CR-19-0950: Event-related responses to alcohol-related stimuli in Mexican-American young adults: Relation to age, gender, comorbidity and "dark side" symptoms

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ABSTRACT

Background: Electrophysiological variables may represent sensitive biomarkers of vulnerability to or endophenotypes for alcohol use disorders (AUD).
Methods: Young adults (age 18–30 yrs, n = 580) of Mexican American heritage were assessed with the Semi-Structured Assessment for the Genetics of Alcoholism and event-related oscillations (EROs) generated in response to a task that used pictures of objects, food, and alcohol-related and non-alcohol-related drinks as stimuli.
Results: Decreases in energy in the alpha and beta frequencies and higher phase synchrony within cortical brain areas were seen in response to the alcohol-related as compared to the non-alcohol-related stimuli. Differences in ERO energy and synchrony responses to alcohol-related stimuli were also found as a function of age, sex, AUD status and comorbidity. Age-related decreases in energy and increases in synchrony were found. Females had significantly higher energy and lower synchrony values than males. Participants with AUD had higher synchrony values specifically in the beta frequencies, whereas those with a lifetime diagnosis of conduct disorder and/or antisocial personality disorder had lower alpha power and synchrony, and those with any affective disorder had lower ERO energy in the beta frequencies. Those with substance-associated affective "dark-side" symptoms had slower reaction times to the task, lower energy in the beta frequencies, lower local synchrony in the theta frequencies, and higher long-range synchrony in the delta and beta frequencies.
Conclusions: These findings suggest that EROs recorded to alcohol-related stimuli may be biomarkers of comorbid risk factors, symptoms and disorders associated with AUD that also can differentiate those with "dark-side symptoms".

1. Introduction

Electrophysiological variables may represent sensitive biomarkers of vulnerability to or endophenotypes for alcohol use disorders (AUD); for extensive reviews see (Begleiter and Porjesz, 1999; Campanella et al., 2014, 2018; Ceballos et al., 2009; Frederick and Iacono, 2006; Kamarajan and Porjesz, 2015; Pandey et al., 2012; Porjesz et al., 2005; Rangaswamy and Porjesz, 2014). A reduction in the amplitude of the P300 or P3 component of the event-related potential (ERP) has received the greatest attention as a possible neurophysiological marker for alcohol dependence risk (Begleiter et al., 1984; Berman et al., 1993; Ehlers et al., 1998, 2001; Elmasian et al., 1982; Hill et al., 1999a,b; Hill et al., 1995, 1990; Hill et al., 1988; O'Connor et al., 1987; Porjesz and

Begleiter, 1990, 1998; Whipple et al., 1988). The findings appear to be the strongest in high risk children when visual tasks are employed (Porjesz and Begleiter, 1990, 1998). Over time several lines of evidence have suggested that reduced P3 amplitudes in adults also may be associated with other psychiatric disorders that have significant comorbidity with AUD (see, for example: (Bearden and Freimer, 2006; Hasler et al., 2004; Iacono, 1998; Pfefferbaum et al., 1995; Pogarell et al., 2007)).

More recently, several studies have used the technique of extracting event-related oscillations (EROs) from ERP data to develop additional and potentially more informative electrophysiological measures of alcohol-related psychopathology. EROs are oscillatory changes in EEG rhythms that are synchronized or enhanced by a time-locked cognitive

and/or sensory stimulus, and are thought to arise by a "phase re-ordering" of the background EEG within specific frequency bands (Anokhin, 2014; Basar et al., 2000; Klimesch et al., 2007; Roach and Mathalon, 2008). There are several aspects of EROs that provide important information about brain functioning in more detail than what can be extracted from ERP waveforms, and thus potentially provide additional insight into brain function and AUD. The application of time-frequency analyses to ERP trials can yield information on the amount of energy in different frequency sub-bands (such as delta, theta, alpha and beta activity) that contribute to the ERP waveform. For instance, using an auditory task, Basar and colleagues were the first to use EROs to determine that the P300 wave is comprised of an amplitude enhancement of delta, theta, and alpha frequency components of the pre-stimulus EEG (see (Basar et al., 1984, 1980; Basar and Stampfer, 1985)). Other phenomena that can be indexed by ERO data are neuronal synchrony measures. These quantify a process whereby groups of neuronal ensembles begin oscillating within a specific frequency range and then enter into precise phase-locking, or synchrony, with each other over a discrete period of time (Lachaux et al., 1999). Measures of neural synchrony or phase-locking, can be measured in local neuronal populations ('local synchrony') or between separate brain regions ('long-range synchrony') (Singer, 1999; Varela et al., 2001), and represent a means whereby large scale communication can be accomplished either within a brain area or between brain areas.

ERO energy measures in different frequency sub-bands have been investigated previously as specific endophenotypes for alcohol-related psychopathology (Andrew and Fein, 2010; Criado et al., 2012; Ehlers et al., 2018, 2015b; Pandey et al., 2012; Rangaswamy and Porjesz, 2014), and there is evidence that they both confirm ERP findings and may also provide additional information (Andrew and Fein, 2010; Jones et al., 2006; Rangaswamy et al., 2007). While these data are intriguing, there are several open questions that are specifically addressed in the present study. In previous studies, the ERP paradigms chosen typically used visual stimuli to elicit EROs, but no studies used paradigms that employed alcohol-related stimuli to elicit EROs. Previous studies also have generally focused on ERO energy measures and have not employed measures of ERO neuronal synchrony. Additionally, since comorbidity of AUD with other mental disorders, specifically depression and anxiety, has been demonstrated to influence ERP findings (Criado and Ehlers, 2007; Fein and Cardenas, 2017) these diagnoses also need to be taken into consideration when interpreting ERO data.

The present study evaluated several new hypotheses using ERO data collected in a community sample of young adults. The aim of the larger study, from which the current data analyses were generated, is to focus on risk factors for AUD in a sample of high-risk Mexican American young adults. The rates of AUD, comorbid mental disorders and endophenotypes in this population have been previously reported (Criado and Ehlers, 2007; Criado et al., 2013, 2014, 2016; Ehlers et al., 2009, 2010, 2012, 2016; Ehlers and Phillips, 2007; Ehlers et al., 2011, 2015a; Ehlers et al., 2014b, 2018; Ehlers et al., 2014c; Gilder et al., 2007; Melroy-Greif et al., 2017a, 2016; Melroy-Greif et al., 2017b; Norden-Krichmar et al., 2015, 2014). We also have described the emergence of negative affective symptoms over the course of AUD in this population and in a larger sample of European Americans and American Indians (Ehlers et al., 2019a). This phenomenon has been called the "dark-side" of alcohol addiction by several authors (see (Koob and Kreek, 2007; Koob and Mason, 2016). We have further demonstrated that "dark-side" symptoms occur in approximately 60% of people with severe AUD and that having an independent anxiety or affective disorder and elevated scores on trait neuroticism are significantly associated with "dark-side" symptoms (Ehlers et al., 2019a). The goal of the present set of analyses were to develop ERO markers of AUD using alcohol-related stimuli. To accomplish this, our specific aims included: 1) to determine if the use of alcohol-related stimuli could elicit differences in ERO responses as compared to non-alcohol-related stimuli; 2) to test for effects of age and

Table 1
Demographics in Mexican American sample (n = 580).

Demographic Variable	n (%)		
	No alcohol use disorder	Alcohol use disorder	Total
Gender			
Male	103 (18)	135 (23)	252 (41)
Female	206 (36)	136 (23)	359 (59)
Income ≥ $20,000/yr			
Yes	227 (42)	205 (38)	432 (80)
No	59 (11)	52 (9)	111 (20)
ASPD/CD			
Yes	14 (2)	35 (6)	49 (8)
No	295 (51)	236 (41)	531 (92)
Any affective or anxiety			
Yes	121 (21)	145 (25)	266 (46)
No	188 (32)	126 (22)	314 (54)
Dark side symptoms			
Yes	3 (1)	46 (8)	49 (9)
No	306 (52)	225 (39)	531 (91)
Age (yrs)[a]	23.13 ± 3.9	24.19 ± 3.6	23.62 ± 3.8
Years of education[a]	13.38 ± 1.7	13.47 ± 1.9	13.42 ± 1.8

[a] Mean and standard error presented; mean ± (SD).

gender on ERO responses; 3) to determine if ERO responses of those with AUD could be discriminated from those without AUD; and 4) to evaluate the influence of co-morbid anxiety and depression and "dark-side" symptoms associated with AUD on ERO responses to alcohol-related stimuli.

2. Methods and materials

2.1. Participants

Participants were recruited using a commercial mailing list that provided addresses of individuals with Hispanic surnames. The sample was drawn from 11 ZIP codes in San Diego County, California that were identified as having a population that was over 20% Hispanic residents and were within 25 miles of the research site. The mailed invitation stated that potential participants must be of Mexican American heritage, between the ages of 18 and 30 years of age, residing in the United States legally, and able to read and write in English. A phone interview was used to screen 1199 potential participants for the presence of the inclusion criteria as listed on the invitation. People were excluded if they were pregnant, breastfeeding or currently had a major medical disorder. For the present set of analyses we also excluded participants who were taking psychiatric drugs that might interfere with the EEG (n = 31). Participants were asked to refrain from alcohol or recreational drug use for 24 h prior to testing. On the test day, after a complete description of the study was provided to the participants, written informed consent was obtained.

2.2. Psychiatric diagnoses

Each participant completed a face-to-face interview with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994). The SSAGA is a poly diagnostic psychiatric interview that has undergone extensive validity and reliability testing (Bucholz et al., 1994; Hesselbrock et al., 1999). Participants were tested for alcohol usage by breathalyzer on the day of the evaluation and none had positive findings. Lifetime diagnoses (present vs. absent) of AUD were defined by DSM-5 criteria, as were affective disorders (major depressive disorder, dysthymia, bipolar I disorder), and anxiety disorders (social phobia, agoraphobia, panic disorder, obsessive compulsive disorder).
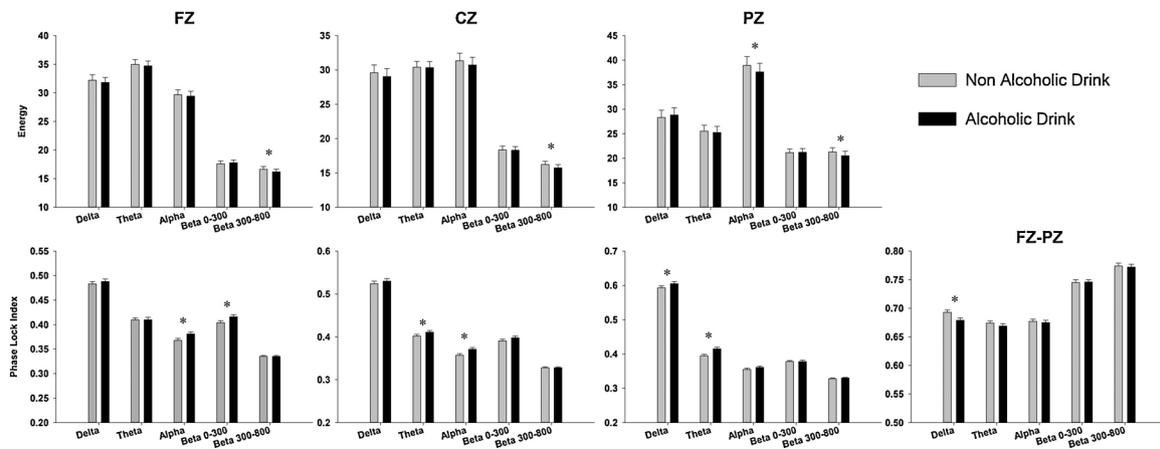
Fig. 1. ERO energy and synchrony in response to alcohol-related stimuli compared to non alcohol related stimuli. Top row: ERO energy for all frequency bands in all three electrode locations (FZ, CZ, PZ) for non alcoholic drinks (shaded bars) and alcoholic drinks (dark bars). Bottom row: ERO phase synchrony for all bands in all electrode locations as well as phase synchrony between electrode sites FZ and PZ is shown for alcohol and non alcohol drink related stimuli. Values presented are means $\pm$ standard error. * indicates p-value < 0.05.

Antisocial personality disorder and conduct disorder (ASPD/CD vs. neither) were defined by DSM-IV criteria. Two symptoms of substance-induced negative affective states ("dark-side" symptoms) associated with severe AUD also were assessed. The first was a measure of withdrawal that queried whether participants ever felt anxious or depressed when they stopped or cut down on drinking. The second measure queried whether participants' drinking had ever caused them to feel depressed or uninterested in things for more than 24 h and to the point that it interfered with their functioning (Ehlers et al., 2019a). Presence of either symptom was considered positive for the trait.

2.3. ERO collection and analyses

We collected seven channels of ERP data (FZ, CZ, PZ, F3, F4, F7, F8) referenced to linked ear lobes with a forehead ground, using the international 10–20 system. An electrode placed left lateral infraorbitally and referenced to the left earlobe was used to monitor both horizontal and vertical eye movement. Visual stimuli were presented on a video screen and consisted of three classes of objects. The first class was pictures of 'non-food or drink objects' (camera, chair, phone, scissors, tennis shoe), the second was 'foods' (corn, banana, apple, canned green beans, white bread) and the third was 'drinks'. The participant was instructed to press one button for food and another button for drink images. Reaction time from the trial onset to the identification of the stimulus was recorded for each trial for the target (food and drink) images. Individual ERP trials were averaged separately for the categories of objects (non-food objects, foods, drinks). However, the drink category was further separated into non-alcoholic drinks (milk carton, Perrier water bottle, Arrowhead water bottle, tall water glass, short water glass) and alcoholic drinks (Jack Daniels bottle, beer in mug, Budweiser can, King Cobra can, wine in glass) for averaging. Fifty trials of each of the 4 classes of stimuli (non-food objects, food objects, nonalcoholic drinks, alcoholic drinks) were presented randomly, for a total number of 200 trials. Thus, each class had equivalent probability. The stimuli were presented for 1000 ms and the inter-stimulus interval was 1000 ms; with a 100 ms pre-trial baseline, the total trial length was 2000 ms. The ERP trials were digitized at a rate of 256 Hz. Individual trials containing excessive eye movement artifacts as well as trials where the EEG exceeded $\pm$ 250 µV (< 5% of the trials) were eliminated before averaging, as described previously (Ehlers et al., 2003).

Data from single trials generated by the ERP stimuli were entered into a time-frequency analysis algorithm, *S*-transform (ST), a generalization of the Gabor transform (Stockwell et al., 1996). The exact code used is a C language, *S*-transform subroutine available from the NIMH

MEG Core Facility web site (http://kurage.nimh.nih.gov/meglab/). These analyses are similar to what has been previously described (Ehlers et al., 2019b; Ehlers et al., 2014c; Ehlers et al., 2015b).

Rectangular regions of interest (ROIs) were defined within the time-frequency analysis by specifying, for each ROI, a band of frequencies and a time interval relative to the stimulus onset time. The 5 ROIs included: the delta band (1–4 Hz, 300–800 ms), theta band (4–7 Hz, 300–800 ms), alpha band (7–13 Hz, 300–800 ms), and beta band (13–30 Hz, 0–300 and 300-800 ms). These regions were chosen *a priori* to coincide with the major EEG frequencies present and the latency windows for each band corresponding to the time region of the N1-P2 (0–300 ms), and the P3a and P3b (300–800 ms) event-related potential components reported previously (Ehlers et al., 2014a). Using mean values over trials, the maximum energy values were calculated for each ROI using 3 electrode locations (FZ, CZ, PZ). PLI (phase lock index) analyses, a measure of synchrony between trials *within* electrode locations, and PDLI (phase difference lock index), a measure of constancy over trials of the difference in phase angle *between* two electrode locations (FZ-PZ), also were calculated as a function of frequency and of time relative to the start of the stimulus for each trial. The range of PLI and PDLI is from zero to 1.0, with high values indicating little variation of phase angle difference.

2.4. Data analysis

Data analyses were based on the four specific aims of this study. All analyses were carried out using SPSS software (IBM SPSS Statistics for Macintosh, Version 20.0, Armonk, NY). Analysis of variance was used to determine group differences for continuous variables and Chi-square tests were used for dichotomous variables. In all analyses, the alpha level (2-tailed) was set at 0.05.

3. Results

3.1. Demographics

Five hundred and eighty participants completed a SSAGA and had valid electrophysiological data available for analysis. Most individuals (60%) were second-generation Mexican Americans, and 88% were second generation or greater. Sample demographics are presented in Table 1. Forty-four percent of the sample had a lifetime diagnosis of DSM-5 AUD. Of those with AUD, over half had mild disorder (mild n = 145, moderate n = 67, or severe n = 59). Those with AUD were more likely to be male (Chi Square = 16.2, p < 0.0001), were older
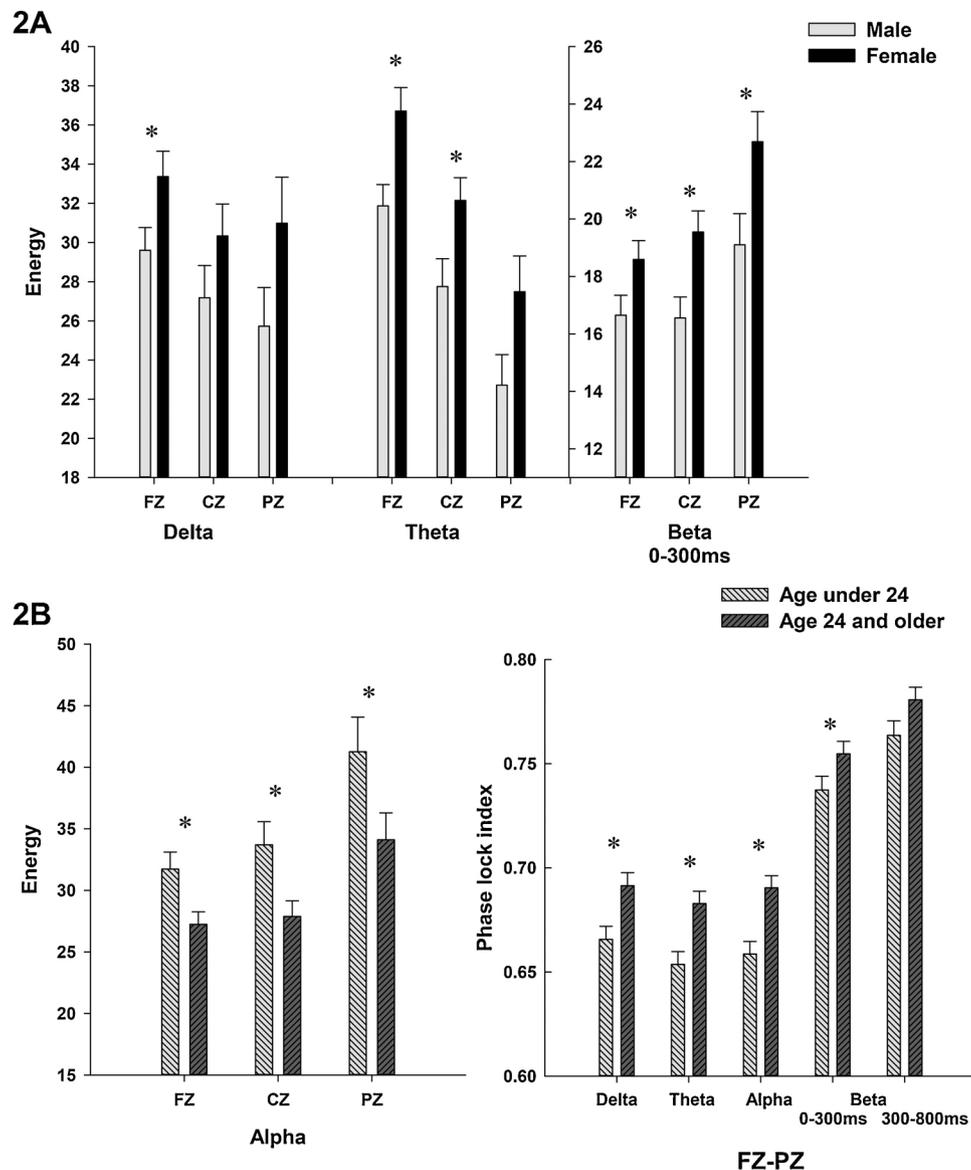
2A

2B

Fig. 2. ERO energy and synchrony in response to alcohol-related stimuli shown as a function of gender (2A) and age (2B). 1A: ERO energy in the delta, theta and beta (0–300 ms) bands for the three electrode locations (FZ, CZ, PZ) in males (shaded bars) and females (dark bars). 1B: ERO energy in the alpha band in FZ, CZ, and PZ electrode locations (left panel), ERO phase synchrony between electrode sites FZ and PZ for all frequency bands (right panel) for participants under age 24 (stripped shaded bars) and ages 24 and older (stripped dark bars). Values presented are means ± standard error. * indicates p-value < 0.05.

($F = 11.6$, $p < 0.001$) and also more likely to have an anxiety or affective disorder (Chi-Square 13.2, $p < 0.0001$), but they did not differ on economic status or education from those without lifetime AUD. In terms of co-morbidities, 36% (n = 210) of the sample had a lifetime diagnosis of affective disorder, with most (n = 198) of those participants meeting lifetime criteria for major depressive disorder: 14% had a lifetime diagnosis of an anxiety disorder; and 8% had a lifetime diagnosis of antisocial personality disorder and/or conduct disorder (ASPD/CD).

3.2. Effect of stimuli

To determine whether ERO responses to alcohol-related stimuli were different as compared to non-alcohol-related stimuli, ERO data (energy and synchrony (PLI, PDLI)) in the 5 time-frequency ROIs) were compared for the two sets of stimuli. Decreases in energy in the alpha frequencies in parietal cortex ($F = 6.2$, $p < 0.01$) and in the beta frequency in the 300–800 ms range in frontal (FZ; $F = 4.5$, $p < 0.03$), central ($F = 3.9$, $p < 0.048$) and parietal (PZ; $F = 4.9$, $p < 0.03$)

cortices were seen in response to the alcohol-related as compared to the non-alcohol-related drinks (Fig. 1). Significantly higher local phase synchrony (PLI) also was found in response to the alcohol vs. non-alcohol-related drinks in frontal cortex in the alpha ($F = 9.7$, $p < 0.002$) and beta (0–300 ms; $F = 8.4$, $p < 0.004$) frequencies, in central cortex (CZ) in the theta ($F = 3.9$, $p < 0.05$) and alpha frequencies ($F = 13.4$, $p < 0.0001$) and in posterior cortex in the delta ($F = 9.0$, $p < 0.003$) and theta frequencies ($F = 22.9$, $p < 0.0001$). However, phase synchrony between electrode sites (PDLI) was found to be lower in response to alcohol-related drinks as compared to non-alcohol-related drinks between frontal and parietal cortices in the delta frequencies ($F = 19.5$, $p < 0.0001$). Subsequent aims focused on variation of responses to the alcohol-related stimuli as well as the differences between the two classes of drink stimuli (alcohol, non-alcohol) across the diagnostic and demographic subgroups of participants.

3.3. Gender and age

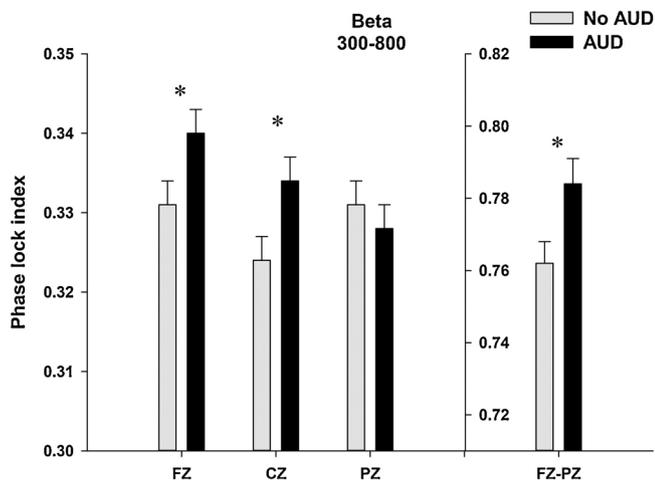The second aim of the study was to test for effects of gender and age

Fig. 3. ERO energy and synchrony in response to alcohol-related stimuli in participants with a lifetime diagnosis of alcohol use disorder (AUD). ERO local phase synchrony for the beta (300–800 ms) frequency band in electrode locations FZ, CZ and PZ (left panel), and ERO synchrony between electrode locations FZ and PZ (right panel), in participants with AUD (dark bars) and with no AUD (shaded bars). Analyses were co-varied for age and gender, values presented are adjusted means ± standard error. * indicates p-value < 0.05.

on ERO energy and synchrony responses to the alcohol-related stimuli. As seen in Fig. 2A, females had significantly higher energy values in response to alcohol-related stimuli than males in several regions: FZ in the delta (F = 4.3, p < 0.04), theta (F = 8.1, p < 0.005) and beta (0–300 ms, F = 3.9,p < 0.05) frequencies, CZ in the theta (F = 5.8, p < 0.02) and beta frequencies (0–300 ms; F = 7.9, p < 0.005), and in PZ in the beta (0–300 ms; F = 5.3, p < 0.02) frequencies. With regards to gender differences in phase synchrony, males had higher PLI synchrony than females in response to alcohol-related stimuli only in the beta (300–800 ms) frequencies in CZ (F = 5.3, p < 0.02), but they also had higher PDLI synchrony (FZ-PZ) in the delta (F = 9.0, p < 0.003) and beta (0–300 ms: F = 24.2, p < 0.0001; 300–800 ms: F = 17.0, p < 0.0001) frequencies. An analysis of the differences in ERO energy and synchrony between the alcohol-related drinks and the non-alcohol related drinks as a function of gender showed that males had larger differences in ERO energy (F = 6.1, p < 0.01) in the delta frequencies but smaller differences in PDLI synchrony in the delta frequencies (F = 3.9, p < 0.05) as well as smaller differences in PLI synchrony in the alpha frequencies (F = 4.5, p < 0.04).

Age differences in ERO responses to alcohol-related stimuli were determined by first conducting a median split of the population (at 24 years) and then comparing those below the median age to those above. Shown in Fig. 2B, increasing age was significantly associated with decreases in energy in the theta frequencies in FZ (F = 8.4, p < 0.004) and CZ (F = 4.8, p < 0.03) as well as the alpha frequencies in FZ (F = 6.9, p < 0.01) CZ (F = 6.7,p < 0.01) and PZ (F = 4.0, p < 0.04). Age also was associated with lower PLI measures of synchrony in the beta (300–800 ms; F = 4.4, p < 0.04) frequencies in PZ and higher PDLI synchrony (FZ-PZ) in all frequency bands (delta: F = 8.4, p < 0.004; theta: F = 11.7, p < 0.001; alpha: F = 14.3, p < 0.0001; beta 0–300 ms: F = 3.7, p < 0.05). An analysis of the differences in ERO energy and synchrony between the alcohol-related drinks and the non-alcohol related drinks as a function of age showed no age-related differences.

3.4. Alcohol use disorders

The third aim was to determine if those participants with a lifetime diagnosis of AUD could be discriminated from those without AUD based on ERO responses to alcohol-related stimuli, when the analyses were

covaried for age and gender. Using ANOVA, no significant differences in ERO energy in response to alcohol-related stimuli were found in any frequency range when those with an AUD were compared to those without an AUD. However, some differences in ERO synchrony were found. In response to the alcohol-related stimuli, participants with AUD had higher PLI values in the beta frequencies (300–800 ms) in FZ (F = 3.8, p < 0.05) and CZ (F = 5.6, p < 0.018) and also had higher PDLI (FZ-PZ) values in the beta frequencies (300–800 ms; F = 5.5, p < 0.02), as seen in Fig. 3. An analysis of the differences in ERO energy and synchrony between the alcohol-related drinks and the non-alcohol related drinks as a function of AUD revealed significant differences in synchrony were seen in CZ in the beta frequencies (F = 4.8, p < 0.03) as a function of AUD.

3.5. Psychiatric comorbidities

The fourth and final aim was to evaluate the influence of comorbidity of anxiety and affective disorders, antisocial personality disorder and/or conduct disorder (ASPD/CD), and the presence of anxiety and depression "dark-side" symptoms associated with AUDs on ERO responses to alcohol-related stimuli. In analyses that covaried for both age and gender, participants with any lifetime ASPD/CD diagnoses were found to have lower alpha energy (F = 4.1, p < 0.04) and synchrony (F = 3.9, p < 0.05) in PZ (Fig. 4A) in response to alcohol-related stimuli, and smaller PLI differences between the drink stimuli in the theta frequencies (F = 6.3, p < 0.01).

In analyses that covaried for both age and gender, participants with any lifetime anxiety diagnosis (ANYAX) were not found to differ on energy or synchrony measures in response to alcohol-related stimuli. An analysis of the differences in ERO energy and synchrony between the alcohol-related drinks and the non-alcohol related drinks as a function of ANYAX also showed no significant differences for people with and without a lifetime anxiety diagnosis. Significant reductions in ERO energy were found in those participants with any lifetime affective disorder (ANYAF) in the beta frequencies in PZ (300–800 ms: F = 3.9, p < 0.05), as seen in Fig. 4B. Those participants with ANYAF had no significant changes in synchrony. An analysis of the differences in ERO energy and synchrony between the alcohol-related drinks and the non-alcohol related drinks as a function of ANYAF showed significant differences in PLI were seen in PZ in the theta frequencies (F = 5.5, p < 0.02) and in PDLI in the beta frequencies (F = 3.8, p < 0.05) as a function of ANYAF.

The two alcohol-associated anxiety and affective symptoms that are typically found in participants with severe AUD (dark-side symptoms) also were evaluated for associations with ERO measures in response to alcohol-related stimuli. Since participants with these symptoms did not differ in age or gender from those individuals who did not have such symptoms, these analyses were not covaried for age or gender. Participants with "dark-side" symptoms had lower energy in the beta frequencies in PZ (F = 3.7, p < 0.05) in response to the alcohol-related drinks. Those with "dark-side symptoms" also had lower PLI synchrony in PZ for theta frequencies (F = 9.3, p < 0.002) frequencies, as well as increases of synchrony in PDLI (FZ-PZ) in the delta (F = 7.1, p < 0.008), theta (F = 8.6, p < 0.003), alpha (F = 7.0, p < 0.008), and beta (0–300 ms: F = 5.6, p < 0.02; 300–800 ms F = 3.8, p < 0.05) frequencies, in response to the alcohol-related drinks, as seen in Fig. 5. An analysis of the differences in ERO energy and synchrony between the alcohol-related drinks and the non-alcohol related drinks as a function of the presence of "dark-side" symptoms showed several significant differences across stimuli. Greater differences in energy between the two stimuli were seen in the beta frequencies in PZ (0–300 ms: F = 6.3, p < 0.01) in those with dark-side symptoms. Additionally, greater differences in synchrony in the beta frequencies (0–300 ms) were seen in all three leads (FZ: F = 6.5, p < 0.01; CZ: F = 5.1, p < 0.02; PZ: F = 5.3, p < 0.02) in those with dark-side symptoms.
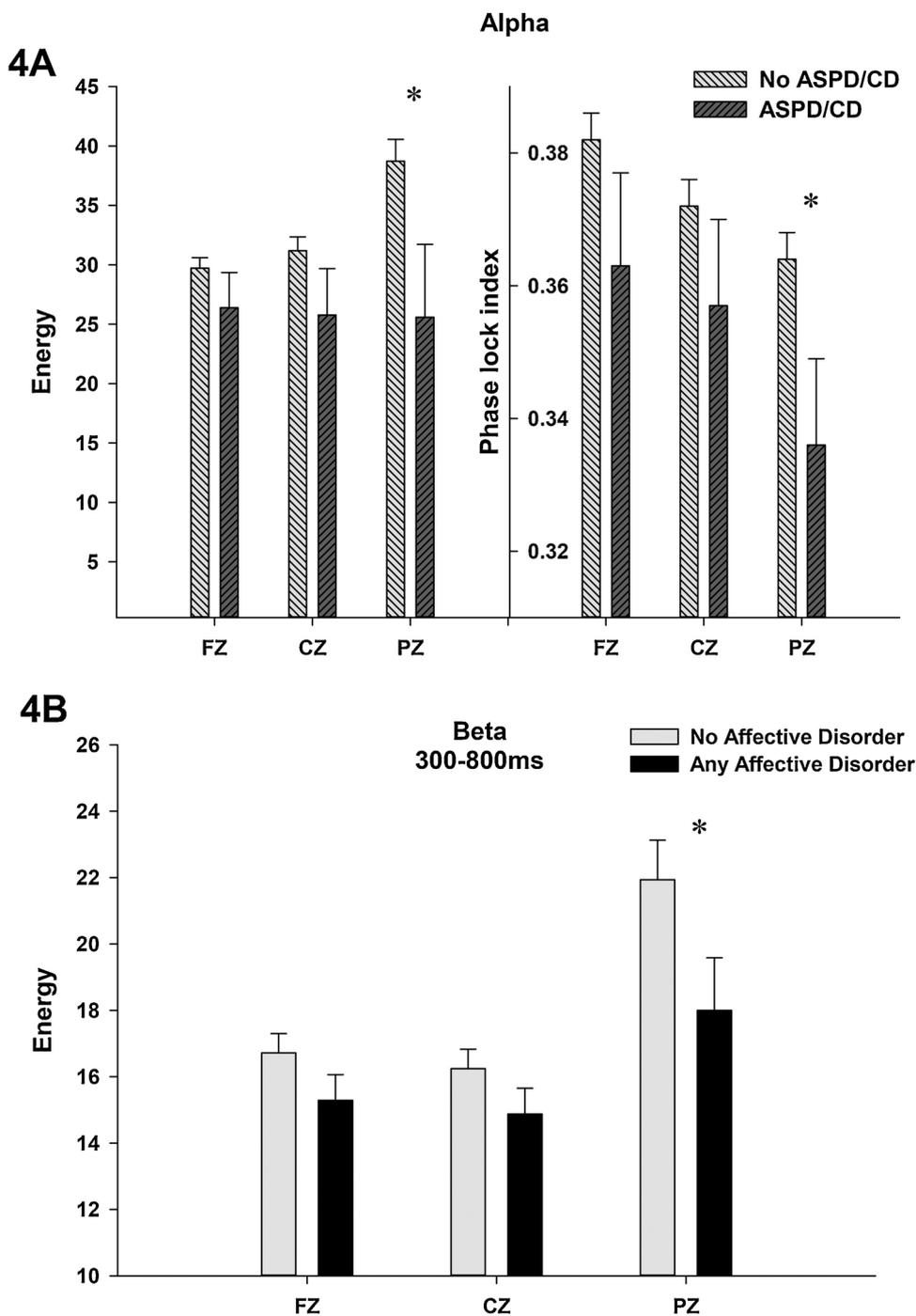
Fig. 4. ERO energy measures in response to alcohol-related stimuli in participants with any affective disorder and antisocial personality disorder/conduct disorder (ASPD/CD). 4A: ERO energy in beta (300–800 ms) band in 3 electrode locations (FZ, CZ, PZ) is shown for subjects with (dark bars) and without (shaded bars) a lifetime diagnosis of any affective disorder. 4B: Alpha band ERO energy (left panel) and phase synchrony (right panel) in electrode locations FZ, CZ and PZ in participants with ASPD/CD (stripped dark bars) and no ASPD/CD (stripped shaded bars). Analyses were co-varied for age and gender, values presented are adjusted means ± standard error. * indicates p-value < 0.05.

3.6. Task performance

The percentage of correctly-identified stimuli (objects, food, drinks) for each participant was calculated and compared for all demographic variables (gender, age group, marital status, economic status, and education) using ANOVA. The percent of correctly-identified stimuli did not differ based on gender, age group (> or < 24 yrs), marital status or education, but a significantly lower percentage of correctly-identified stimuli was found in participants with lower economic status (< \$20 K/yr) compared to those of higher economic status. No significant differences in the percentage of correctly-identified stimuli were found for respondents with AUD, ASPD/CD, ANYAXAF, or for those with dark-side symptoms. The reaction time from the time of stimulus onset to the button push for the correctly-identified stimuli

(food, drinks) for each participant was also calculated and compared for diagnostic and demographic variables using ANOVA. There were no significant differences in reaction time based on age group, however, gender differences were found. As seen in Fig. 6A, women had significantly longer reaction times to the identification of the alcoholic (F = 12.8, p < 0.001) and non-alcoholic drinks (F = 12.0, p < 0.001) but not to the food. No significant differences in reaction time were found for the AUD, ASPD/CD, ANYAX, ANYAF diagnostic categories, however, those with dark-side symptoms (Fig. 6B) had significantly longer reaction times to all three classes of stimuli (alcoholic drinks: F = 8.2, p < 0.004; non-alcoholic drinks: F = 8.9, p < 0.003; food: F = 5.2, p < 0.02).
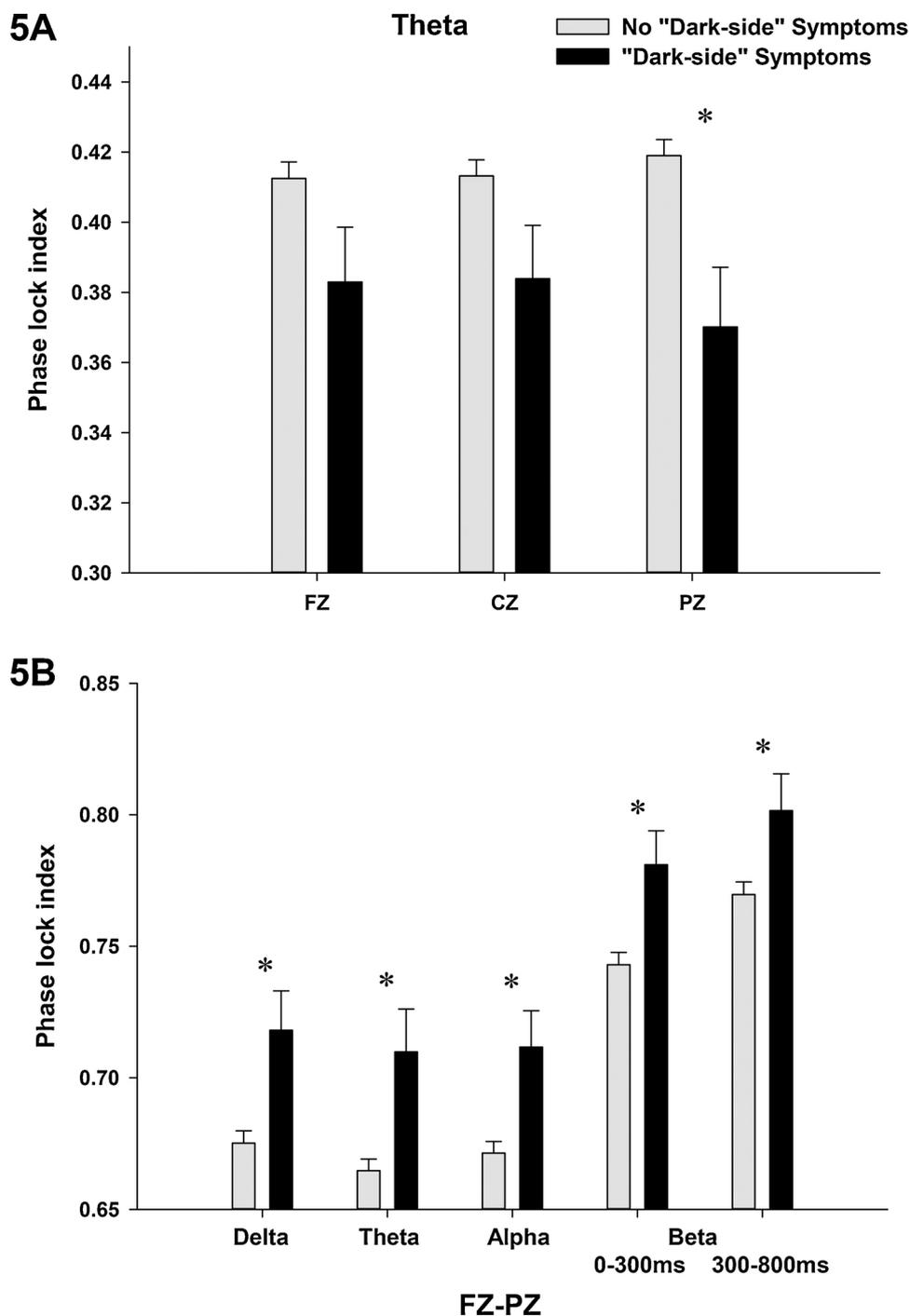
Fig. 5. ERO synchrony measures in response to alcohol-related stimuli in participants with (dark bars) and without (shaded bars) alcohol-associated anxiety and/or affective "dark side" symptoms. 5A: Local synchrony as indexed by phase lock index within the 3 electrode locations (FZ, CZ, PZ) is shown for the theta frequency band. 5B: ERO synchrony between 2 electrode locations (FZ-PZ) is shown for all frequency bands. Values presented are means ± standard error. * indicates p-value < 0.05.

4. Discussion

Numerous studies have demonstrated that electrophysiological variables, especially a reduction in the P3 component of the event-related potential, may be biomarkers of vulnerability to or endophenotypes for alcohol use disorders (AUD); for extensive reviews see (Begleiter and Porjesz, 1999; Campanella et al., 2014, 2018; Ceballos et al., 2009; Frederick and Iacono, 2006; Kamarajan and Porjesz, 2015; Pandey et al., 2012; Porjesz et al., 2005; Rangaswamy and Porjesz, 2014). The goal of the present set of analyses was to extend

those studies by developing ERO markers of AUD using alcohol-related stimuli. Our first specific aim was to determine if ERO responses to alcohol-related stimuli differed from non-alcohol-related stimuli. Decreases in energy in the alpha and beta frequencies and higher phase synchrony within cortical brain areas, in several frequency bands, were seen in response to the alcohol-related as compared to the non-alcohol-related stimuli. These findings suggest alcohol-related stimuli may engage increased interactions within brain areas, as indicated by increased local synchrony.

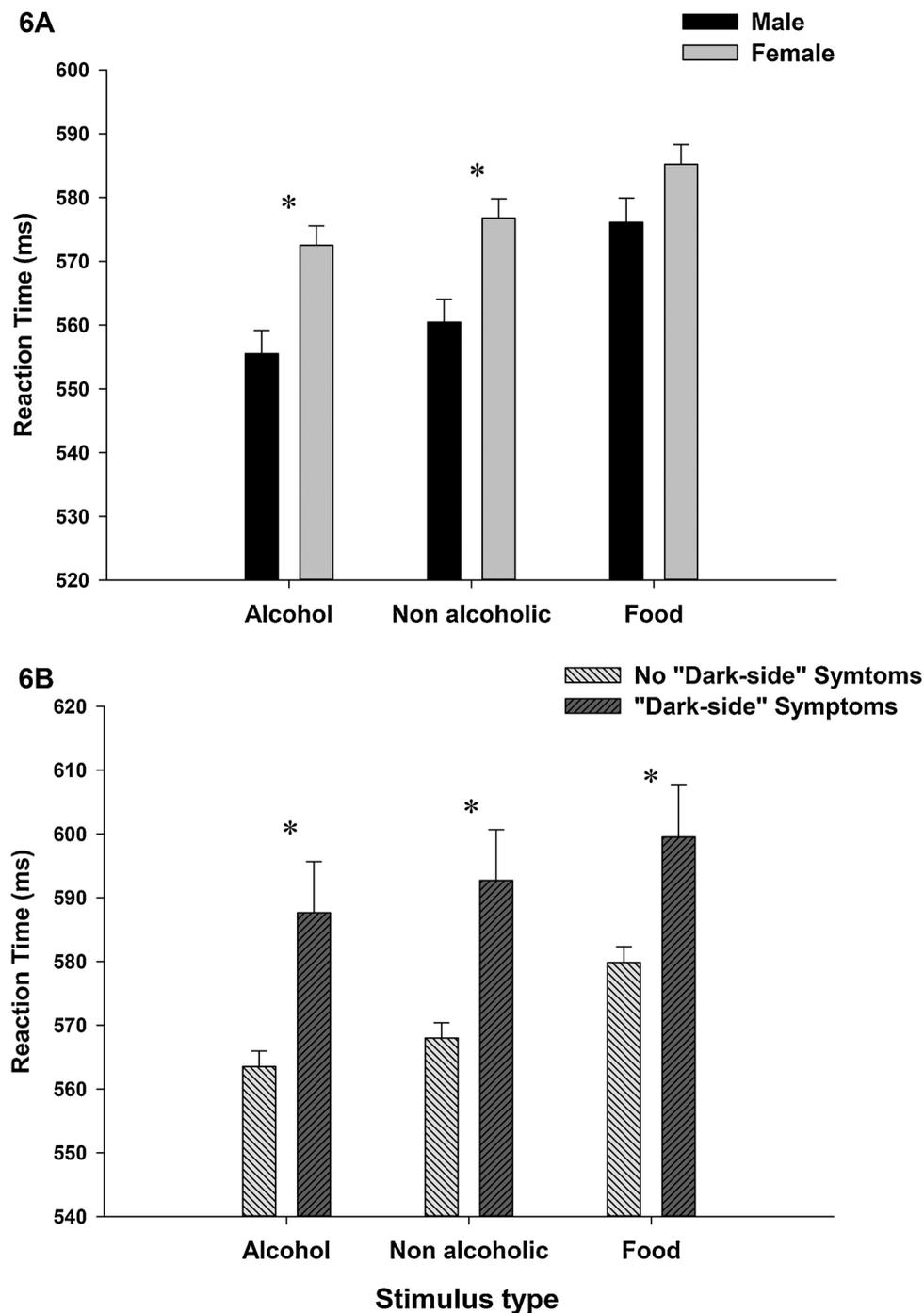Secondly, we determined if gender and age had significant

Fig. 6. Participant's response time to identify visual stimuli is shown by gender and alcohol-associated anxiety and/or affective "dark side" symptoms. 6A: Reaction times (in milliseconds) for each stimuli is shown for males (dark bars) and females (shaded bars). 6B: Reaction times (co-varied for gender) shown for subjects with alcohol-associated anxiety and/or affective "dark side" symptoms, (stripped dark bars) and without (stripped shaded bars). Values presented are means ± standard error. * indicates p-value < 0.05.

influences on ERO energy and synchrony responses to alcohol-related stimuli. Females were found to have significantly higher energy values than males in the delta, theta, and beta frequencies. Increases in ERO energy in females has been previously reported even in simple visual tasks (Guntekin and Basar, 2007), and theta power was found to be significantly higher in females in a gambling task (Kamarajan et al., 2008) and in visual and auditory oddball tasks (Chorlian et al., 2015). In the present study, males had higher PLI synchrony than females in the beta frequencies and higher PDLI synchrony in the delta and beta frequencies, a finding not previously reported. Age also was significantly associated with ERO findings in the current study. Decreases

in energy and higher PLI measures of synchrony in the theta frequencies and increases in PDLI synchrony were found in all frequency bands in the older participants. These findings are consistent with previous studies reporting decreases in theta energy over developmental periods using visual and auditory oddball tasks (Chorlian et al., 2015; Ehlers et al., 2014c; Yordanova and Kolev, 1996). We also have previously demonstrated that increases in PLI and PDLI synchrony occur during both adolescent and young adult development (Ehlers et al., 2019b; Ehlers et al., 2014c). Since it has been suggested that the human brain becomes "neurobiologically adult" in the early 20 s (Mills et al., 2016), it is possible that ERO phase locking may represent a neurobiological

marker of brain maturation, and that this marker differs between males and females.

The main aim of the present study was to determine if measures of ERO power and synchrony in response to the alcohol-related stimuli differed in participants with AUDs. There was some evidence of variation as participants with AUD were found to have higher PLI and PDLI values in the beta frequencies to the alcohol-related stimuli. Increased beta activity has been reported in many studies in human alcoholics during waking and sleep (Bauer, 2001; Fein and Allen, 2005; Porjesz et al., 2005; Rangaswamy et al., 2002). EEG beta has been suggested to represent a sign of neural excitability or "disinhibition" when seen in alcoholics (Porjesz et al., 2005). It has also been demonstrated to be a good endophenotype in genetic studies of families with alcohol use disorders (Meyers et al., 2017; Porjesz et al., 2002). Although there have been no published studies of ERO responses to alcohol-related stimuli, to date there have been several reports of increased amplitudes of several ERP components in response to various alcohol-related stimuli in alcoholics and binge drinkers (Dickter et al., 2014; Herrmann and Knight, 2001; Herrmann et al., 2000; Martinovic et al., 2014; Petit et al., 2015; Thurin et al., 2017; Watson et al., 2016). The increase in amplitude of a number of different ERP components observed in these studies may be the result of enhanced expectations of the effects of alcohol, but they also may reflect a general hyperexcitability associated with abstinence from heavy drinking (Begleiter and Porjesz, 1999).

Since AUD is frequently comorbid with other mental disorders such as ASPD/CD, depression and anxiety, and this comorbidity has been demonstrated to influence ERP findings (Bearden and Freimer, 2006; Criado and Ehlers, 2007; Fein and Cardenas, 2017; Hasler et al., 2004; Iacono, 1998; Pfefferbaum et al., 1995; Pogarell et al., 2007), we also evaluated the influence of these disorders on ERO responses to alcohol-related stimuli. Participants with a lifetime diagnosis of ASPD/CD were found to have significantly lower alpha ERO energy and synchrony. Lower voltage EEG alpha has long been associated with AUD and increased risk for alcohol dependence (Arentsen and Sindrup, 1963; Coger et al., 1978; Ehlers et al., 2015b; Enoch et al., 1995, 1999; Jones and Holmes, 1976; Varga and Nagy, 1960). It has also been shown to be associated with ASPD (Calzada-Reyes et al., 2012).

We also sought to determine if there was a different set of ERO responses in association with the presence of internalizing diagnoses. No changes were seen in participants with lifetime diagnoses of any anxiety disorders, however, reductions in ERO energy in the beta frequencies were found in participants with a lifetime diagnosis of any affective disorders. Alterations in beta oscillations have been suggested by a number of authors to underlie depressive disorders (Fingelkurts and Fingelkurts, 2015; Li et al., 2017), as have higher frequency gamma oscillations (Fitzgerald and Watson, 2018).

The presence of the two alcohol-associated anxiety and affective "dark-side" symptoms that are typically found in participants with severe AUD (Ehlers et al., 2019a) also were evaluated for associations with ERO measures in response to alcohol-related stimuli. Those with "dark-side" symptoms had: 1) longer reaction times to the target stimuli, 2) lower energy in the beta frequencies, 3) lower PLI synchrony in the theta frequencies, and 4) higher PDLI synchrony in the delta and beta frequencies. Thus it appears that those participants with dark-side symptoms have ERO signatures that are a mixture of those found in AUD and affective disorders. However, neither AUD nor affective disorders were associated with higher PDLI synchrony. The finding of higher PDLI synchrony in participants with dark-side symptoms is not likely due to the effects of heavy drinking as *lower* PDLI synchrony in the beta frequencies has been observed in young adults with a history of adolescent binge drinking (Ehlers et al., 2019b). Instead, higher PDLI synchrony may represent a measure of hyperarousal or increased difficulty of the task in those participants with dark-side symptoms since they also had increased reaction times for stimuli identification.

5. Conclusions

In this study, young adults of Mexican-American heritage were assessed with the SSAGA and EROs were generated in response to a task that used pictures of objects, food and alcohol-related and non-alcohol-related drinks as stimuli. Females, who are less likely to have externalizing disorders, overall had significantly higher ERO energy values than males. The only difference that was associated with AUD was higher local and long-range synchrony in the beta frequencies. A lifetime diagnosis of any affective disorder was associated with significant reductions in ERO energy in the beta frequencies. Those participants with substance-associated affective "dark-side" symptoms had both lower ERO energy in the beta frequencies and also had lower local synchrony in the theta frequencies. Taken together, these findings suggest ERO biomarkers can discriminate people with and without AUD, and that these biomarkers also may be sensitive to the presence of affective symptomatology, and especially dark-side symptoms of AUD.

Contributors

All authors participated in analyzing and interpreting the data and in drafting and reviewing the manuscript. All meet ICMJE criteria for authorship and have read and approved the final version of the manuscript.

Declaration of Competing Interest

All authors completed and submitted the ICMJE form for Disclosure of Potential Conflicts of Interest. The authors declare no conflicts of interest.

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