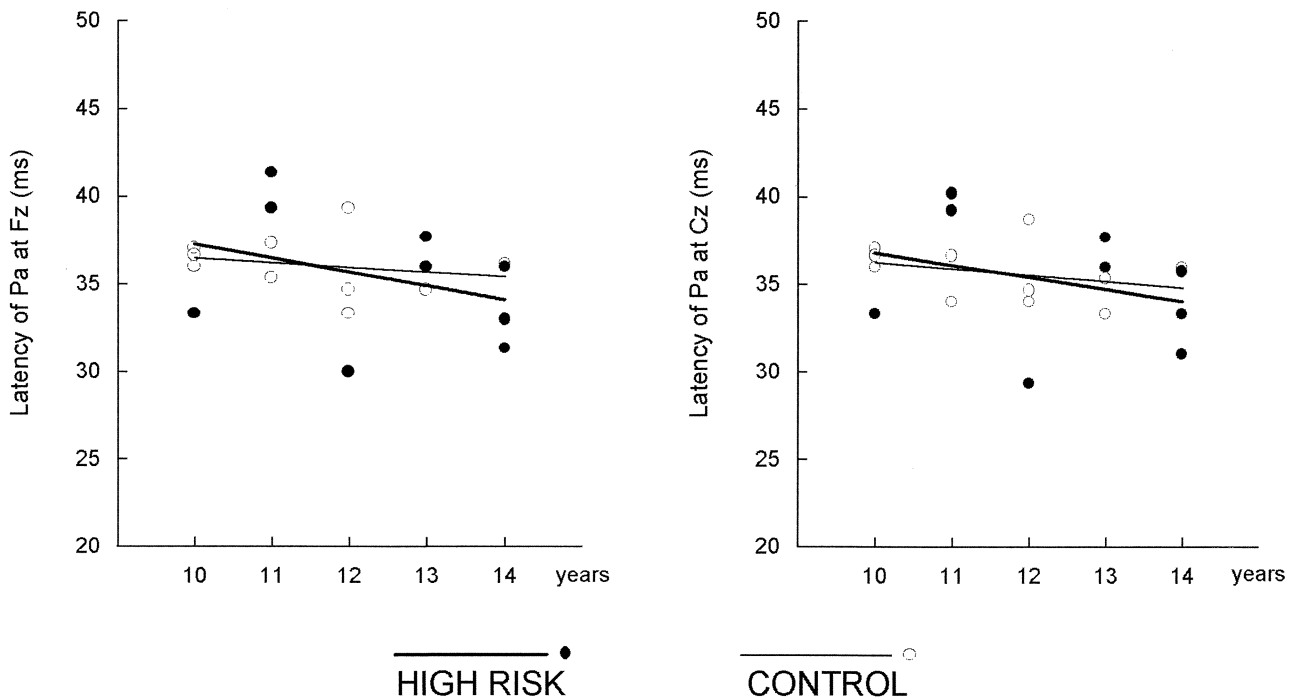


Figure 3. Graph illustration of the interaction effect between groups (control/high-risk) and age on the latency of Pa.

subject factor electrode site was significant for the amplitude of Pb ($F [1, 24] = 23.571, P = 0.000$), and the latency of Pa ($F [1, 10] = 9.915, P = 0.010$) and Pb ($F [1, 24] = 4.870, P = 0.037$).

DISCUSSION

The results of the present study indicate significant differences between children of alcoholics with a multigenerational family of alcoholism and normal controls in the middle-latency auditory evoked response. Both the Pa and Pb peaks showed some kind of risk group effect. The latencies of Pb were shorter for the HR than for the control children, and the latency of Pa manifested a risk group by age interaction. Also, the Pa amplitude appeared significantly smaller in the high-risk group.

The MAEP waveforms showed a good reproducibility, although the complete set of components (Na-Pa-Nb-Pb) was not detected in all the children. Probably the percentage of detectability would have been increased by using a higher number of stimuli; nonetheless, the rate of 62% for Pa and 81% for Pb is in the range of other reports. Kraus et al. stated that Pa detectability was less than 50% under 10 years of age

and 60–100% over 10 [23]; in another study Kraus et al. [24] present their data in a figure showing around 80% detectability in the 10–15-year-old group; Tucker and Ruth [35] report a prevalence of Pa of 90% in 9–12-year-old subjects; Suzuki and Hirabayashi [34] describe that in 8–11-year-old subjects Pa reaches the adult range of latency, and the latter part of the waveform is still similar to that of young children. With regard to Pb, Nelson et al. [26] found a recordable Pb in six out of nine 10–14-year-old children using a stimulation rate of 1.1/s.

The finding of shorter latency of Pb cannot be compared with other studies, because to our knowledge there are no previous reports assessing this MAEP component in alcoholics or high-risk subjects. The neural origin of Pb has been first related to the reticular activating system projections to the thalamic intralaminar nuclei [11, 17], and more recently to cortical generators in the primary auditory cortex [12, 25], with the cortical generators representing probably the main contribution to scalp recordings. Pb amplitude is sensitive to changes in arousal level and it has been related to preattentive gating mechanisms [11, 19, 38]. No basic studies have been focused on the functional

significance of the temporal dynamics of Pb, which would help to interpret the earlier resolution of this peak in high-risk subjects compared to controls.

Pa latency manifested a significant interaction between the risk group factor and age. It is difficult, from these preliminary results, to interpret this interaction and its relation with the familial vulnerability to alcoholism. The shortening of Pa latency is a normal process during development [34, 35], which at this study appeared more pronounced in the high-risk group. This could indicate either a different rhythm of development between the groups, or a progression toward significant shorter Pa latency in the children of alcoholics compared with control population at the end of adolescence. This last possibility would be consistent with the shorter Pb latency in the high-risk group at the present study; it would also be reminiscent of the shorter Na and Pa latencies previously found in both chronic alcoholics [16] and animal models of alcoholism [18], and may indicate the presence of anomalous information transmission along the thalamocortical pathways previous to alcohol abuse. Although robust conclusions are prevented by the small size of the sample, and the limited age range (10–14 years), the results in our opinion warrant continuous investigation focused on this MAEP component.

A second significant difference between the two risk groups concerned the amplitude of Pa. The decreased voltage of this component in the high-risk group was a statistically robust effect and an unexpected finding, inasmuch as abstinent chronic alcoholics have been previously reported to presented slightly enhanced Na-Pa amplitude [16]. Methodological differences between the two studies do not appear to be the cause of this discrepancy. Increases in Pa or Na-Pa amplitudes have been reported in other clinical populations apart from alcoholics, such as Alzheimer patients [28], prefrontal damage [22], and also in normal aging [2], and have been usually related with deficits in inhibitory processes controlling the ascending information from thalamus to cortex. Due to deficits in electrophysiological inhibition, which have been previously proposed in children of alcoholics, a larger Pa amplitude was expected in the high-risk group. These unexpected results, to be taken cautiously pending replication in future studies, may lead one to speculate that alcohol abuse in adults might in part be understood in terms of pharmacological compensation of a previously anomalous neural functioning.

In summary, the results of this preliminary report showed differences between children of alcoholics with a multigenerational family history of alcoholism and controls in the middle-latency evoked responses. The differences appeared in the latency of Pb, the changes in Pa latency with age, and the amplitude of Pa. The characteristics of the MAEPs of the high-risk subjects did not match the pattern of abnormalities previously observed in chronic alcoholics. Nonetheless, the results pointed to the presence of differences between children of alcoholics and controls that might be further analyzed with larger samples covering a wider range of ages.

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