Psychiatry Research 188 (2011) 237–244

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

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

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ARTICLE INFO

Article history:
Received 25 October 2010
Received in revised form 5 April 2011
Accepted 12 April 2011

Keywords:
Alcohol dependence
ERPs
N400
Frontal disinhibition
Prepulse inhibition
Startle
Mexican Americans

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 years) 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 400 ms 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.

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 ms) (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 ms) 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 ms 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 ms) or long (more than 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

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0165-1781/$ – see front matter
doi:10.1016/j.psychres.2011.04.010

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; Sugawara 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 P300s 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; Campanella et al., 2009; Crews and Boettiger, 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 have 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 (Grillon 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 was 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 if 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 h 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, and 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 ms $n=30$) and prepulse-startle stimuli (85 dB white noise burst for 20 msec-duration) immediately (<5 ms) followed by the startle (115 dB white noise burst for 40 ms $n=15$). Each individual startle and/or prepulse startle trial is separated by an interval of 15 s. Background white noise was presented for the entire session at a level of 60 dB. The behavioral