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Mismatch negativity in young children of alcoholics from high-density families¹

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Abstract

The mismatch negativity (MMN) component of event-related potentials was recorded from a group of young children of alcoholics (n = 19, 8 females) with a high-density family history of alcoholism and from a control group (n = 23, 12 females), between 8 and 15 years of age. A dichotic listening task was used, and subjects had to pay attention to an oddball paradigm in one ear and ignore the stimuli in the other ear. The event-related potentials elicited by the standard unattended tones were subtracted from those elicited by the infrequent deviant unattended tones, and the MMN was measured at 10 frontal and central electrodes. No group differences were observed in peak latency, peak amplitude, and mean amplitude of the MMN. These results indicated that preattentive mechanisms of mismatch detection were not impaired in young subjects at high risk for alcoholism. Results are discussed in relation to differences in electrophysiological indexes of automatic versus controlled information processing and in relation to the characteristics of the sample.

Key Words: Event-Related Potentials (ERPs), Mismatch Negativity (MMN), Alcoholism, High Risk, Children of Alcoholics.

Research into family risk for alcoholism using event-related potentials (ERPs) has provided evidence of anomalies in the neurophysiological processing of stimuli in children of alcoholics. Differences between subjects at risk for alcoholism and controls have been reported affecting the P300 (P3b) component elicited by relevant (target) stimuli during focused attention tasks. This positive-going centroparietal wave has been found to be diminished in amplitude in nonaffected children of alcoholics, both young¹⁻⁶ and adult⁷⁻¹⁵. The reduced P300 reported in alcoholics has also been associated more with a family history of alcoholism than to alcohol consumption itself¹⁶,¹⁷. The diminished P300 in subjects at risk for alcoholism has been interpreted as an index of a deficiency in cortical inhibition necessary to limit cortical excitation to task specific areas. This lack of inhibition would underlie a deficit in the ability to compare the incoming stimuli with the template of the nontarget stimuli in working memory, so that each incoming event is evaluated anew¹⁸. Although some other studies have not found differences between high-risk (HR) subjects and controls in P300 amplitude¹⁹⁻²⁸, and some have related the reduction of P300 with the confluence of family history of alcoholism and a history of other psychopathological disorders, such as antisocial personality disorder¹¹,²⁹⁻³¹, reviews of the literature have considered that diminished P300 is a valuable candidate as a phenotypic marker of vulnerability to alcoholism³²,³³. Several factors, such as the sensory modality and difficulty of the task, the age of the

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subjects, the sample selection criteria or the presence/absence of other psychiatric problems in the families, may explain the discrepancies among studies 32,33.

The ERP components related to the processing of infrequent irrelevant events have also been assessed in children of alcoholics in several recent reports. Nontarget infrequent stimuli interspersed in an oddball task elicit a P300 component with a parietocentral distribution in the context of an easy perceptual discrimination task, or a P300 component larger in amplitude and shorter in latency at the central and frontal scalp locations (P3a) in the context of a difficult perceptual discrimination task 34, 35. Using an easy discrimination visual task, nontarget infrequent stimuli elicited a reduced P300 in a sample of young HR subjects (9 to 18 years old) 36. A similar paradigm elicited a delayed latency of the parietocentral P300 in males and a delayed latency of the frontal Ne wave in females, sons, and daughters of alcoholic fathers from 8 to 15 years of age 37. In the context of a difficult perceptual discrimination between target and standard, a well-differentiated infrequent non-target elicited a smaller P3a in a group of adult children of alcoholics (19 to 30 years old) than in the control group at frontal, central, parietal, and temporal electrodes. Therefore, the abnormalities associated with a vulnerability to alcoholism are not limited to the processing of the relevant information.

Another ERP component associated with the processing of infrequent irrelevant stimuli is the mismatch negativity (MMN), obtained when a physically deviant sound occurs in a series of unattended standard auditory stimuli. MMN has been interpreted as an index of the automatic detection of a mismatch between an incoming deviant stimulus and the sensory-memory trace produced by a repetitive unattended stimulus 38. It represents a preattentive mechanism that can act as a switch for attention focus when deviation exceeds a threshold, and is then followed by P3a 39. Evaluation of MMN in subjects at risk for alcoholism may clarify if the electrophysiological abnormalities reported in the controlled processing of infrequent relevant (P3b) and irrelevant (Ne, P3a) attended stimuli are already present in the automatic detection of unattended deviant events.

MMN has been found to be sensitive to the acute effects of alcohol, with low doses of ethanol causing a reduction in MMN amplitude 40-42. It has been hypothesized that the substance only affects the frontal MMN subgenerators, because MMN reduction did not occur at electrodes located over the Silvian fissure 42. With regard to the effect of chronic alcoholism, one study assessed the ERPs elicited by infrequent tones in an unattended oddball paradigm during a reading task in detoxified alcoholics (n = 63), compared with controls 43. The N2 elicited by these infrequent unattended stimuli was used as an index of the automatic mismatch processes, and revealed a decreased amplitude in the alcoholic group. Another report found a delayed rise in MMN in a group of 23 detoxified chronic alcoholics 44.

Two reports have recently assessed MMN in subjects at genetic risk for alcoholism. One compared a sample of 20 children of alcoholics and 20 controls aged between 9 and 18 45. The MMN elicited by a deviant auditory tone during a reading task was measured with the aim of determining if the dysfunction in effortful information processing indicated by P300 reduction in these subjects also affects automatic processing. No differences were observed between groups in the amplitude, latency, and scalp topography of MMN, suggesting that the reported differences in MMN in alcoholics may represent a state marker for alcoholism.
The other study assessed MMN in a group of 16 young adult alcoholics (18 to 26 years old). Based on the hypothesis that subjects at risk for alcoholism present a deficit in cortical inhibition indicated by P300 amplitude anomalies, MMN was measured as an index for the activity of the excitatory glutamatergic system. The MMN elicited by an oddball unattended paradigm during a reading task revealed a greater amplitude in the HR subjects than in the controls. This result supports the hypothesis of an increased neural hyperexcitability in subjects with genetic vulnerability to alcoholism. Therefore, there is no agreement about the presence of deficits in the neurophysiological indexes of automatic processing of information in the auditory modality in subjects with a genetic vulnerability to alcoholism.

To contribute to the clarification of this issue, the present study evaluated the MMN obtained during a dichotic listening task in a sample of young subjects, both males and females, between 8 and 15 years of age. A group composed of children of alcoholics with a positive family history of alcoholism and without other psychopathological disorders in the families was compared with a control group with a negative history of alcoholism and psychopathological disorders.

**METHODS**

**Subjects**

The subjects were 42 males and females ranging from 8 to 15 years of age. The high risk (HR) group (n = 19, 8 females, mean = 11.7 ± 2.1 years) consisted of children of alcoholic fathers with a high-density family history of alcoholism. The subjects in the HR group were selected from community treatment centers, where their fathers had been diagnosed and treated. All of the alcoholic fathers met DSM-III-R criteria for alcohol dependence (diagnosis made by the staff of the centers 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 centers 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 group (n = 23, 12 females, mean = 11.4 ± 2.4 years) consisted of children of nonalcoholic fathers without a family history of alcoholism. To guarantee homogeneity with regard to sociodemographic 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 exclusionary 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, noncorrected 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 semistructured 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", 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) \(^{48}\). 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 1). Subjects from the two groups were randomly distributed across environmental variables, such as the ERPs assessment time (time of day, month), recency of food ingestion, or handeness. \(^{49}\) The presentation order of the tasks was the same for all the subjects.

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

<table>
<thead>
<tr>
<th>Table 1. Demographic Characteristics of Control and HR Groups</th>
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<tbody>
<tr>
<td>Controls (n = 23)</td>
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<td>-------------------</td>
</tr>
<tr>
<td>Gender (f/m)</td>
</tr>
<tr>
<td>Age (range)</td>
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<td>Mean (SD)</td>
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<tr>
<td>Education (years)</td>
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<td>Handedness (R/L/A)</td>
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\(f/m, \text{female/male}; \text{R/L/A, right/left/ambidextrous}\)

\(\chi^2\) comparison

Once electrodes had been put in place, subjects sat in a comfortable armchair, in an electrically isolated, sound- and light-attenuated laboratory. They received general instructions to avoid moving during the tests and to pay attention to the individual instructions before each test. Subjects were tested using several experimental paradigms. This report includes the ERP waveforms recorded during the performance of a dichotic listening task.

The stimuli were pure sine-wave monaural tones of 50 msec (10 msec rise/fall time) generated by the Stirn module of a Neuroscan system and presented dichotically at an intensity of 90 dB SPL through headphones. 1000-Hz standard tones (probability of 0.8) and 1500-Hz deviant tones (probability of 0.2) were randomly presented with an interstimulus interval of 600 ± 100 msec. Two blocks of 400 stimuli (200 to each ear) were presented in two consecutive runs, with a 3-min interblock interval. In each run, subjects were told to pay attention to stimuli in a designated ear and to ignore stimuli in the other, and to press a button with the preferred hand when a deviant tone was
detected among the attended stimuli. In the second run, they had to pay attention to the tones in the other ear. The assignment of each ear when listening was counterbalanced across subjects. A brief training sample was run to ensure acceptable task performance. Response time, correct responses, and false alarms were recorded.

**ERP Recording**

Electroencephalographic (EEG) activity was recorded at 10 scalp sites: Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, and C4 (Standard Electrode Position Nomenclature 50), using tin electrodes inserted in an electrocap (Electro-Cap International, Inc.), 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 (0.1 to 30 Hz) and amplified 10 K (Grass Neurodata 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 KΩ or below.

EEG was continuously sampled at a rate of 256 Hz. The signal was processed off-line: first, EEG was corrected for ocular artifacts, using the algorithm developed by Semlitsch and colleagues 51; then, EEG was epoched from 50 msec prestimulus to 500 msec poststimulus, linear detrends were eliminated, and the signal was adjusted to 0 µV prestimulus baseline. Trials exceeding ±100 µV at any scalp electrode were identified by visual inspection and rejected. The first 10 epochs of each block, epochs corresponding to deviant stimuli preceded by another deviant stimulus, and those corresponding to false alarm responses were also rejected. Finally, trials were averaged according to type of stimuli and attention condition.

**Data Analysis**

To obtain MMN, difference waves were obtained in each subject at each electrode by subtracting the ERPs elicited by the nonattended standards from the ERPs elicited by the nonattended deviants in each ear. Because replicability of the difference waves obtained in the two ears was high in all subjects, the difference waves from the two ears were averaged, and statistical analyses were performed on these averages.

The MMN was determined as the largest amplitude negative peak within a time window from 100 to 250 msec. Peak latencies (msec), peak amplitudes (µV), and mean amplitudes (µV) of MMN at each electrode were measured with a semiautomatic 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; peaks were then verified and adjusted by visual inspection, and those that 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.

The MMN measurements were organized into three electrode groupings: frontal pole and inferior frontal (Fp1, Fp2, F7, F8), medial frontal (F3, F4, Fz), and central (C3, C4, Cz). Preliminary Risk Group by Gender and Risk Group by Age analyses were made for determining the inclusion of gender and age variables in the design. Because there were no significant interactions in these analyses, both genders were considered
jointly, and age was included as a covariate. Therefore, a Risk Group by Electrode mixed-model analysis of covariance (ANCOVA), with the Risk Group as between-subjects factor, the Electrode as within-subject factor, and Age as a covariate were used to assess group differences in the MMN peak latency, peak amplitude, and mean amplitude in each of the electrode groupings. Degrees of freedom were corrected by the conservative Greenhouse-Geisser estimate when appropriate. The behavioral data (response time, percentage of correct responses, and false alarms) were assessed using an ANCOVA comparison between the risk groups with age as a covariate.

RESULTS

Behavioral Performance

Table 2 summarizes the behavioral data for each group. No significant differences between the risk groups were observed for response time, percentage of correct responses, and percentage of false alarms ($p > 0.05$).

| Table 2. Behavioral Data for Control and HR Groups |
|---------------------------------|---------------------------------|
| Controls (n = 23) | HR (n = 19) |
| Mean | SD | Mean | SD | $p$ |
| Response time (msec) | 510 | 76.9 | 499 | 91.5 | 0.799 |
| % Correct | 70.5 | 20.7 | 69.1 | 16.3 | 0.542 |
| % False alarms | 1.4 | 3.7 | 2.9 | 5.6 | 0.284 |

ERP Measurements

Figure 1 illustrates the grand mean of the difference waves (deviant minus standard) for the control and HR groups. The difference waves were clearly negative at all the electrodes in the latency range of MMN (100 to 250 msec), due to the more negative ERPs elicited by deviant than standard unattended stimuli. The frontocentral distribution of the MMN usually reported in the literature was corroborated at this study, where the two groups manifested larger amplitudes in the medial frontal and medial central electrodes than in the frontal pole and inferior frontal electrodes. The descriptive statistics of the data are summarized in Table 3.

The mixed-model ANCOVAs of the MMN parameters for the unattended condition demonstrated no significant differences between the two risk groups at any region for the peak latency [pole-inferior frontal: $F(1,39) = 2.95, p > 0.094$; medial frontal: $F(1,39) = 1.02, p > 0.320$; central: $F(1,39) = 2.02, p > 0.163$], peak amplitude [pole-inferior frontal: $F(1,39) = 0.58, p > 0.450$; medial frontal: $F(1,39) = 0.08, p > 0.778$; central: $F(1,39) = 0.56, p > 0.457$], and mean amplitude [pole-inferior frontal: $F(1,39) = 0.02, p > 0.894$; medial frontal: $F(1,39) = 0.55, p > 0.465$; central $F(1,39) = 0.97, p > 0.332$]. There were also no significant ($p > 0.05$) Risk Group by Electrode interactions. Individual ANCOVAs at each electrode confirmed the absence of significant group differences at any location.
Fig. 1. Grand mean waveforms of the MMN for the control (n = 23) and HR (n = 19) groups.

Table 3. Mean MMN Peak Latency (msec), Peak Amplitude (µV), and Mean Amplitude (µV) within a Latency Window of 100-250 msec in the Control and HR

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 23)</th>
<th>HR (n = 19)</th>
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<tbody>
<tr>
<td></td>
<td>Peak latency</td>
<td>Peak amplitude</td>
</tr>
<tr>
<td></td>
<td>Mean  SD</td>
<td>Mean SD</td>
</tr>
<tr>
<td>Fp1</td>
<td>168.64 23.64</td>
<td>-2.89 2.85</td>
</tr>
<tr>
<td>Fp2</td>
<td>168.30 23.46</td>
<td>-3.06 2.23</td>
</tr>
<tr>
<td>F7</td>
<td>170.40 25.64</td>
<td>-1.71 3.65</td>
</tr>
<tr>
<td>F8</td>
<td>171.69 21.18</td>
<td>-3.29 2.39</td>
</tr>
<tr>
<td>F3</td>
<td>172.28 24.33</td>
<td>-5.45 2.97</td>
</tr>
<tr>
<td>F4</td>
<td>169.88 22.36</td>
<td>-5.39 2.25</td>
</tr>
<tr>
<td>Fz</td>
<td>175.50 27.26</td>
<td>-5.72 2.75</td>
</tr>
<tr>
<td>C3</td>
<td>167.34 28.30</td>
<td>-5.00 3.49</td>
</tr>
<tr>
<td>C4</td>
<td>166.92 23.41</td>
<td>-4.69 3.06</td>
</tr>
<tr>
<td>Cz</td>
<td>170.25 22.35</td>
<td>-5.17 3.23</td>
</tr>
</tbody>
</table>
DISCUSSION

The comparison between a group of subjects with a multigenerational family history of alcoholism and a control group indicated that there were no differences between the groups for MMN peak latency, peak amplitude, and mean amplitude. These results were in agreement with those previously found in a sample of young HR subjects and did not coincide with those reporting arger MMN amplitude in adult children of alcoholics.

These results indicated that preattentive mechanisms of mismatch detection that have been found to be sensitive to the acute and chronic effects of alcohol were not impaired in nonaffected genetically vulnerable subjects. Previous reports have found that HR subjects manifest anomalies in ERP components related to controlled attention and discrimination processes, such as P300 and the Late Positive Complex, or N400, and even in those related to the switch of attention focus on intrusive events in the attended channel. However, there was no evidence of abnormal values in several electrophysiological indexes of automatic processing of sensory input, either in specifically designed studies (auditory brainstem potentials) or evaluated in the course of the P3 studies referred to previously (N1, P2). The present report evaluating MMN supports the conclusion that the differences between children of alcoholics and controls do not appear in the automatic processing of auditory information.

Because abnormal MMN amplitude in HR subjects has been found in one laboratory the origin of the different results should be briefly discussed. The studies differed in the age range of the samples (adults versus children), but this does not seem to be the key to the discrepant results: MMN appears early in ontogenetic development and presents similar values from 6 or 7 years of age to adulthood. Furthermore, preliminary analyses of the interactions between risk group and age in the MMN parameters at the present study discarded a progressive appearance of differences during development in the age range assessed. A more important difference between the present sample and that assessed by Zhang and colleagues could be the psychopathological background of alcoholic families. In the present investigation, not only an individual but also a family history of psychiatric disorders were exclusionary criteria. Moreover, the presence of psychopathological traits other than alcoholism was small in all of the sample interviewed (50 alcoholic families). Abnormal ERP values have been associated not only with familial vulnerability to alcoholism, but also with the concurrence of other psychopathological disorders. The absence of this psychopathological background could be the reason for the absence of abnormalities in MMN in subjects with a family history of alcoholism found in this research.

In summary, the present study indicated that electrical brain activity associated with preattentive detection of a deviant stimulus reflected in MMN is not altered in a sample of young children of alcoholics with a high family density of alcoholism and an absence of other psychopathological traits.
ACKNOWLEDGMENTS

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29. Hesselbrock VM, Bauer LO, O'Connor S, Gillen R: Reduced P300 amplitude in relation to family history of alcoholism and antisocial personality disorder among young men at risk for alcoholism. Alcohol Alcohol 2(Suppl.):95-100, 1993


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