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N4 component responses to pre-pulse startle stimuli in young adults: relationship to alcohol dependence

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Abstract

Both physiological and behavioral studies provide evidence to suggest that deficits in frontal cortical control circuits may contribute to the risk for developing alcohol dependence. Event-related potential (ERP) and eye blink responses to startle and short delay prepulse-plus-startle stimuli, and psychiatric diagnoses were investigated in young adult (age 18-30 yrs) men (n=135) and women (n=205) Mexican Americans. Women displayed a significant increase in the amplitude of the eye blink response to both the startle and pre-pulse-plus-startle stimuli. None of the psychiatric diagnoses were associated with differences in eye blink responses. ERP responses to the startle and prepulse-plus startle stimuli included a negative polarity wave at approximately 400ms that was of the highest amplitude in the frontal leads (N4S). Women were found to have significantly higher amplitude N4S responses than men. Participants with alcohol dependence demonstrated significantly less inhibition and more facilitation of the N4S component by the pre-pulse stimuli. This finding was not associated with a diagnosis of: any other drug dependence disorder (including nicotine), anxiety or affective disorder, or conduct/antisocial personality disorder. The present study suggests that gender and a lifetime diagnosis of alcohol dependence may selectively contribute to this frontal late wave electrophysiological response to prepulse-plus-startle stimuli.

Keywords

Alcohol Dependence; ERPs; N400; frontal disinhibition; Prepulse Inhibition; Startle; Mexican Americans

1. Introduction

The identification of neurophysiological markers associated with psychiatric disorders in general and alcohol dependence in particular may help in determining the causal relationship between clinical phenomena associated with the disorder and basic molecular processes. Electrophysiological studies of individuals with alcohol dependence and subjects with a family history of alcoholism have demonstrated that deficits in a number of event-related potential (ERPs) components, with robust findings observed for late positivities (300-450

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msec) (this literature is very large and there are a number of excellent reviews, see Begleiter and Porjesz, 1999, Porjesz and Begleiter, 2003, Porjesz et al., 2005, Campanella et al., 2009]) and more recently late negativities (300-650 msec) as well (see Roopesh et al., 2009, 2010).

Another psychophysiological measure that has been used to assess risk for and the consequences of alcohol use is the acoustic startle reflex (ASR) and prepulse inhibition of the startle (PPI). The startle reflex is actually a constellation of responses usually indexed by eye blink responses in humans but also by electrophysiological recordings from cortical areas (see Swerdlow et al., 1992, Ford et al., 1999). Prepulse inhibition of the startle (PPI) refers to the fact that if a weak stimulus is presented 30-500 msec prior to the presentation of the startle stimuli (prepulse) the behavioral response to the startle will generally be reduced in amplitude. It has been suggested that prepulse inhibition is an index of automatic sensorimotor gating (Geyer and Swerdlow, 2001). Whereas, prepulse facilitation (PPF) refers to the phenomena whereby the behavioral response to the startle is enhanced by weak stimuli (prepulses) presented at very short (less than 20 msec) or long (more that 500 ms) intervals prior to the startle stimuli. PPF has been suggested to reflect a combination of alerting, attention and/ or arousal (see Filion et al., 1998; Ludewig et al., 2003, Hsieh et al., 2006). The neuroanatomical substrates of the behavioral response to ASR/PPI/PPF have been extensively investigated in both humans and animals (see Swerdlow et al., 1994; Braff et al., 2001a, 2001b; Kumari et al., 2005). While most studies have focused on describing brain stem and midbrain contributions to the behavioral response to startle stimuli (see Fendt et al., 2001) it is clear that it involves a complex neural network extending from brainstem nuclei via the thalamus to higher order cortical areas that may regulate cognitive responses to startle (Schall et al., 1999, Fendt et al., 2001; Kumari et al., 2005; Campbell et al., 2007; Neuner et al., 2010). There is some evidence that the cognitive response to ASR/PPI may share a common underlying neurophysiology with some behavioral and clinical measures of cognition that require response inhibition (See Filion et al., 1999). For instance, both performance on the Wisconsin Card Sorting Task and PPI of startle have been suggested to reflect prefrontal cortical function and dysfunction (see Filion et al., 1999, Swerdlow and Geyer 1999).

Startle stimuli not only elicit a behavioral response but also generate a series of electrophysiological responses that can be averaged from the EEG and may be useful in the understanding of the cognitive responses to startle stimuli and its potential relationship to alcohol dependence. A number of studies have described startle ERP paradigms in humans that have been reported to generate N1, P2 and P3 and late wave components using scalp electrodes (see Roth et al., 1982, 1984; Putnam and Roth, 1990; Ford et al., 1999; Ornitz et al., 2001). Most studies have focused on the P300 component of the startle elicited ERP. The amplitude of the P300 startle ERP has been demonstrated to respond to both PPI and PPF, task determinants, as well as allocation of attention, changes in arousal, and emotional context. (see Roth et al., 1982,1984; Putnam and Roth 1987, 1990; Ford and Pfefferbaum, 1991; Suguwara et al., 1994; Hirano et al 1996; Schupp et.al., 1997, Cuthbert et al., 1998; Ornitz et al., 2001). The neural generators of the P300 to startling noises are not entirely known. It has been suggested that the neural circuits involved in blink responses to startle are different from those that generate the cortical ERP responses (Schupp et al., 1997; Ford et al., 1999). In addition, P300s generated by startle also appear to have different neural substrates than P300s elicited by standard auditory oddball targets (Ford et al., 1994). ERP responses to oddball targets have been suggested to arise from the temporal-parietal junction (Knight et al., 1989; Menon et al., 1997), whereas; it has been suggested that startle P300's most likely involve more frontal cortical structures (Ford et al., 1994,1999). Other ERP responses to startle include a negative-going late wave response (slow wave) in the 360-600 ms range that has been described in young normal controls (Putnam and Roth, 1990). This

late wave response, was found to be maximal in frontal areas and was also found to show the greatest enhancement in amplitude due to changes in task requirements in that study (Putnam and Roth, 1990). This negativity may be an important index of cognitive responses to startle stimuli involving frontal cortical areas, however, it has not been extensively studied, especially in relation to psychiatric diagnosis.

Impairments in frontal lobe function and associated behaviors such as impulsivity and executive functioning have long been important theoretical constructs in the understanding of alcohol dependence (see Pfefferbaum et al., 1997; Begleiter and Porjesz, 1999; Crews and Boettinger, 2009; Campanella et al., 2009; Field et al., 2010). Behavioral responses (eye blinks) to a number of startle paradigms have been shown to be altered in patients with alcohol dependence. Increases in startle magnitudes have been observed during early withdrawal and abstinence (see Krystal et al., 1997; Saladin et al., 2002). Attenuated startle responses have also been observed in abstinent alcoholics when startle stimuli were associated with alcohol-related stimuli (Grusser et al., 2002). Additionally, reduced eye blink responses to startle stimuli associated with unpleasant stimuli has been seen in alcoholics with antisocial personality disorder (ASPD) (Miranda et al., 2003). Modulation of the startle by alcohol- associated cues has also been linked with relapse to drinking in alcohol dependent patients in treatment (Loeber et al., 2007).

Startle paradigms have also been incorporated into studies evaluating risk for alcohol dependence by evaluating offspring of alcohol dependent individuals. In one study, startle potentiation to negative stimuli was not found in participants with a family history of alcohol dependence as compared to individuals without such a family history (Miranda et al., 2002). In another study, responses to PPI but not to startle were found to be impaired in children with a parental history of alcohol dependence as compared to children of normal controls (Grillion et al., 1997). These two studies suggest that behavioral responses to some aspects of startle may represent a pre-existing or trait variable associated with risk for alcohol dependence. However, ERP studies that may index more of the cognitive responses to startle paradigms have not been recorded in participants with either a personal or family history of alcohol dependence, or other psychiatric disorders that are co-morbid with alcohol dependence.

The present investigation sought to explore the use of a startle paradigm, that uses startle and short delay prepulse-plus-startle stimuli, that elicit a large frontal negative slow wave. The study extends our initial studies of background EEG variants, and P300 ERP responses to facial expressions, in a population of young adult Mexican Americans at high risk for the development of alcoholism (see Criado and Ehlers, 2007; Ehlers and Phillips, 2007). The present study evaluated several new hypotheses. First, we sought to describe late wave frontal ERP component responses (designated the N4S) to startle and prepulse/startle stimuli in this population and determine if they differed by sex. Secondly, we evaluated whether the late wave N4S component to startle and prepulse/startle were altered as a function of the diagnosis of alcohol dependence and/or a family history of alcohol dependence. Thirdly, we also assessed whether any potential changes in N4S were seen in disorders previously found to be co-morbid with alcohol dependence in this population: antisocial personality disorder/ conduct disorder (ASPD/CD) and affective/anxiety disorders (ANYAXAF) and other drug dependence (Gilder et al., 2007).

2. Materials and methods

2.1. Participants

Participants were recruited using a commercial mailing list that provided the addresses of individuals with Hispanic surnames in 11 zip codes in San Diego County that were

identified as having a population that was over 20% Hispanic heritage and were within 25 miles of the research site. The mailed invitation stated that potential participants must be of Mexican American heritage, be between the ages of 18 and 30 years, be residing in the United States legally, and be able to read and write in English. Potential participants were requested to phone research staff for more information. During the phone interview potential participants were screened for the presence of the inclusion criteria as listed above and printed on the mailed invitation, and were excluded it they were: pregnant or nursing, currently had a major medical or neurological disorder, or a head injury that might bias the ERP testing. Participants were asked to refrain from alcohol or any other substance use for 24 hours prior to testing. On the test day, after a complete description of the study to the participants, written informed consent was obtained using a protocol approved by The Institutional Review Board of The Scripps Research Institute.

2.2. Psychiatric diagnoses

Each participant completed an interview with the face-to-face Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994), which was used to make substance use and other psychiatric disorder diagnoses according to DSM-III-R criteria. The SSAGA is a fully structured, polydiagnostic psychiatric interview that has undergone both reliability and validity testing (Bucholz et al., 1994; Hesselbrock et al., 1999). Family history of alcohol dependence was assessed using the Family History Assessment Module (FHAM) (Rice et al., 1995). Participants were eliminated from the current data analyses if they were taking psychoactive medication that may affect the ERP or had a positive breath-analyzer test on the day of the evaluation. Lifetime history of alcohol dependence, other drug dependence (marijuana, stimulants, sedatives, hallucinogens, opiods, nicotine), antisocial personality disorder/conduct disorder (ASPD/CD), major depressive disorder with impairment, and “any anxiety disorder” (social phobia, agoraphobia, panic disorder or obsessive compulsive disorder) in this population were defined by DSM-III-R criteria.

2.3. Startle ERP collection and analyses

Recordings were obtained from participants who were seated on a hospital bed in a sound-attenuated room. Acoustic startle stimuli were presented binaurally through headphones. The behavioral response to the startle (eye blink) is recorded using electrodes placed below and lateral to the eye as described by Braff et al. (2001b). The auditory stimuli consist of 45 trials. These trials include randomly presented startle stimuli (115 dB white noise burst for 40 msec n=30) and prepulse-startle stimuli (85 dB white noise burst for 20 msec-duration) immediately (<5 msec) followed by the startle (115 dB white noise burst for 40 msec n=15). Each individual startle and/or prepulse startle trial is separated by an interval of 15 seconds. Background white noise was presented for the entire session at a level of 60 dB. The behavioral variables assessed included: ASR magnitude on startle trials and prepulse trials as determined by quantification of the eye blink response as described below.

Seven channels of ERP data (FZ, CZ, PZ, F3, F4, F7, and F8, referenced to linked ear lobes with a forehead ground, international 10-20 system) were obtained using gold-plated electrodes with impedance held below 5 KΩ. Frontal electrodes were emphasized in the montage as previous data had suggested that ERP decrements in frontal areas distinguished subjects with a risk for alcohol dependence (see Bauer, 1997). An electrode placed left lateral infraorbitally and reference to the left earlobe was used to monitor both horizontal and vertical eye movements. ERP signals were amplified (time constant 0.3 s, 35 Hz low pass) using a Nihon Kohden EEG machine and were transferred on-line to a PC. The combined gain of the EEG amplifiers and the analog-to-digital multiplexer amplifier was 50K.

The eye blink and ERP trials were simultaneously digitized at a rate of 256 Hz (bandwidth 0.5-35 Hz). Individual trials where the EEG or eye blink exceeded ±250 microvolts (<5% of the trials) were eliminated before averaging. The N4S component of the ERP was quantified using a computerized peak detection routine that identifies baseline-to-peak amplitudes (in μV) within the specified latency window (350-500 msec). The eye blink amplitude was also assessed using this routine. The latency window for the eye blink was 50-120 msec. The baseline was determined by averaging the 150 ms of pre-stimulus activity obtained for each trial. The routine is user-driven and each peak detection must be verified by the user. All peaks were quantified by one investigator, and verified by a second investigator, both of whom were blind to participants' characteristics.

2.4. Data analysis

Data analyses focused on the three specific aims: (1) to describe late wave frontal ERP component responses (designated the N4S) to startle and prepulse/startle stimuli and determine if they differed by sex; (2) to evaluate whether the eye blink and/or N4S component responses to startle and prepulse/startle were altered as a function of the diagnosis of alcohol dependence and/or a family history of alcohol dependence; (3), to asses whether N4S responses were altered in other conditions typically co-morbid with alcohol dependence (e.g. antisocial personality disorder/conduct disorder (ASPD/CD) and affective/anxiety disorders (ANYAXAF) and other drug dependence).

To reduce the number of independent analyses performed on inter-related N4S data and to reduce the overall probability of Type 1 error, a principal component analysis (PCA) was performed. These analyses have been used previously in a number of different ethnic populations (see Bauer and Hesselbrock 1999a, 1999b, 2001, 2003; Ehlers et al., 2001). The N4S amplitudes for the seven electrode locations for the startle and prepulse startle stimuli were entered into the PCA. For each of the stimuli, varimax rotation yielded two components. The electrode sites loading on the first factor for the startle alone stimuli were: the frontal leads (FZ, F3, F4, F7, F8) (loadings= .861, .847, .882, .712, .844), and on the second factor for the startle alone stimuli were the two more posterior leads (CZ, PZ) (loadings= .790, .930). The percent of the variance explained by the first factor was 53% and the second factor was 30% for a total of 83% of the variance of the N4S amplitude to the startle explained by this model. The PCA for the prepulse plus startle stimuli revealed that the electrode sites loading on the first factor were: the frontal leads (FZ, F3, F4, F7, F8) (loadings= .853, .857, .870, .745, .823), and on the second factor for the prepulse plus startle stimuli were the two more posterior leads (CZ, PZ) (loadings= .779, .927). The percent of the variance explained by the first factor was 53% and the second factor was 30% for a total of 83% of the variance of the N4S amplitude to the prepulse plus startle being explained by this model.

N4S amplitudes were averaged across the electrode sites within each of the two identified components 1 = (FZ, F3, F4, F7, F8), 2 = (CZ, PZ) generating a mean for each of the two regions. These regionally averaged scores were generated for each stimulus condition (startle, prepulse-startle), generating mean amplitudes for each of the two component regions for each stimulus category for each individual. These regionally averaged N4S amplitudes were used as dependent variables.

In order to test hypothesis 1, the eye blink and regionally averaged N4S amplitude responses to startle and prepulse/startle stimuli were compared between men and women using ANOVA. To test hypothesis 2, eye blink and regionally averaged N4S component responses to startle and prepulse/startle were compared between those participants with a lifetime diagnosis of alcohol dependence and those without this diagnosis using ANCOVA (co-varying for sex). In a second set of analysis, eye blink and regionally averaged N4S

component responses to startle and prepulse/startle were compared in participants with and without a first degree family history of alcohol dependence. These analyses were accomplished in a subset of the population that had no lifetime diagnoses of: alcohol dependence, antisocial personality disorder/conduct disorder (ASPD/CD), affective/anxiety disorders (ANYAXAF) or other drug dependence using ANCOVA (co-varing for sex). To test hypothesis 3, eye blink and regionally averaged N4S component responses to startle and prepulse/startle were compared between those participants with and without other psychiatric disorders commonly co-morbid with alcohol dependence: antisocial personality disorder/conduct disorder (ASPD/CD), affective/anxiety disorders (ANYAXAF) and other drug dependence using ANCOVA (co-varing for sex). Statistical significance was set at the 0.05 probability level.

3. Results

3.1. Descriptive data and sex differences in eye blink and N4S responses to startle and prepulse plus startle stimuli

Demographic data on the 340 participants with valid ERP data are presented in table 1. The sample contained more women participants (n=205, 60%) than men (n=135, 40%). Lifetime DSM-III-R alcohol dependence was found in 33% (n=44) of the men and 22% (n=45) of the women. Of those participants with lifetime alcohol dependence 28% (n=25) had three dependence symptoms in the last month. A first degree family history of alcohol dependence was found in 40% (n=135) of the population. Nine percent of the females (n=18) and 17% (n=23) of the males were diagnosed with conduct disorder or conduct/ASPD. Thirty two percent of the females (n=65) and twenty-four percent of the males (n=32) were found to have a lifetime diagnosis of affective and/or anxiety disorder. Thirty-eight percent of the men (n=51) and 30 percent of the women (n=61) had a diagnosis of another drug disorder (nicotine, cannabis, hallucinogens, stimulants, sedatives, opioids). As previously described, alcohol dependence was significantly co-morbid with: other drug dependencies, ASPD/CD, anxiety and affective disorders (see Gilder et al., 2007).

In this study, the presentation of auditory stimuli in the form of startle and short delay pre-pulse plus startle tones produced a robust eye blink response. Mean values for the eye blink response are presented in table 1. As predicted, using a short delay prepulse, low levels of prepulse inhibition were seen using this paradigm. This startle paradigm also produced a series of waves that could be averaged from the EEG as seen in figure 1. A series of small waves (< 7 microvolts) occurred between 10 and 100 ms in all three leads. These waves were followed by a large (10-20 microvolts) negative going wave (N1) that occurred at around 120 milliseconds in the frontal areas and at 105 milliseconds in the centro-pariental areas, that was of highest amplitude in the central leads. The N1 potential was followed by a large positive going wave (15-25 milliseconds) that occurred between 200 and 300 milliseconds and was of highest amplitude in central leads. This was followed by a negative wave that peaked at 400 milliseconds that occurred earlier and at higher amplitude in frontal areas. The late 400 millisecond wave (N4S) is the subject of this investigation.

When these N4S responses were compared in the entire population between men and women significant sex differences emerged as also seen in figure 1. Women were found to have significantly higher amplitude N4S responses to the startle (Frontal: $F=11.36$; $df=1,339$; $p<0.001$, Centro-parietal: $F=8.5$; $df=1,339$; $p<0.004$) and pre-pulse startle (Frontal: $F= 6.5$; $df=1,339$; $p<0.01$, Centro-parietal: $F=5.2$; $df=1,339$; $p<0.02$) stimuli. Women also displayed an increase in the eye blink response to startle ($F=9.5$; $df=1,339$; $p<0.002$) and pre-pulse startle stimuli ($F=11.9$; $df=1,339$; $p<0.001$).

3.2. Associations of eye blink and N4S responses to startle and prepulse plus startle stimuli in Mexican American young adults with alcohol dependence, family history of alcohol dependence, and co-morbid diagnoses

N4S amplitudes were also evaluated in the frontal and centro-parietal leads in this population (n=340), as a function of alcohol dependence. Multivariate ANOVA, that co-varied for sex, revealed that those participants with a lifetime DSM-III-R diagnosis of alcohol dependence had significantly increased amplitude N4S responses to the prepulse/startle stimuli as compared to those participants with no alcohol dependence diagnoses, in the frontal areas, as seen in figures 2 and 3 ($F= 4.28$; $df=1,339$; $p<0.04$). Multivariate ANOVA also revealed no significant associations between ASPD/CD, AXAF, or OTHER DRUG diagnoses, and N4S amplitudes (data not shown). There was no significant association between a family history of alcohol dependence and N4S amplitudes although there was a trend in the same direction as that found for alcohol dependence, more pre-pulse facilitation to startle stimuli in frontal areas in family history positive participants($F=1.77$; $df=1,339$; $p<0.19$) (data not shown). There were no significant associations found between eye blink response to the startle or pre-pulse plus startle and alcohol dependence, family history of alcohol dependence or any of the co-morbid diagnoses.

4. Discussion

In the present study a startle plus short delay (<5 ms) prepulse plus startle paradigm was used to generate behavioral (eye blink) and ERP responses to the stimuli. Short delay long duration prepulses have been demonstrated to produce prepulse facilitation (PPF) in some paradigms (Hsieh et al., 2006). The present study used short delay and short duration prepulses, and this combination did not produce significant PPF or PPI in eye blink responses in this study. It has been suggested that eye blink responses may be highly sensitive to differences in a number of parameters of the startle stimuli including background noise, prepulse duration, frequency and interval. Additionally, it has been further suggested that differences in these parameters may explain failures to replicate associations between psychiatric diagnoses and eyeblink responses to the startle in some studies (see Hsieh et al., 2006). This was likely the case in the present study where eye blink responses were not found to be associated with any of the psychiatric diagnoses investigated.

Using the startle plus short delay (<5 ms) prepulse plus startle paradigm the present study did confirm previous studies that described an ERP component, in the 360-600 ms range, that could be elicited by startle/prepulse startle stimuli (Putnam and Roth, 1990). A late negative component in the 400ms range, designated the N4S was identified in the present study. It has been suggested that the neural circuits involved in blink responses to startle are different from those involved in the cortical ERP responses (Schupp et al., 1997; Ford et al., 1999). The N4S identified in the present study was found to be of the highest amplitude in the frontal areas perhaps suggesting that it may be a reflection of frontal cortical involvement in cognitive responses to startle stimuli.

The present study also extends previous studies by uncovering a series of relationships between the amplitude of this N4S ERP component, sex and alcohol dependence. In this study women displayed higher eye blink responses and also higher N4S amplitude responses to both the startle and pre-pulse startle stimuli. These data confirm our previous data analyses in a subset of the present population demonstrating that women had higher P450 amplitude responses in a facial expression recognition task using affective stimuli (happy and sad faces) than men (Criado and Ehlers, 2007). Taken together these data could be interpreted as either a greater electrophysiological response to emotional stimuli in women or a less intense response to emotional stimuli in men. Greater ERP responses to emotional

stimuli in women have been reported in a number of populations. For instance, higher amplitude and longer latency P450 responses were found to happy and sad faces in women as compared to men using a facial discrimination paradigm (Orozco and Ehlers, 1998). In another study using facial expressions as stimuli, the N2b component was found to be delayed in men in response to happy stimuli as compared to fearful ones (Campanella et al., 2004). Larger P450 ERP components to negative emotional images in women as compared to men have also been reported (Yuan et al., 2009). These data also confirm what has been reported previously for simple oddball tasks (see Hoffman and Polich, 1999) where women were found overall to have higher amplitude P350 and P450 ERP components than men. However, gender effects on behavioral responses to startle have been inconsistent with some studies finding no effects of sex (Ludewig et al., 2003), and others finding that women show less PPI compared with men (Aasen et al., 2005; Kumari et al., 2008). In the present study, although overall amplitudes were different between men and women, the difference between the amplitude of the startle compared to the prepulse/startle was not different between men and women in either the N4S or the eye blink data.

The present study also evaluated whether a relationship existed between the N4S startle ERP response and a diagnosis of alcohol dependence and other co-morbid disorders. Data from a number of electrophysiological and behavioral genetics studies have converged on the idea that substance dependence and antisocial behavioral disorders comprise a spectrum that may have common risk factors (Begleiter and Porjesz, 1999; Waldman and Slutske, 2000; Iacono et al., 2003; Button et al., 2005; Du et al., 2006; Patrick et al., 2006). There is also ample evidence supporting an association between low P3 amplitude and these externalizing disorders (Bauer et al., 1994; Bauer, 1997; Bauer and Hesselbrock, 1999a, 1999b, 2003; Costa et al., 2000; Iacono et al., 2002, 2003; Kamarajan et al., 2005, 2006). Our previous studies in a subset of the present population found that a personal history of ASPD/CD was associated with significant reductions in P450 amplitudes; specifically to happy faces in frontal and centro-parietal areas and only in men, not in women. In the present study, although a facilitation of the N4S by prepulse stimuli was found in those participants with a lifetime diagnosis of alcohol dependence, a lifetime diagnosis of ASPD/CD was not associated with changes in the N4S response to the startle or pre-pulse stimuli. Therefore the N4S facilitation found associated with alcohol dependence in the present study does not appear to be a generalized marker of externalizing diagnoses.

It is not known whether the N4S facilitation of startle responses following pre-pulse stimuli seen in alcohol dependent participants in the present study is an endophenotype associated with alcohol dependence or represents a marker of alcohol exposure. Behavioral responses to startle are known to be impacted by both risk for alcoholism and chronic ethanol exposure in humans and animal models (Grillon et al., 1997; Krystal et al., 1997; Grusser et al., 2002; Saladin et al., 2002; Miranda et al., 2002, 2003; Chester et al., 2004; Zimmermann et al., 2004; Loeber et al., 2007). Generally behavioral responses to startle are decreased following ethanol administration or consumption humans (Hutchison et al., 1997, 2003; Grillon et al., 2000; Saladin et al., 2002; Zimmermann et al., 2004; Moberg and Curtin, 2009) and in rodents (Pohorecky et al., 1976; Rassnick et al., 1992; Sandbak et al., 2000; Slawecki et al., 2006).

However, during the early phases of ethanol withdrawal, ASR is increased in human alcoholics (Krystal et al., 1997) and in rats previously treated with alcohol and then withdrawn (Pohorecky et al., 1976; Rassnick et al., 1992; Macey et al., 1996; Vandergriff et al., 2000; Chester et al., 2004). It has been suggested the enhanced acoustic startle response (ASR) during the early phases of withdrawal is an index of increased anxiety (Gulinello et al., 2003; Harris and Gewirtz, 2004). As such, assessment of the startle response may provide an index of persistent anxiety-like behavior following ethanol exposure. No

significant associations were found between the presence of anxiety or affective disorders and the eye blink or N4S response to the startle in the present study. However, it is possible that the facilitation of the N4S response to pre-pulse startle stimuli could represent a marker of subclinical anxiety from alcohol exposure in the alcohol dependent participants.

Both startle and PPI has been demonstrated to be impaired in children with a parental history of alcoholism (Grillon et al., 1997, 2000; Miranda et al., 2002; Zimmermann et al., 2004). Decreases in the eye blink responses to startle or pre-pulse startle were not found to be associated with a personal or family history of alcohol dependence in the present study. However, the present study used a different set of eliciting stimuli than previous investigations in that a short delay between prepulse and the startle stimulus was employed. However, in the present study, a trend was found for an association between facilitation of the N4S response to pre-pulse startle stimuli and a family history of alcohol dependence. Thus it is not clear at this time whether the facilitation of startle responses following pre-pulse stimuli seen in alcohol dependent participants in the present study is an endophenotype associated with alcohol dependence or represents a marker of alcohol exposure or a gene-environment interaction.

Although the relationship between late positive complexes (P300) and alcohol dependence has been extensively studied, fewer studies have explored late negativities in the 350-600 msec range. In one study a lexical decision task was employed to study 87 alcohol dependent subjects and 57 community controls. In that study alcohol dependent participants were found to display less attenuation of the N400 response to primed words when compared to unprimed words (Roopesh et al., 2010). Additionally, similar findings were observed for a group of high risk offspring of alcoholics as compared to low risk children where the same finding of a lack of attenuation for primed words was observed (Roopesh et al., 2009). These data and additional data demonstrating significant heritability of the N400 component (Almasy et al., 1999, 2001) suggests that the N400 recorded by Roopesh and colleagues may be an endophenotype associated with alcohol dependence. The N4S generated in the present study is not comparable to the classic N400 typically used in linguistic tasks and as used by Roopesh and colleagues (2009, 2010) and is closer to a passive auditory oddball paradigm. However, it should be noted that N400s have been generated to signed words, drawings, photos, videos, objects and environmental sounds (see Kutas and Federmeier, 2011 for review). In that context, the N4S recorded in the present study may index a process whereby an individual is determining whether the startle stimulus is something to “react to” as a “meaningful” environmental noise or whether it should be ignored. Typically, N400s to linguistic stimuli are found to be maximal at centro-parietal sites (Kutas and Van Petten, 1988). The N4S observed in the present study was found to be maximal in frontal areas, and it may have more commonality with what has been described as an “anterior negativity” (Kutas and Van Petten, 1994) that is more “automatically” generated.

Although the cognitive concomitants of the N4S recorded in the present study are currently unknown, the fact that it indexes the presence of alcohol dependence may still be an important finding. Impairments in frontal lobe function and associated behaviors such as impulsivity and executive functioning have been an important theoretical constructs in the understanding of alcoholism (see Pfefferbaum et al., 1997; Begleiter and Porjesz, 1999; Crews and Boettinger, 2009; Campanella et al., 2009; Field et al., 2010). Additional studies will be necessary to determine if the facilitation of the N4S ERP potential by prepulses indexes any of those anatomical or behavioral variables.

In summary, these data suggest that the N4S response to startle/pre-pulse startle stimuli in Mexican American young adults differs depending on sex and the presence of an alcohol

dependence diagnosis. However, the results of this study should be interpreted in the context of several limitations. First, the findings may not generalize to the general American population of mixed heritage or all Mexican Americans, or all Hispanic young adult Americans. Over half of the participants in the present were women and thus findings many not generalize to previous studies that have focused on samples of entirely male participants. Second, the study was limited to young adults between the ages of 18 and 30 years, and the sample size may limit the interpretation of the relationship between the N4S and the variance in severity or chronicity of alcohol dependence. Further studies employing a longitudinal design will be required to test the relationship of N4S amplitude, sex, alcohol dependence and co-morbid disorders. The lack of participants with psychotic disorders and bipolar disease limits the ability to test whether N4S facilitation is also found in those patient populations. Despite these limitations, this report represents an important step in an ongoing investigation to determine risk and protective factors associated with development of substance use disorders in this select Mexican American population.

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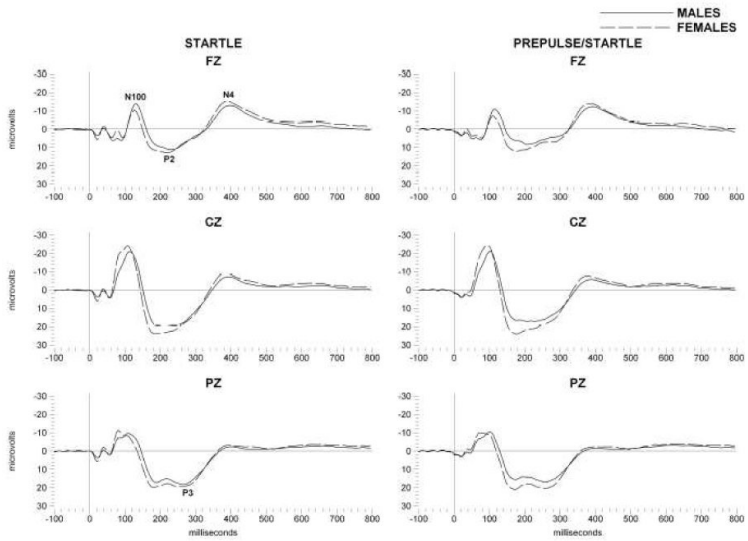

Figure 1.

Grand averages of event-related potentials (ERPs) elicited by startle (left column) and prepulse startle (right column) stimuli in Mexican American young adults. Averages are presented for frontal (Fz) and central (Cz) and parietal (Pz). The N4 component is indicated; solid lines are for male participants and dashed lines for females. X axis represents time (milliseconds, ms) after presentation of the startle stimuli, Y axis is amplitude in microvolts.

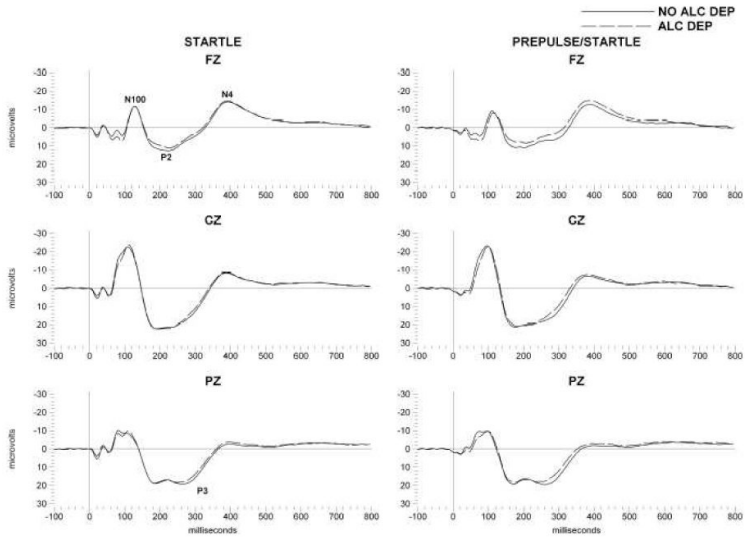

Figure 2.

Grand averages of event-related potentials (ERPs) elicited by startle (left column) and prepulse startle (right column) stimuli in Mexican American young adults. Averages are presented for frontal (Fz) and central (Cz) and parietal (Pz). The N4 component is indicated; solid lines are for participants without a diagnosis of alcohol dependence and dashed lines for participants with a diagnosis of alcohol dependence. X axis represents time (milliseconds, ms) after presentation of the startle stimuli, Y axis is amplitude in microvolts.

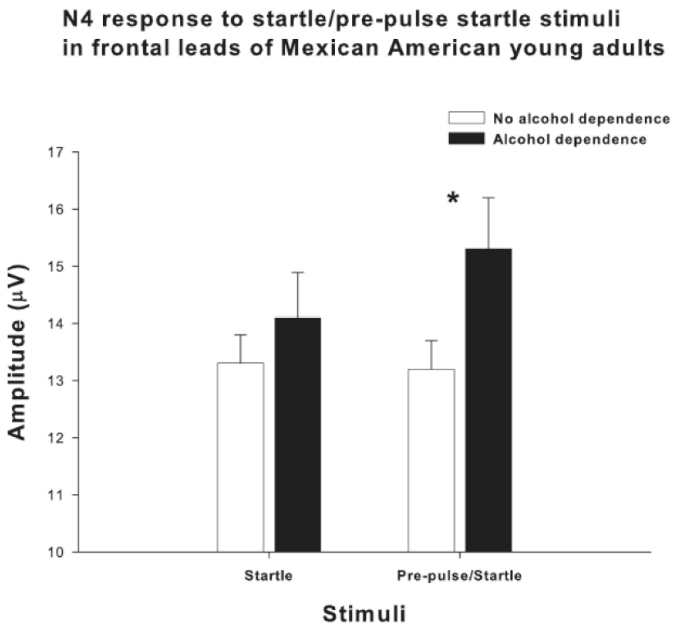

Figure 3.

N4 component amplitudes (microvolts) to startle and prepulse startle stimuli in those participants with a lifetime diagnosis of alcohol dependence in the black bars, and in those without an alcohol dependence diagnosis in the open bars. Values are given as means ± SEM. Asterisk indicates a significant difference between groups. (*$p<0.04$)

Table 1

Demographic characteristics and eye blink responses to the startle stimuli of Mexican American participants comparing alcohol dependence groups, Antisocial personality disorder/conduct disorder groups, and anxiety or affective disorder groups (n = 340)

Demographic	Total sample (n =340)	Alcohol dependence (n = 89)	Antisocial personality disorder and/or conduct disorder (n = 41)	Anxiety or affective disorder (n = 97)	Other drug dependence (n=112)
Age (years)	23.5 (3.69)	24.0 (3.77)	24.6 (5.76)	22.9 (3.94)	23.5 (3.17)
Gender (n)					
Male	135	44 [1]	23 [1]	32	51
Female	205	47	18	65	61
Years of education	13.24 (1.84)	13.26 (1.89)	12.3 (1.92) [2]	13.1 (1.97)	12.64 (2.12) [2]
Income					
< $20,000	55	15	13 [3]	14	19 [3]
> $20,000	285	74	28	83	93
Eye blink amplitude to startle (microvolts)	42.31 (41.30)	41.07 (41.13)	39.38 (41.17)	37.69 (40.87)	41.33 (40.96)
Eye blink amplitude to startle following prepulse (microvolts)	41.29 (40.93)	40.1 (40.47)	36.83 (40.53)	36.32 (40.25)	39.66 (40.34)
% prepulse inhibition	2.41	2.36	6.48	3.63	4.04

Values are Means (SD) unless indicated

[1] $p < 0.05$ gender difference diagnosis vs. no diagnosis

[2] $p < 0.05$ education difference diagnosis vs. no diagnosis

[3] $p < 0.05$ income difference diagnosis vs. no diagnosis