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Evoked K-complexes and altered interaction between the central and autonomic nervous systems during sleep in alcohol use disorder

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ABSTRACT

There is evidence for impairment in both central nervous system (CNS) and autonomic nervous system (ANS) function with prolonged alcohol use. While these impairments persist into abstinence, partial recovery of function has been demonstrated in both systems during sleep. To investigate potential ANS dysfunction associated with cortical CNS responses (impairment in CNS-ANS coupling), we assessed phasic heart rate (HR) fluctuation associated with tones that did and those that did not elicit a K-complex (KC) during stable N2 non-rapid eye movement (NREM) sleep in a group of 16 recently abstinent alcohol use disorder (AUD) patients (41.6 ± 8.5 years) and a group of 13 sex- and age-matched control participants (46.6 ± 9.3 years). Electroencephalogram (EEG) and electrocardiogram (ECG) data were recorded throughout the night. Alcohol consumption questionnaires were also administered to the AUD patients. AUD patients had elevated HR compared to controls at baseline prior to tone presentation. The HR fluctuation associated with KCs elicited by tone presentation was significantly smaller in amplitude, and tended to be delayed in time, in the AUD group compared with the control group, and the subsequent deceleration was also smaller in AUD patients. In both groups, the increase in HR was larger and occurred earlier when KCs were produced than when they were not, and there was no difference in the magnitude of the KC effect between groups. Phasic HR changes associated with KCs elicited by tones are impaired in AUD participants, reflecting ANS dysfunction possibly caused by an alteration of cardiac vagal trafficking. However, only the timing of the HR response was found to relate to estimated lifetime alcohol consumption in AUD. The clinical meaning and implications of these novel findings need to be determined.

Introduction

Alcohol Use Disorder (AUD) and alcohol misuse present major problems for both individuals and society. AUD costs the US economy over US $200 billion a year (Bouchery, Harwood, Sacks, Simon, & Brewer, 2011), and is associated with a number of health problems (Rehm, 2011), including poor cardiovascular (CV) function (Gardner & Mouton, 2015; Malpas, Whiteside, & Maling, 1991; Yokoyama et al., 1991), brain structural alterations (Sullivan, Harris, & Pfefferbaum, 2010; Zahr, Kaufman, & Harper, 2011), and functional brain impairments – as evidenced by altered functional MRI (Fein & Cardenas, 2015), EEG and evoked potentials (Kamarajan & Porjesz, 2015), and cognitive function (Oscar-Berman & Marinković, 2007). AUD is also associated with alterations in sleep architecture and sleep EEG (Chakravorty, Chaudhary, & Brower, 2016; Colrain, Nicholas, & Baker, 2014).

The CV system is controlled by the sympathetic and vagal branches of the autonomic nervous system (ANS). In AUD populations, there is evidence for vagal neuropathy, which likely contributes to CV dysfunction (Barter & Tanner, 1987; Duncan, Johnson, Lambie, & Whiteside, 1980; Villalta, Estruch, Antunez, Valls, & Urbano-Marquez, 1989). Furthermore, a post mortem study found a reduction in the myelinated fibers of the vagus nerve in AUD patients compared with controls (Guo, McLeod, & Baverstock, 1987). Several studies using heart rate variability (HRV) to assess

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ANS activity in AUD have also shown abnormal ANS regulation in AUD both during wake (Karpyak, Romanowicz, Schmidt, Lewis, & Bostwick, 2014; Quintana, Guastella, McGregor, Hickie, & Kemp, 2013) and sleep (de Zambotti, Willoughby, Baker, Sugarbaker, & Colrain, 2015; Ganesha, Thirthalli, Muralidharan, Benegal, & Gangadhar, 2013; Irwin, Valladares, Motivala, Thayer, & Ehlers, 2006). However, we (de Zambotti et al., 2015) and others (Hirsch, Bishop, & York, 1993; Tan, Johnson, Lambie, & Whiteside, 1984; Villalta et al., 1989) have demonstrated that vagal function improves with abstinence, indicating that at least partial ANS recovery is possible. Evidence also suggests that measures of ANS function are reliable and sensitive predictors of adverse CV events (Barron & Lesh, 1996; Curtis & O'Keefe, 2002; Schwartz, La Rovere, & Vanoli, 1992); therefore, simple, non-invasive measures of ANS, such as HRV, might provide clinically useful information.

In addition to ANS dysfunction, AUD patients show altered electroencephalographic (EEG) activity during sleep, characterized by a significant reduction in slow wave (delta) frequency activity throughout sleep (see Colrain et al., 2014 for review). AUD patients also show reduced delta EEG activity (Colrain, Turlington, & Baker, 2009) and a lower incidence and amplitude of both spontaneous and evoked K-complexes (KCs) compared with age-matched healthy controls (Colrain, Crowley, Nicholas, Padilla, & Baker, 2009; Nicholas, Sullivan, Pfefferbaum, Trinder, & Colrain, 2002). KCs are single slow waves, characteristic of NREM sleep, and are thought to provide a protective function that maintains sleep in the presence of external stimuli (Colrain, 2005; De Gennaro, Ferrara, & Bertini, 2000; Forget, Morin, & Bastien, 2011; Nicholas, Trinder, & Colrain, 2002). Furthermore, similar to the recovery observed in ANS function, KC amplitude also shows partial recovery with abstinence (Colrain, Padilla, & Baker, 2012; Willoughby, de Zambotti, Baker, & Colrain, 2015).

During sleep, tonic changes in ANS activity are evident (e.g., NREM sleep shows a shift in ANS control toward vagal dominance compared with wake and REM sleep) (de Zambotti, Trinder, Silvani, Colrain, & Baker, 2018). There are also phasic ANS fluctuations (e.g., ANS changes modulated by sympathetic activity and vagal inhibition in response to micro-arousals) (Trinder, Waloszek, Woods, & Jordan, 2012). The ANS also responds to stimuli presented during sleep; the sympathetic nervous system is activated and heart rate is increased in association with an arousal (Trinder et al., 2003).

During N2 sleep (Iber, Ancoli-Israel, Chesson, & Quan, 2007), spontaneous and evoked KCs are associated with changes in the ANS, such as peripheral vasoconstriction and HR acceleration (Berg, Jackson, & Graham, 1975; Johnson & Karpan, 1968; Monstad & Guilleminault, 1999), and heart rate has been shown to increase following a KC (Hornyak, Cejnar, Elam, Matousek, & Wallin, 1991) or a KC burst (Sforza, Jouny, & Ibanez, 2000), although to a smaller extent than seen following microarousals (2–4 bpm as compared to 8–14 bpm) (Sforza et al., 2000). In a recent study (de Zambotti, Willoughby, Franzen, Clark, Baker, & Colrain, 2016)we conducted a detailed investigation into the amplitude and timing of HR changes, associated with both spontaneous and evoked KCs during sleep in a population of healthy older adolescents (17–20 years old). Our results showed a significantly larger biphasic HR fluctuation (tachycardia followed by bradycardia) in association with both spontaneous KCs and tones that evoked a KC, compared with tones that did not elicit a KC, consistent with that seen to tone-elicited KCs by Berg et al. (1975).

The goal of the present study was to determine whether KC-related modulation of HR could be used as a functional marker of ANS dysfunction during sleep in abstinent alcoholic men and women. We investigated the event-related cardiac modulation following evoked KCs in a population of recently abstinent AUD participants and a group of age- and sex-matched control participants. While we have shown in separate studies that KC incidence and amplitude are reduced (Colrain, Crowley et al., 2009; Nicholas, Sullivan et al., 2002) and that ANS function is altered (de Zambotti et al., 2015), there have been no studies evaluating the coupling of CNS and ANS responses during sleep in AUD. We hypothesized that AUD participants would show a blunted HR response. We also examined the relationship between the HR response and measures of alcohol consumption to investigate the extent of alcohol-dependent damage to the systems controlling HR.

Material and methods

Participants

Seventeen participants with AUD recruited from residential treatment centers around the San Francisco Bay Area and 13 healthy controls (recruited from the local community) participated in this study. One AUD participant was excluded owing to technical problems in data collection. Detailed participant characteristics and screening procedures have been previously described (de Zambotti et al., 2015; Willoughby et al., 2015). Participants completed a structured alcohol history questionnaire (Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998) and the structured clinical interview for DSM-IV-TR (First, Spitzer, Gibbon, & Williams, 2002). All AUD participants met the criteria for alcohol dependence for at least 3 years and were studied within their first month of abstinence (ranging from 8 to 30 days sober). Control participants did not meet the criteria for any Axis I psychopathology. Table 1 shows demographic details and alcohol history for the participants.

The study was approved by the Institutional Review Board at SRI International. All participants gave informed consent prior to the study and were compensated for their participation.

Procedure

All participants underwent a screening/adaptation polysomnography (PSG) night to screen for clinically significant sleep disorders. They returned to the laboratory for an experimental recording night, which, for AUD participants, was conducted within one month of their last drink.

KCs were elicited using 80-dB tones presented at 1000 Hz for 50 msec (with a 2-msec rise and fall time) using Compumedics NeuroScan Stim software (Compumedics Ltd., Abbotsford, Victoria, Australia) though E-A-RTONE 3A insert earphones (3M Auditory Systems, Indianapolis, Indiana, United States). Tones were presented after 30 min of stable sleep, were paused if the participant showed signs of awakening, and were restarted once stable sleep had resumed. There was a random 15–30-sec inter-stimulus interval. All of the participants reported good hearing and confirmed they could hear the tones before going to bed.

PSG recording

Standard PSG measures, including EEG, electrooculogram, electromyogram, and electrocardiogram (ECG), were recorded according to the American Academy of Sleep Medicine guidelines (Iber et al., 2007). Thirty-second epochs were scored according to standard criteria into wake, N1, N2, N3, and REM stages. Selected epochs did not contain microarousals scored according to AASM criteria (Berry et al., 2015).

EEG and ECG analysis

The EEG and ECG data were analyzed offline using the EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) toolboxes for MATLAB (MathWorks, Natick, Massachusetts,

Table 1
Demographic details and alcohol consumption history for Alcohol Use Disorder (AUD) and Control participants.

	Controls Mean (SD)	AUD Mean (SD)	*p* value
Number	13	16	–
Sex	F: 6/M: 7	F: 7/M: 9	–
Age (years)	46.62 (9.29)	41.62 (8.53)	$p = 0.14$
Education (years)	17.14 (2.14)	12.62 (2.09)	$p < 0.001$
Ethnicity	Caucasian: 9 African American: 1 Hispanic: 1 Asian: 2	Caucasian: 11 African American: 2 Hispanic: 3 Asian: 0	–
BMI (kg/m^2)	24.45 (3.30)	25.74 (3.20)	$p = 0.26$
Days since last drink	–	16.18 (5.82)	–
Length of alcohol dependence (years)	–	15.96 (8.86)	–
Estimated Lifetime Alcohol Consumption (kg)	49.57 (112.55)	1453.31 (1307.69)	$p < 0.001$

United States). The EEG was re-referenced to the average of the mastoids and filtered at 0.3–30 Hz using a 4th order Butterworth filter. Epochs 500 msec before to 2000 msec after tone presentation were extracted and baseline-corrected to the 500-msec pre-stimulus period. Epochs of N2 sleep were characterized as KCP (containing a KC elicited by the tone) or KCN (not containing a KC following the tone), based on visual inspection of the Fz and Cz channels according to our standard laboratory procedure (Colrain, Crowley, et al., 2009; Crowley, Trinder, & Colrain, 2002) and blind to group membership. The number of KCs elicited was not significantly different across the Control and AUD groups (mean ± SD; AUD: 92.13 ± 42.26; Control: 125.77 ± 75.44; $p = 0.14$).

The ECG was filtered at 1–50 Hz with a half–amplitude transition band of 1 Hz. Inter-beat intervals (IBIs) were calculated as the difference between R wave peaks, identified using a custom algorithm and checked for accuracy by visual inspection. IBIs were derived for the IBI in which the tone was presented (IBI 0 in Fig. 1), the 5 prior IBIs (IBIs −5 to −1), and the 8 subsequent IBIs (IBIs 1 to 8; see de Zambotti et al., 2016 for further details).

HR measures were averaged across trials to create an event-related HR response. To obtain a stable baseline HR measure, HR in the fourth to second IBIs preceding the tone presentation (IBIs −4 to −2) were averaged (reported as beats per minute [bpm]). Maximum HR was defined as the highest HR in the five IBIs following the tone. Change in HR was calculated as percent increase in HR from the baseline to the maximum HR. The latency of the maximum HR was defined simply as the IBI in which maximum HR was attained (again in the five IBIs following tone presentation). To capture the HR slowing following the initial acceleration, the HR change from baseline was calculated for the mean of the last two IBIs (IBI 7 and IBI 8).

Group (AUD vs. Control) and K-complex-related (KCP vs. KCN) differences in HR measures were tested using repeated-measures ANOVA. Pearson's correlations were calculated between alcohol consumption measures and HR measures for both KCP and KCN conditions in the AUD subjects only.

Results

AUD participants had a significantly higher lifetime alcohol consumption ($p < 0.001$) and significantly fewer years of education than controls [$t(27) = -3.83$, $p < 0.001$]. The groups did not differ in age or BMI (see Table 1).

Baseline HR prior to tones

Baseline HR was higher in AUD participants (70.05 ± 11.62 bpm) than in controls (55.47 ± 6.60 bpm) [$F(1,27) = 15.69$, $p < 0.001$], but there was no significant overall effect of KCP (63.63 ± 12.51 bpm) vs. KCN (63.40 ± 11.86 bpm). There was a significant interaction between group and KCP/KCN [$F(1,27) = 4.32$, $p < 0.01$], in which there was a slight elevation in baseline HR prior to KCP (70.41 ± 12.02 bpm) compared to KCN (69.70 ± 11.58 bpm) in AUD, but no difference prior to KCP or KCN in controls (KCP: 55.28 ± 6.90; KCN: 55.66 ± 6.55 bpm).

Percentage increase from baseline to maximum HR

The percentage increase in HR from baseline to the maximum was lower in AUD participants (2.19 ± 1.89%) than in controls (3.85 ± 2.12%) [$F(1,27) = 10.13$, $p < 0.01$]. Percentage HR increase was significantly higher overall in KCP (3.94 ± 2.14%) than in KCN (1.93 ± 1.64%) [$F(1,27) = 27.74$, $p < 0.001$]. There was, however, no group by KCP/KCN interaction (AUD: KCP 3.10 ± 2.11%, KCN 1.28 ± 1.09%; Control: KCP 4.97 ± 1.74%, KCN 2.72 ± 1.89%). Raw HR values showing the increase are presented in Fig. 1A.

Percentage deceleration following maximum HR

The percentage deceleration from the maximum HR following a tone to the HR in the last IBI was lower in AUD participants (0.09 ± 1.37%) than in Controls (−1.46 ± 1.74%) [$F(1,27) = 9.24$, $p < 0.01$]. Percentage HR deceleration did not differ overall between KCP (−0.75 ± 1.96%) and KCN (0.46 ± 1.46%), and there was no group by KCP/KCN interaction (AUD: KCP 0.41 ± 1.47%, KCN 0.26 ± 0.78%; Control: KCP −1.73 ± 1.79%, KCN −1.19 ± 1.71%). Raw HR values showing this decrease are presented in Fig. 1B.

Timing of maximum HR after tone presentation

There was a trend for time to maximum HR response (number of inter-beat intervals [IBI]) following tone presentation to be slightly delayed in AUD (3.78 ± 0.66 IBI) compared to Controls (3.31 ± 0.97 IBI) [$F(1,27) = 3.86$, $p = 0.06$]. The time to maximum HR response was significantly shorter in KCP (3.34 ± 0.77 IBI) compared to KCN (3.79 ± 0.86 IBI) [$F(1,27) = 8.55$, $p < 0.01$]. There was a trend for a group by KCP/KCN interaction [$F(1,27) = 3.16$, $p = 0.08$] with the KCP/KCN difference tending to be smaller in AUD (KCP: 3.69 ± 0.48 IBI; KCN: 3.88 ± 0.81 IBI) than in Controls (KCP: 2.92 ± 0.86 IBI; KCN: 3.69 ± 0.95 IBI). The full-time course of HR from pre-tone baseline through to eight inter-beat intervals following the tone is presented in Fig. 2 for both groups and both KC conditions.

Relations between ANS response and drinking variables

Within the AUD group, there were no significant correlations between the magnitude of HR acceleration or of HR deceleration

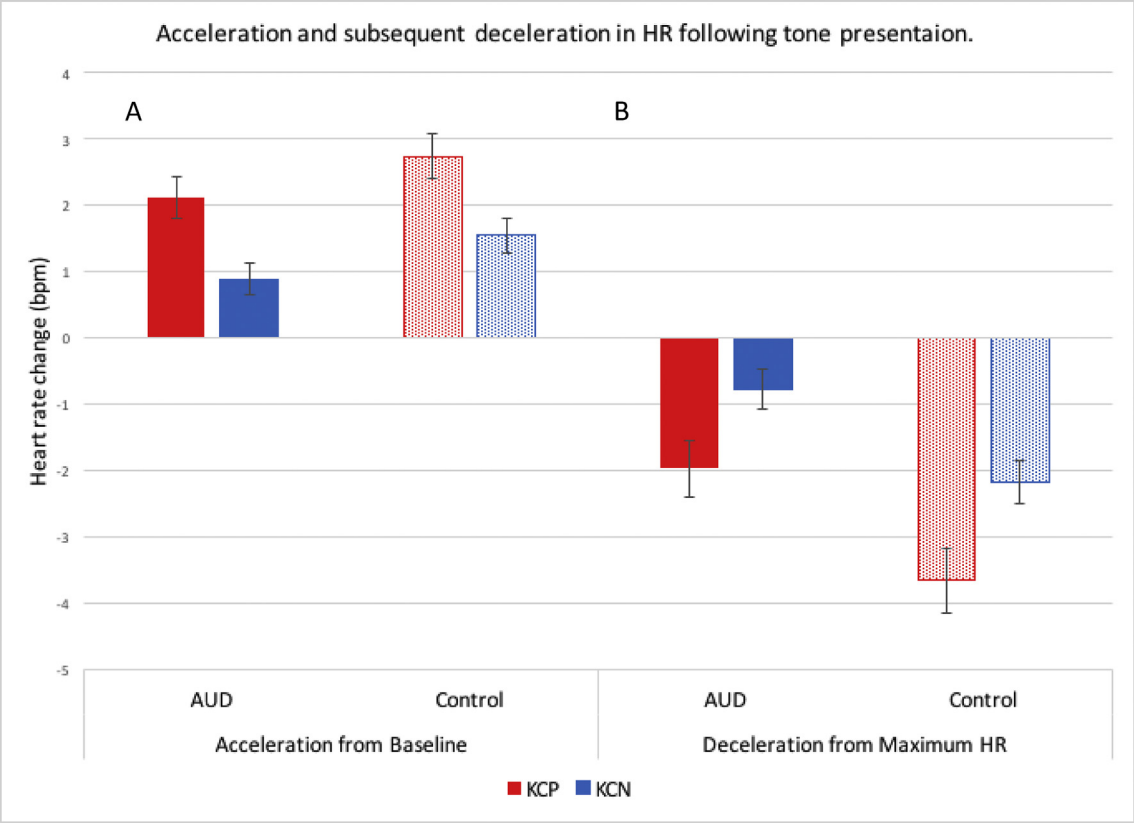

Fig. 1. Heart rate changes observed following tone presentation that did (KCP, red bars) or did not (KCN, blue bars) elicit a K-complex during N2 sleep for the AUD (solid bars) and Control (shaded bars) groups. Left panel: Maximum acceleration in heart rate above baseline (IBI −4 to IBI −2). Right panel: Maximum deceleration in heart rate (up to IBI +8) from the maximum acceleration observed following tone presentation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and any of the alcohol consumption measures (time since last drink, length of alcohol dependence, and log estimated lifetime alcohol consumption). However, the time to maximum HR following a tone was significantly correlated with log estimated lifetime alcohol consumption for both the KCP ($r = 0.53$, $p < 0.05$) and KCN ($r = 0.56$, $p < 0.05$) conditions.

Discussion

Our results show that the initial increase in HR following tones presented during N2 sleep is both smaller and tends to be delayed in recently abstinent AUD participants compared with healthy controls. Inspection of Fig. 2 suggests that the delay is caused, at

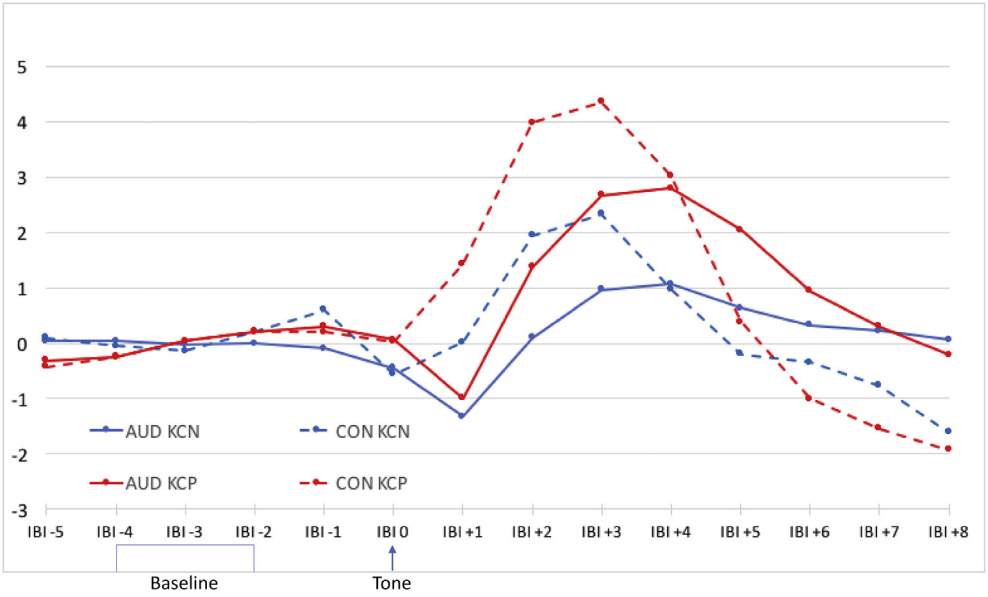

Fig. 2. Percent change in heart rate from baseline (IBI −4 to IBI −2) following tone presentation that did (KCP, red lines) or did not (KCN, blue lines) elicit a K-complex during N2 sleep for the AUD (solid lines) and Control (dashed lines) groups. The tone was presented during IBI 0. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

least in part, by a delay in the initiation of the HR response. Furthermore, the decrease in HR following the initial increase was also significantly larger in controls than AUD participants. While this measure does not capture the full extent of the HR slowing (the peak in deceleration may have occurred after the analysis period), the reduced bradycardia seen in the AUD group is likely maintained through the rest of the HR response. These findings complement other research showing both ANS (de Zambotti et al., 2014; Ganesha et al., 2013; Irwin et al., 2006) and CNS (Colrain, Crowley, et al., 2009; Willoughby et al., 2015) alterations during sleep in those with AUD. The fact that the data were obtained during sleep rules out other potential confounding causes of group differences such as attention, effort, or motivation, such as the orienting response (Friedman, Cycowicz, & Gaeta, 2001).

Our results clearly confirm our previous finding and that of Berg et al. (1975) that tones that produce KCs are associated with a greater HR increase than tones that fail to elicit a KC, although they failed to replicate the previous result of baseline HR being lower prior to KCP vs. KCN (de Zambotti et al., 2016). They extend previous work by showing that the timing of the HR increase is shorter in KCP than in KCN responses.

There is now considerable evidence that ANS modulation is compromised with AUD (de Zambotti et al., 2014; Ganesha et al., 2013; Irwin et al., 2006). However, the relative contribution of the potential sources – central control mechanisms, ANS integrity, and the organs innervated by the ANS – to the ANS dysfunction found in AUD is still unknown. The decrease in KC amplitude found with AUD in previous studies suggests altered cortical function (Colrain, Crowley, et al., 2009; Colrain et al., 2012; Nicholas, Sullivan, et al. 2002; Willoughby et al., 2015), perhaps secondary to AUD-related cortical shrinkage (Colrain, Crowley, Nicholas, Afifi, Baker, Padilla, Turlington et al. 2010; Colrain, Sullivan, Rohlfing, Pitel, Chanraud & Pfefferbaum, 2010). While little evidence is available for impairments in sub-cortical CV control in humans, evidence from experiments in rodents suggests excessive alcohol use causes brainstem abnormalities (including the medulla oblongata) (Agar et al., 1999; Lai et al., 2013; Luo, Tahsili-Fahadan, Wise, Lupica, & Aston-Jones, 2011). It is, therefore, possible that alteration in the neural control of HR through vagal pathways may also be implicated in our results of altered HR fluctuation to tone-elicited KCs. The finding of vagal neuropathy seen in AUD patients suggests that the ANS itself is compromised and is likely to play at least some part in the reduced CV responsivity found with AUD (Barter & Tanner, 1987; Duncan et al., 1980; Villalta et al., 1989). However, we cannot exclude other effects of alcohol, such as cardiomyopathy, which suggest that damage to the organs themselves (e.g., the heart) may also play a role in the ANS dysfunction seen in AUD (Gardner & Mouton, 2015; Laurent & Edwards, 2014). This is consistent with our finding that the timing of the HR increase in AUD was correlated with estimated lifetime alcohol consumption in the AUD participants.

The HR fluctuation associated with KCs reported here in the control group is consistent with our previous research into the HR changes associated with KCs in adolescents. The overall magnitude of the HR acceleration was similar to that reported previously (around 5% for the control participants in this study compared with approximately 7% in our previous study, despite the controls in the present study having a lower average baseline HR). Similarly, the latency of the maximum change in HR for KCP was similar in the control participants in this study (approximately IBI position 2.9), compared with our previous one (approximately IBI position 2.5). Experimental and analytical procedures were identical for both studies, so the small differences can probably be attributed to the different ages of the participants; the mean age of the control participants in the present study was approximately 47 years, whereas the mean age for participants in the previous study was approximately 19 years, and it is known that KC production is sensitive to age (Colrain, Crowley et al., 2010).

It is clear that ANS responses are seen in the absence of cortical arousal and in the absence of a KC; however, the magnitude of the ANS response is greater when a KC is also produced. A necessary caveat, however, is that some responses associated with small KCs or desynchronizations may have been included in the KCN category. One possible interpretation of these results is that both the KC and HR changes are parallel responses to the external tone stimulus. This is not a new idea, and was indeed proposed by Ackner and Pampiglione to explain their finding of associations between KCs and autonomically mediated vasomotor responses (Ackner & Pampiglione, 1957). In this explanation, the stimulus (if it survives perceptual gating) would have two effects – one on the ANS, where the stimulus results in low-level autonomic arousal, and another on the CNS, where a KC is elicited to protect sleep from cortical arousal by continued stimulus processing. Prior research has also shown that there is a relationship between HRV measures of vagal or sympathovagal balance and EEG measures of SWS (Kuo & Yang, 2004; Miyashita et al., 2003; Rothenberger et al., 2015; Yang, Lai, Lai, & Kuo, 2002). This linkage allows for a hypothesis of associations between CNS and ANS responses to a phasic event such as a KC, considered an indication of CNS-ANS coupling sleep (de Zambotti et al., 2018). Importantly, our recent study in adolescents showed identical cardiac acceleration to both tone-evoked and spontaneous KCs, with a smaller change associated with tones that did not produce a KC (de Zambotti et al., 2016), consistent with the present finding.

The results of the present study extend our previous findings of alterations in KC (Colrain, Crowley, et al., 2009; Colrain et al., 2012; Nicholas, Sullivan, et al., 2002; Willoughby et al., 2015) and in HR during sleep (de Zambotti et al., 2015) in AUD. It also extends the findings of KC-related modulation of HR (de Zambotti et al., 2016) to show that there are alterations in the CNS-ANS coupling associated with long-term alcohol abuse, highlighting the potential clinical utility of this measure. The existence of a selective alteration in cardiac vagal trafficking and the neural or non-neural origin of this hypothesized alteration will need to be determined.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alcohol.2019.09.005.

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