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Mismatch Negativity: No Difference Between Treatment Naïve Alcoholics and Controls

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Abstract

Background—A number of studies have examined the mismatch negativity (MMN) evoked potential as a measure of a brain inhibitory deficit in alcoholics or those at risk for alcoholism. The current study examined MMN in actively drinking treatment naïve alcohol dependent individuals. This study examined the association of MMN with risk factors for alcoholism, with post-alcohol withdrawal hyper-excitability, and with alcohol use variables.

Methods—Electroencephalograms were gathered on 84 subjects (42 controls, 42 treatment naïve alcohol dependent individuals) during a non-attending MMN experiment. Alcoholism family history density, the number of externalizing disorder symptoms, and psychological indices of deviance proneness served as measures of risk factors associated with the vulnerability to alcoholism. Alcohol use variables were used as measures of alcoholism severity.

Results—There were no differences in the MMN integral, amplitude, or latency between control and treatment naïve alcohol dependent subjects. There also were no significant associations of MMN measures with any of the measures of alcoholism vulnerability, with any of the alcohol use variables, or with the prevalence or severity of symptoms of post-alcohol withdrawal hyper-excitability.

Conclusions—While there is a strong association between alcohol abuse and symptoms of disinhibition and deviance proneness, the Mismatch Negativity response does not offer any direct physiological evidence of this phenomenon.

Keywords

Mismatch negativity; alcoholism; EEG; family history density; externalizing symptoms

Introduction

There have been a number of recent studies indicating that the brains of alcoholics process stimuli differently than those of non-alcoholics. This has been demonstrated in the areas of target detection, (Polich et al., 1994), orienting (Fein et al., 1995), aspects of inhibitory function (Ahveninen et al., 2000), response to reward and punishment (Bechara et al., 2001; Lejoyeux et al., 1998; Lejoyeux et al., 1999), and behavioral disinhibition (LeMarquand et al., 1999). These differences may be a consequence of the alcohol use itself, or they may reflect differences in biological vulnerabilities that predispose an individual to the risk of alcoholism (Begleiter et al., 1984). Predisposition to alcoholism has been linked to a number of factors that include

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a positive family history of alcoholism, the presence of conduct disorder and antisocial personality disorder, and the presence of disinhibited personality traits (Chassin et al., 1999a; Chassin et al., 1999b; Finn et al., 2002; Finn et al., 2000). Furthermore, current theories propose that disinhibition is a fundamental mediator of the inherited predisposition toward alcohol dependency (Begleiter and Porjesz, 1999; Cloninger, 1987; Sher et al., 1991; Tartar et al., 1985). Much of the data suggest that early onset alcoholism is not a unique problem, but is related to a cluster of disinhibited traits. It has been proposed that behavioral phenomena such as psychopathy, antisocial and impulsive traits, and alcoholism, should be viewed as variable expressions of a generalized disinhibitory complex (Gorenstein and Newman, 1980).

The Mismatch Negativity (MMN) is a pre-attentive brain response to changes in auditory stimulation, and has been proposed in recent studies as a measure of the brain inhibitory deficit associated with alcoholism or the vulnerability to alcoholism (Kathmann et al., 1995; Zhang et al., 2001). Lack of inhibition, or even disinhibition, is thought to be reflected by an increase in MMN amplitudes seen in individuals who are at a high risk for alcoholism (Zhang et al., 2001). If increased MMN amplitude is associated with alcoholism and/or a predisposition to alcoholism, then it should be present in treatment naïve alcohol dependent individuals, and it should co-vary with the factors that may predispose an individual to alcoholism, such as positive family history of alcoholism, symptoms of conduct and antisocial personality disorder, and disinhibited personality traits (Finn et al., 2002).

We recently published a study (Fein et al., 2004) on long-term abstinent alcoholics that examined the effects of prior alcohol abuse, abstinence duration, and alcoholism family history density on MMN measures. The MMN amplitude was assessed in adult, long-term abstinent alcoholics, and non-alcoholic controls (N = 76). The study found that MMN measures were not associated with alcohol use, familial alcoholism vulnerability, externalizing symptom counts (antisocial personality and conduct disorder), or psychological measures of deviance proneness (psychopathic deviance, socialization). That study, however, left open the question of the effects on the Mismatch Negativity measures of both active alcohol abuse and of alcohol withdrawal associated CNS hyper-excitability (Ahveninen et al., 2000; Alling et al., 1982).

The current study examines Mismatch Negativity in actively drinking, treatment naïve alcoholic dependent individuals compared to light-to-non-drinking controls. The study addresses the effects on MMN of active abusive drinking, alcoholism vulnerability (including deviance proneness and the presence and history of externalizing symptoms), and post-withdrawal hyper-excitability.

Materials and Methods

Participants

A total of 84 participants were recruited from the San Francisco Bay area via postings of community-based flyers, advertisements on an Internet site, and referrals from participants. The treatment naïve alcohol dependent sample (TxN) was recruited by advertising for 'heavy social drinkers' or 'men and women who have a high tolerance for alcohol'. Inclusion criteria for the TxN group was that they currently meet DSM-IV-R (American Psychiatric Association, 2000) criteria for alcohol dependence and that they never have sought treatment. In fact, none of the TxN subjects labeled themselves as alcoholic and we never use the word alcoholism in our advertisements or in their assessment procedures. This was done so as not to deter possible participants from entering the study. Almost by definition, treatment naïve alcohol dependent individuals are in denial about their alcohol problems, and we did not want to directly confront that denial and risk creating a hostile environment. However, when a subject did acknowledge their problems with alcohol and ask for help, information was always provide as to where that individual may best receive possible treatment (including a referral to Alcoholics Anonymous).

The study sample consisted of 42 TxN subjects (23 males and 19 females) and gender and age matched controls (C). Table 1 presents subject demographics, alcoholism family history density, alcohol use variables, the number of externalizing disorder symptoms and two personality measures of deviance proneness. Inclusion criteria for the control group was a lifetime drinking average of less than 30 alcohol-containing drinks per month, having never exceeded 60 drinks per month.

Assessment—A computerized version of the Diagnostic Interview Schedule (DIS) (Robins, 1998) was used to establish psychiatric and substance abuse diagnoses. Exclusion criteria for both groups were: i) history or presence of and Axis I diagnosis on the DIS; ii) history of drug dependence other than nicotine; iii) significant history of head trauma or cranial surgery; iv) history of diabetes, stroke, hypertension, or other significant neurological diseases which required medical intervention; v) laboratory evidence of hepatic disease; vi) clinical evidence of Wernicke-Korsakoff syndrome; or vii) current substance abuse other than alcohol (aside from caffeine or nicotine).

Procedures

All participants were informed of the study's procedures and signed a consent form prior to their participation. All of the procedures performed during the experiments had received approval from the Institutional Review Board. There were a total of four sessions that varied in length from one to three hours. The sessions involved clinical, neuropsychological, electrophysiological, and neuroimaging assessment. The clinical interview included a review of the participant's medical history and a detailed assessment of the individual's alcohol-use history, including a history of withdrawal symptoms. After the first day, all participants got a blood draw to exclude individuals with hepatic disease. The electroencephalogram (EEG) studies took place on the third visit. This paper examines only the Mismatch Negativity Experiment in conjunction with measures of the density of the family history of alcoholism, externalizing symptom counts, deviance proneness measures, and alcohol use variables. All subjects were asked to abstain from drinking alcohol 24 hours prior to each session, and a breathalyzer was administered preceding each session in order to ensure their compliance with that request. A breathalyzer score of 0.000 was required in order to continue with the session, and no individuals in this study failed the breathalyzer test. All of the participants received monetary compensation for their time and travel expenses, as well as a completion bonus after finishing the entire study.

Measures

Alcohol Use Variables—Alcohol use variables were defined based on the subject's responses to the lifetime drinking history questionnaire (Sobell et al., 1988), which was designed to capture relevant features of consumption behavior. A standard drink was defined as 12 ounces of beer, 1.5 ounces of liquor, or 5 ounces of wine. Alcohol lifetime duration was defined as the total number of months in which the subject was actively drinking. Lifetime average dose was defined as the average number of standard drinks per month. The peak use variables indicated maximum levels of consumption. Peak dose was defined as the maximum monthly consumption of standard alcohol drinks, and the peak duration was the total number of months (possibly discontinuous) that a participant engaged in this peak use. Separate lifetime use histories, using the same methodology as the lifetime drinking history, were gathered for all other drugs (except caffeine and nicotine) used more than experimentally in order to determine whether a subject met inclusion/exclusion criteria.

Familial Alcoholism-Risk—The Family Drinking History Questionnaire, which was based on the Family Tree Questionnaire (Mann et al., 1985), assessed the density of the participants' family history of alcoholism. The Family Drinking History Questionnaire was scored, and

assignment into Family History positive and Family History negative groups were determined according to the methods presented by Stoltenburg (Stoltenberg et al., 1998) for Family History Density (FHD). Biological parents that were identified by the participant as problem drinkers were given a score of 0.50. Grandparents that were identified as problem drinkers were given a score of 0.25; all other relatives were not included in the final score. The highest FHD score possible is 2, and the lowest is 0. Participants who scored 0.50 and above were placed in the family history (FH) positive group, those scoring below 0.50 were placed in the FH negative group.

Withdrawal Symptoms—Post-alcohol withdrawal hyper-excitability (PAWH) was measured using a self-report questionnaire where subjects ($n=30$) estimated (on a 0 to 10 point scale) the frequency and distress caused by physical and psychological symptoms experienced during alcohol withdrawal. For the frequency estimate, a 0 meant never, 1 corresponded to 10 % of the times one ceased drinking, up to a 10 which indicated symptom was experienced 100% of the time one ceased drinking. For the degree of distress caused by the presence of the symptom, a 0 meant not at all distressing, a score of 5 meant somewhat distressing, and a 10 meant “unbearable.” The symptoms were compiled from the Diagnostic Interview Schedule (DIS) (Robins, 1998), the alcohol dependence scale (Skinner and Allen, 1982), and SSAGA interviews (Bucholz et al., 1994). We computed the average frequency and intensity over the following eight symptoms (for TxN group only) that measure PAWH: i) shakes (hands tremble, shake inside); ii) feel tense, nervous or anxious; iii) feel fidgety or restless; iv) have trouble concentrating v) heart pound or beat rapidly; vi) feel hypersensitive to stimuli (e.g. light, sound, touch); vii) have difficulty sleeping; and viii) have memory problems.

Disinhibitory Symptoms and Traits—Externalizing disorder symptoms were measured by a total count of the symptoms for conduct disorder (CD) and antisocial personality (ASP) from the DIS (Robins, 1998). Personality traits of deviance proneness were assessed with the Psychopathic Deviance (Pd) Scale of the MMPI-2 (Hathaway, 1989), and the Socialization Scale of the California Psychological Inventory (CPI). These measures have been consistently associated with alcoholism-risk and behavioral disinhibition (Finn et al., 2002; Finn et al., 2000).

EEG/MMN Measures—The EEG was gathered on the participants’ third visit to the lab. The participant was seated in a small, sound-attenuated room containing a computer monitor, a response box, EEG amplifier, and other relevant lab equipment. Over time the lab progressed from 40-channel to 64-channel EEG recordings. Data were gathered either using the NuAmp 40-channel single-ended amplifier system or the SynAmps2 64-channel single-ended amplifier system (both manufactured by Neuroscan, Inc.). Ground was positioned 4 cm above the nasion for participants with the 40-channel cap, and 8 cm above the nasion for those with the 64-channel cap. All of the recordings were referenced to the right ear. The analysis reported here is restricted to the AFZ, FZ, FCZ, and CZ channels, which were recorded for all subjects. Electrodes were placed above and below the left eye in order to monitor blinks and eye movements. The NuAmps amplifier had a fixed input range of ± 130 mV with 22-bit resolution, and a resolution of $0.062 \mu\text{V}$. The SynAmps2 amplifier had an input range of ± 333 mV with 24-bit resolution, and a resolution of $0.040 \mu\text{V}$. Recordings did not begin until all impedances were less than 10 kOhms. Eleven EEG experiments were performed, with Mismatch Negativity (MMN) being the eighth experiment (approximately 50 minutes from the onset of the experiments).

Mismatch Negativity—For the first 38 participants ($\text{TxN} = 11$, $\text{C} = 27$), the Mismatch experiment involved the presentation of 400 stimuli: 350 standard tones, and 50 mismatch tones, with the mismatch tone presented pseudo-randomly on one-eighth of the trials. We then

increased the number of stimuli for the last 46 participants ($TxN = 31$, $C = 15$) to 500 stimuli (440 standard tones, and 60 mismatch tones). The stimuli had a duration of 100 msec, with a 600 msec delay between the stimuli, and a stimulus intensity level of 60dB. Subjects were randomized as to whether the mismatch tone was the low (500 Hz) or the high (2000Hz) frequency tone. Prior to starting the experiment the participant was asked to choose something to read from a collection of books and magazines in the lab. As the subject became focused on the reading, the technician started the experiment. All data reduction (filtering, epoching, artifact rejection) was performed offline.

All stimuli were presented using E-Prime (Psychology Software Tools, Inc.). The EEG data was acquired using Scan 4.2 (Neuroscan, Inc.) for the participants run on the NuAmps system, and Scan 4.3 (Neuroscan, Inc.) for the participants run on the SynAmps2 system. E-prime and Scan were run on two separate computers. The two computer systems were connected in a way that for each stimulus the E-Prime computer sent out an appropriate signal (between 4 and 5 msec after the stimulus event) to the Scan computer, indicating the type of stimulus so that the information could be integrated into the continuous data recording on the Scan computer. The timing of the E-Prime computer/Scan computer interface was verified using an oscilloscope and 4 msec were subtracted for all Scan timings so that events were accurate to within one msec.

Data Analysis

The continuous raw data were processed offline using the Edit software in Scan 4.3 (Neuroscan, Inc.). The first step in processing the data involved computing the vertical eye movement channel by taking the difference between the recordings above versus below the left eye. This was only needed for the 40-channel recordings, as the 64-channel system had a number of high-level differential inputs on which the vertical left eye movement was directly recorded. The files were then epoched from 100 msec before to 496 msec after the stimulus events. Epochs with eye movements or blinks exceeding $\pm 75 \mu V$ were excluded. Only subjects with 30 or more artifact free mismatch epochs were included in the final analysis. The data were then bandpass filtered from 0.5 to 15 Hz (at 48dB per octave, zero phase shift). Average mismatch and standard responses were computed, as was the difference between the mismatch and the standard. The area under the curve of the mismatch minus the standard response was then integrated from 100 to 192 msec as the measure of MMN. The amplitude and latency of the MMN was measured from the trough of the MMN difference wave. The MMN measurements follow the methods used by Zhang (Zhang et al., 2001). The analysis presented below was restricted to AFz, Fz, FCz, and Cz recordings. The data were analyzed using the Statistical Analysis System (SAS). The amplitude, latency and area data were analyzed by Analysis of Covariance, which was carried out using the General Linear Model procedure implemented in SAS, with group, gender and interaction effects included. The data were analyzed both without baseline correction and after correcting for the baseline recorded from the 100 msec pre-stimulus. The association of the MMN measures with alcoholism risk factors and alcohol use variables were analyzed using Spearman correlations within and across groups. Spearman correlations were also used to analyze the association between MMN measures and post-alcohol withdrawal hyper-excitability.

Results

The treatment naïve (TxN) sample had a trend toward greater alcoholism family history density than controls ($F_{1,80} = 3.64$, $p = 0.06$). The TxN sample differed significantly from the C sample on the CPI Socialization Scale, the MMPI-Pd scale, and the number of externalizing disorder symptoms. Group membership accounted for 21.7% of the variance on the CPI socialization scale ($F_{1,80} = 22.49$, $p < .0001$), with no gender or group by gender effects. The MMPI-Pd

scale also yielded a significant group membership effect accounting for 8.8% of the variance ($F_{1,80} = 7.79$, $p < 0.01$), with no gender or group by gender effects. There were significant group and gender effects for the externalizing disorder symptom counts, with group membership accounting for 9.4% of the variance ($F_{1,80} = 9.18$, $p < 0.01$), and gender accounting for 8.1% of the variance ($F_{1,80} = 7.88$, $p < 0.01$). Additionally, gender accounted for 5.9% of the variance of average lifetime drinking dose ($F_{1,80} = 19.8$, $p < 0.0001$) and 6.3% of the variance of peak drinking dose ($F_{1,80} = 16.59$, $p = 0.0001$).

Figure 1 presents the baseline corrected group average mismatch and standard responses at AFz, Fz, FCz and Cz, along with the MMN integrals. It illustrates a strong MMN component at all electrodes for both groups. Analysis of Covariance (ANCOVA) did not reveal any significant MMN group, gender or group by gender interaction effects for latency, amplitude, or area at AFz, Fz, FCz, or Cz (for both the baseline corrected and non-baseline corrected data). For both baseline corrected and non-baseline corrected data, group accounted for less than 0.8% of the variance at each electrode site (all p 's > 0.40).

No significant Spearman correlations were observed within or across groups of MMN area (integral) with Family History Density (FHD) scores, the number of externalizing symptoms, deviance proneness personality scores, or alcohol use variables. Figure 2 presents the raw data showing no group difference in MMN integrated amplitude and illustrates the lack of association between FH status and MMN integrated amplitude. We also examined the association between MMN area and the average frequency and intensity of the eight symptoms of post-alcohol withdrawal hyper-excitability. The analysis was limited to the TxN subjects who had completed the questionnaire that quantified their withdrawal symptoms ($n=30$). The questionnaire used a zero-to-ten-point scale, and the average frequency across all of withdrawal symptoms was 3.3 with a standard deviation of 1.8 and an average intensity of 4.2 with a standard deviation of 1.7. Thus, on average subjects experienced withdrawal symptoms 33% of the time that they ceased drinking and on average the symptoms distressed them 'somewhat' (corresponding to a rating of 4). There were no significant correlations, suggesting that post-alcohol withdrawal hyper-excitability did not affect MMN area (all $|r$'s < 0.11 , p 's > 0.58 for frequency, and all $|r$'s < 0.25 , p 's > 0.21 for intensity).

Discussion

The Mismatch Negativity paradigm used in this, and in our prior paper (Fein et al., 2004) was very similar to that of Zhang's (Zhang et al., 2001), which detected an increased MMN response in individuals at a high risk for alcoholism. In the prior study, a strong MMN response was observed, but it did not differ between groups. The goal of the current study was to extend our prior results to address MMN differences in active alcoholics and in the presence of post-alcohol withdrawal hyper-excitability. We did not find any MMN differences in our active alcoholics compared to age and gender-matched controls, nor did we find any association of the MMN response with indices of the frequency or severity of post-alcohol withdrawal hyper-excitability. The MMN responses we observed in this paper not only mirror those of our last paper, but also look quite similar to MMN responses observed by others (Jaaskelainen et al., 1996; Zhang et al., 2001).

We acknowledge that there are slight differences between the MMN paradigm we used and that use by Zhang (Zhang et al., 2001). The largest difference was in the reference used; Zhang (Zhang et al., 2001) used a nasion reference, while we used a right earlobe reference. Other minor differences exist in the exact stimulus characteristics used, online vs. offline artifact rejection and input impedances. Regarding the choice of reference, we note that the right earlobe or right mastoid has been used in many of the MMN alcoholism studies, and that the MMN responses look comparable across studies. Moreover, we contend that if the difference

in findings between our studies and Zhang's are a result of the slight differences in methodology and hardware that, in itself, is evidence that the association of MMN amplitude with alcoholism is not robust.

While the treatment naïve group exhibited a trend toward a greater family history density of alcoholism than controls, our sample had less of a family history of alcoholism loading than either our earlier study (Fein et al., 2004), or Zhang's (Zhang et al., 2001) study. However, we did not find any significant correlation between the MMN area and family history density, which fails to support the hypothesis that the MMN is a marker for the predisposition to alcoholism.

In our prior paper, in long-term abstinent, treated alcoholics, we found a strong group difference between alcoholics and controls in deviance proneness, and in externalizing symptoms. In the current study, the groups differ on these measures, but not as strongly as they did in the prior study. We believe this was due to the greater severity of alcoholism in the treated vs. treatment naïve samples (Fein and Landman, in press). Nonetheless, in both studies we fail to find any association between MMN measures and measures of deviance proneness or externalizing symptoms. While there is a strong association between alcohol abuse and symptoms of disinhibition and deviance proneness, the Mismatch Negativity response does not offer any direct physiological evidence of this phenomenon. Thus, the findings presented in this paper and our previous paper (Fein et al., 2004) brings into question the degree that Mismatch Negativity indicates disinhibition in alcoholics.

We acknowledge that our studies do not close the door on any association of MMN amplitude with alcoholism. Both of our studies excluded individuals with a lifetime diagnosis of Antisocial Personality Disorder or Conduct Disorder. It is possible that MMN is abnormal in alcoholics with much more severe externalizing symptoms or deviance proneness than was the subject of our studies. Moreover, our sampling did not select for individuals who were experiencing severe withdrawal from alcohol; thus, we cannot say that post-withdrawal hyper-excitability is not associated with an increased MMN response when that withdrawal is more severe. However, while our sample might not demonstrate the entire range of alcoholism severity and co-morbidity, we believe that our sample is more representative of alcoholics in the general population, since only about 10% of individuals meeting criteria for alcohol dependence or abuse ever seek treatment (Grant, 1994).

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Figure 1. Group average ERP responses to the standard (dashed lines) and mismatch stimuli (solid lines). Data have been baseline corrected for activity from the 100 ms pre-stimulus interval. The group average MMN integrals from 100 – 190 ms are displayed as the filled in areas between the standard and mismatch curves. No group difference was observed at any of the electrodes (all p 's > 0.40)

Figure 2.

Scatter plots of the MMN integrals for the baseline corrected data. Within each group, family history positive subjects are represented by triangles, and family history negative subjects are represented by circles. The averages for each group are represented by horizontal lines. The figure illustrates that the MMN integral does not differ between the subject groups or between family history positive and family history negative subjects (all p 's > 0.12).

Table 1**Characteristics of Participant Groups**

Variable	Tx Naïve		Control		Effect Size (%)		
	Male (n=23)	Female (n=19)	Male (n=23)	Female (n=19)	Group	Sex	Group-Sex
Age (years)	33.2 ± 8.7	30.0 ± 6.7	33.1 ± 8.6	30.1 ± 3.7	0.0	3.8	0.0
Years Education	16.4 ± 1.6	16.1 ± 1.2	16.1 ± 2.4	16.5 ± 1.2	0.0	0.0	1.2
Family History Density Score	0.36 ± 0.40	0.63 ± 0.54	0.29 ± 0.37	0.32 ± 0.41	4.1	2.8	2.0
Alcohol Use Variables							
Duration of Active Drinking (mos)	210.2 ± 107.9	176.7 ± 80.8	150.1 ± 104.3	125.9 ± 99.7	7.5 ^a	2.0	0.0
Average Lifetime Drinking Dose (std. Drinks/mos)	99.3 ± 38.1	58.5 ± 21.1	8.5 ± 8.3	4.7 ± 4.0	66.0 ^a	5.9 ^{***}	4.1 ^a
Duration of Peak Drinking (mos)	61.8 ± 61.3	59.5 ± 56.5	87.4 ± 127.6	32.3 ± 23.3	0.0	3.2	2.3
Peak Drinking Dose (std. drinks/mo)	170 ± 73.3	98.3 ± 40.4	19.7 ± 18.1	12.4 ± 10.2	59.4 ^a	6.3 ^{***}	4.1 ^a
Deviance Proneness Personality Measures							
California Psychological Inventory - Socialization Scale	32.3 ± 5.1	31.5 ± 5.8	36.3 ± 4.1	37.7 ± 4.3	21.7 ^{***}	0.0	1.1
Minnesota Multiphasic Personality Inventory - Pd Scale	21.2 ± 5.8	21.4 ± 5.1	17.7 ± 3.1	19.2 ± 4.6	8.8 ^{**}	0.7	0.5
^b Externalizing Sx (#)	12.6 ± 8.0	7.4 ± 7.4	7.2 ± 6.8	4.2 ± 3.0	9.4 ^{**}	8.1 ^{**}	0.6

Measures are reported mean ± standard deviation.

* Effect is significance: $p \leq 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$

^a significance levels for group comparisons of alcohol use variables are not valid since alcohol use was part of the group selection criteria.

^b Sum of antisocial personality disorder and conduct disorder symptoms from the DIS