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An Exploratory Factor Analysis of the Stimulant, Sedative, and Affective Responses to Alcohol

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Background: Subjective response (SR) to acute alcohol reflects individual variance to the sensitivity of alcohol's pharmacological effects. It has been argued that measures of stimulation and sedation may not fully capture the full-range SR, with 2 novel domains proposed: high arousal negative and low arousal positive. While substantial progress has been made in the field of SR and alcohol use risk, it remains unknown how these novel domains correspond to traditional SR measures. Therefore, the current study examined the latent structure of traditional and novel SR measures at rising breath alcohol concentrations (BrACs) during alcohol administration.

Methods: Heavy drinkers (n = 67; 36M/31F) participated in an intravenous alcohol administration. Questionnaires assessing stimulation, sedation, mood, valence and arousal, and craving were assessed at baseline and at BrACs of 20, 40, and 60 mg%. A series of exploratory factor analyses were conducted to examine the latent factor structure of SR at each time point. Correlations examined the association between the generated factors and measures of problematic alcohol use.

Results: The analysis generated a 3-factor solution, consistent across all time points. The factors measured the following effects of SR: (i) stimulation and positive mood, (ii) sedation and aversive effects, and (iii) tension reduction. The tension reduction factor was most commonly associated with problematic alcohol use in this sample.

Conclusion: This study extends upon the literature evaluating the biobehavioral effects of alcohol by examining a novel combination of SR to alcohol measures. This study demonstrates that the proposed low arousal positive domain, which loaded onto the tension reduction factor, provides novel information not captured by previous SR measures. Going forward, studies of alcohol's subjective effects should use this dimensional approach to reduce multiple comparisons across a wide range of scales and to build a literature grounded on the underlying structure of SR as a translational phenotype for AUD.

Key Words: Subjective Response, Factor Analysis, Stimulation, Sedation, Tension Reduction.

SUBJECTIVE RESPONSE (SR) to acute alcohol reflects individual variance to the sensitivity of alcohol's pharmacological effects. SR has a long and rich history in alcohol research and has been proposed as a translational phenotype for alcohol use disorder (Ray et al., 2016). SR to alcohol is thought to be biphasic in nature, with individuals reporting greater stimulatory, pleasant, and arousing effects during the ascending limb of the blood alcohol curve and reporting greater sedative and negative effects during the descending limb (Earleywine and Martin, 1993). Individual variation in these stimulant and sedative effects has been proposed to confer risk for heavy drinking and the development of AUD. Two prominent theoretical models suggest differing patterns of SR which may predispose individuals to this risk. The Low Level of Response Model (LLR; (Schuckit, 2009)) proposes that individuals who report an attenuated response to alcohol are most at risk for increased alcohol use and misuse, potentially reflective of an individual's innate or chronic tolerance to alcohol (Morean and Corbin, 2008; Schuckit et al., 2008). Conversely, the differentiator model (DM (Newlin and Thomson, 1990)) suggests that individuals who experience greater positive, or stimulant effects during the ascending limb and decreased negative, sedative effects during the descending limb are at the greatest risk, potentially reflecting a sensitization process (Wise and Bozarth, 1987).

Both models have evidence to support the relationship of SR phenotypes and alcohol use risk. For the LLR model, studies showed a robust predictive relationship between reduced SR, measured by the Subjective High Assessment Scale (SHAS), and the development of AUD (Schuckit and Smith, 1996; Schuckit et al., 2004). The SHAS appears to best measure "terrible feelings" associated with drinking (Schuckit, 1985) and is more strongly related to the sedative effects of alcohol SR (Ray et al., 2009; Ray et al., 2010), suggesting that the SHAS captures the aversive effects of alcohol. Support for the DM indicates that the greater subjective stimulation and reward and lower sedation predict binge

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drinking escalation and AUD symptomology (King et al., 2016; King et al., 2014; King et al., 2011). These studies relied on the Biphasic Alcohol Effects Scale (BAES), a measure thought to capture the stimulant and sedative effects of alcohol.

More recently, it has been suggested that measures of stimulation and sedation may not fully capture the range of responses to acute alcohol. Work from our group suggests 4 domains of SR combining items from the SHAS, BAES, and mood and craving measures: stimulation/hedonia, craving/motivation, sedation/motor intoxication, and negative affect (Bujarski et al., 2015; Ray et al., 2009). Similar efforts have been made to create a new scale to measure the full range of arousal and valence SR experienced during alcohol ingestion. The Subjective Effects of Alcohol Scale (SEAS) is a 14-item questionnaire which captures 4 affective quadrants: high arousal positive (e.g., lively and fun), low arousal positive (e.g., relaxed and calm), high arousal negative (e.g., aggressive and demanding), and low arousal negative (e.g., dizzy and woozy (Morean et al., 2013)). Alcohol has significant effects on mood, both through the elevation of positive mood, which is largely captured through measures of stimulation and hedonia, and through the alleviation of negative mood, captured by a tension reduction factor and by the low arousal positive SEAS quadrant. Given that relief from negative affect and withdrawal symptoms is thought to be a critical component of the addiction cycle (Koob and Volkow, 2016), and the evidence that negative mood induction motivates alcohol seeking and increases alcohol seeking (Amlung and MacKillop, 2014; Zack et al., 2006), it is crucial to measure negative mood as part of SR to alcohol.

The developers of the SEAS scale evaluated the relationship between the SEAS, BAES, and SHAS measures (Morean et al., 2013), which identified largely the predicted associations between the 3 measures. Moreover, SEAS scores accounted for significant variance in total drinks, frequency of binge drinking, and experiencing alcohol-related problems (Morean et al., 2013). Despite the promise of including a measure that captures the full range of SR to acute alcohol, few studies have incorporated the SEAS into their study design. Therefore, the field may be leaving out an important dimension of SR, by only focusing on the stimulating and sedating effects of alcohol. Given that SR to alcohol has the potential to serve as a research domain criterion (Ray et al., 2016), as it represents a phenotype that can describe the phenomenology of AUD and can offer insights into treatment, it is critical that a parsimonious, yet complete, range of domains be captured in this construct.

While substantial progress has been made in the field of SR and alcohol use risk, there is still room for improvement in this phenotype. It remains unknown how the SEAS measure relates to measures of mood and craving, which are important determinants of alcohol seeking. It is also currently unknown if the SEAS domains of high arousal negative and low arousal positive provide new information not obtained in previous SR measures. Finally, the SEAS SR measure has not yet been evaluated using intravenous (IV) alcohol administration with a community sample of heavy drinkers. To fill these gaps, we evaluated SR to IV alcohol in a sample of non–treatment-seeking heavy drinkers. Specifically, we collected SR measures (SEAS, BAES, and SHAS), a measure of positive and negative mood (Profile of Mood States (POMS)), and a measure of alcohol craving (Alcohol Urge Questionnaire) at baseline and at 3 levels of rising BrAC. We then examined the latent structure among the above measures at each time point. Based on previous work (Bujarski et al., 2015; Zimmermann et al., 2008), we anticipated the emergence of 4 factors capturing positive feelings/stimulation, negative feelings/sedation, negative mood, and alcohol craving. We also explored the relationship between the identified factors and alcohol use measures to assess whether the severity of problematic alcohol use was associated with a specific subjective response pattern to IV alcohol in this sample.

MATERIALS AND METHODS

Participants

This study was approved by the Institutional Review Board at the University of California, Los Angeles (UCLA). Non–treatment-seeking heavy drinkers were recruited between April 2015 and August 2016 from the Los Angeles community through online advertisements and fliers. Advertisements recruited Caucasian individuals who drank alcohol regularly to participate in a study about responses to alcohol administered intravenously. Initial eligibility screening was conducted through online and telephone surveys followed by an in-person screening session. Upon arrival, participants provided written informed consent, were breathalyzed, and provided urine for toxicology screening. Participants then completed a battery of self-report questionnaires and interviews. All participants were required to have a BrAC of 0 mg% and to test negative on the urine toxicology screening (except cannabis). Female participants were required to test negative on a urine pregnancy test.

Full inclusion and exclusion criteria for this study have been previously published (Bujarski et al., 2018). Briefly, participants were required to be between the ages of 21 and 45 and engage in current heavy drinking patterns (14 + drinks/wk for men and 7 + drinks/wk for women). Participants were excluded if they were seeking treatment for their alcohol use, met diagnostic criteria for a substance use disorder other than nicotine or alcohol, had clinically significant physical abnormalities indicated by a physical examination and liver function laboratories, or had significant alcohol withdrawal, as indicated by a score of ≥ 10 on the Clinical Institute Withdrawal Assessment for Alcohol—Revised (CIWA-Ar (Sullivan et al., 1989)). Additionally, all study participants were Caucasian due to an exploratory genetic study aim, not discussed herein.

Alcohol Administration Procedure

Participants arrived at the UCLA Clinical and Translational Research Center (CTRC) in the morning. Vital signs, height, and weight were measured, and participants were provided with a standardized meal. IV lines were placed by a registered nurse. The alcohol infusion lasted approximately 180 minutes. During the alcohol infusion, participants were seated in a comfortable chair and were not permitted to view the infusion pump or the technician's screen. Study staff remained in the room throughout the study to administer questionnaires and breathalyze the participant.

Alcohol was administered intravenously (6% ethanol v/v in saline) to assess SR to alcohol independently from learned responses to alcohol cues, and to have precise experimental control over BrAC (Li et al., 2001). The pharmacokinetic model implemented by the Computerized Alcohol Infusion System (CAIS) was used (Plawecki et al., 2008; Zimmermann et al., 2009; Zimmermann et al., 2008; Zimmermann et al., 2011). CAIS estimates BrAC based on the infusion time course and the participants' sex, age, height, weight, and breathalyzer readings. Participants were administered alcohol designed to reach target BrACs of 20, 40, and 60 mg%. BrAC was clamped at each target concentration, while participants completed questionnaires (see below). Following the 60 mg% time point, participants completed a self-administration paradigm (see Bujarski et al., 2018 for details). The self-administration data were not used in the current study and will not be discussed further. After 180 minutes, the infusion ended and the IV line was removed. Participants were discharged from the CTRC when their BrAC fell below 40 mg% or 0 mg% if they were driving.

Measures

Alcohol Use Measures. The Timeline Followback (TLFB) was administered in interview format to capture daily alcohol (as well as cigarette and cannabis) use over the 30 days prior to the visit (Sobell et al., 1988). Two indicators of alcohol quantity and frequency were calculated from the TLFB: number of drinking days and drinks per drinking day. The Structured Clinical Interview for DSM-5 (SCID; First et al., 2015) was assessed for current AUD and exclusionary diagnoses. Participants also completed the Alcohol Use Disorder Identification Test (AUDIT (Saunders et al., 1993)) and the Penn Alcohol Craving Scale (PACS (Flannery et al., 1999)).

Subjective Response Measures. Subjective responses to alcohol were assessed at baseline (i.e., BrAC = 0.00 g/dl) and at target BrACs of 20, 40, and 60 mg%. The following scales were used:

Biphasic Alcohol Effects Scale—The BAES is a self-report measure assessing subjective response to alcohol and is composed of 2 subscales: stimulation and sedation, which are each composed of 7 items (Martin et al., 1993). Stimulation is measured by items such as elated, excited, and stimulated, while sedation is measured by items including down, inactive, and sedated. The items in the BAES are listed alphabetically and are rated on a 10-point scale. Cronbach's alphas for BAES-Stim from baseline through the rising BrAC levels were as follows: 0.86, 0.91, 0.92, and 0.93, respectively. Cronbach's alphas for BAES-Sed from baseline through the rising BrAC levels were as follows: 0.86, 0.83, 0.86, and 0.84, respectively.

Subjective High Assessment Scale—The SHAS is a self-report measure evaluating feelings of alcohol intoxication (Schuckit, 1984). The SHAS is comprised of 13 items; sample items are drunk, nauseated, and dizzy. Each item is rated on a 10-point scale ranging from "not at all" to "extremely." Cronbach's alphas for the SHAS across baseline through rising BrAC levels were as follows: 0.85, 0.89, 0.89, and 0.91, respectively.

Subjective Effects of Alcohol Scale—The SEAS measures subjective response to alcohol across a range of arousal and valence (Morean et al., 2013). The SEAS is comprised of 14-items which assess 4 domains: high arousal positive (lively, talkative, fun, funny), high arousal negative (aggressive, demanding, rude), low arousal positive (mellow, secure, relaxed, calm), and low arousal negative (dizzy, wobbly, woozy). Items are rated on a 10-point scale ranging from "not at all" through "moderately" to "extremely." Cronbach's alphas for high arousal positive were as follows: 0.89, 0.88, 0.93, and 0.92. Cronbach's alphas for high arousal negative were lower than previously reported (Morean et al., 2013): 0.40, 0.68, 0.54, and 0.79. Cronbach's alphas for low arousal positive were as follows: 0.88, 0.89, 0.85, and 0.82. Cronbach's alphas for low arousal negative were as follows: 0.75, 0.74, 0.88, and 0.87.

Profile of Mood States—An adapted 40-item version of the POMS scale was used to assess positive and negative affect (Lorr et al., 1971). Two subscales of the POMS were used: positive mood and negative mood. Sample items for positive mood include lively, active, cheerful, joyful, and elated. Sample items for negative mood include nervous, anxious, sad, lonely, and downhearted. Each item is rated on a 5-point scale ranging from "not at all" to "extremely." Cronbach's alphas for positive mood were as follows: 0.95, 0.93, 0.95, and 0.95. Cronbach's alphas for negative mood were as follows: 0.94, 0.91, 0.92, and 0.91.

Alcohol Urge Questionnaire—The AUQ is an 8-item questionnaire assessing alcohol craving (Bohn et al., 1995). Items are assessed on a 7-point scale in which participants are asked to endorse their agreement or disagreement with statements regarding their desire to drink. Reliability estimates for the AUQ were as follows: 0.89, 0.89, 0.86, and 0.90.

Data Analysis

A series of exploratory factor analysis (EFA) were conducted in SAS University Edition v.9.4 to examine the latent factor structure of SR at 4 time points: baseline and at BrAC of 20, 40, and 60 mg %. For each SR measure (i.e., POMS-Pos. Mood, POMS-Neg. Mood, SHAS, BAES-Stim., BAES-Sed., SEAS-High Pos., SEAS-High Neg., SEAS-Low Pos., SEAS-Low Neg., and AUQ), the prior communality estimate for each variable was set to its squared multiple correlation with all other variables. A principal factor analysis method was used to extract factors followed by an oblique (promax) rotation. An oblique rotation was used to allow for correlation among the resulting factors (Costello and Osborne, 2005). Factor structure was determined by eigenvalue >0.75 and examination of the scree plot. Additionally, a series of maximum likelihood factor analysis were conducted at each time point to obtain chi-square values for multiple factor analysis runs to provide further support for the best number of common factors. A factor loading threshold of 0.40 was used to determine whether a variable significantly loaded onto a factor (O'Rourke and Hatcher, 2013; Pituch and Stevens, 2015).

A consistent pattern emerged regarding the number of factors at each time point. Notably, at BrAC = 60 mg%, a Heywood case was observed such that communality estimates for the EFA at this time point exceeded 1. This Heywood case was likely due to our relatively smaller sample size. Therefore, the analysis at this time point set the upper bound of any communality to 1. At no other time points was a Heywood case observed. While our sample size did not meet the traditional recommendation of ≥ 10 participants per variable (Everitt, 1975), previous research has suggested reliable results can still be achieved with smaller sample sizes (de Winter et al., 2009). Previous research has suggested that the minimum sample size in EFA depends on several parameters (de Winter et al., 2009). Specifically, de Winter and colleagues (2009) found that an EFA can produce reliable results for $N < 50$ when data are well conditioned (i.e., high level of factor loading, low number of factors, and high number of variables). In our present sample, while our factor loading was on the low to medium end (cutoff = 0.40), we retained a low number of factors ($n = 3$) based on our eigenvalue cutoff and examination of the scree plots. Lastly, our total number of variables ($n = 9$) was selected with the aim of increasing the ratio of number of variables to number of factors, as this has been shown to improve factor recovery (MacCallum et al., 1999). Consequently, given the small sample size we were unable to choose an exceedingly large number of variables; therefore, we carefully selected which variables

to include as to not undermine the quality of the dataset (de Winter et al., 2009). In addition, we divided our sample by gender and replicated the methods above to qualitatively compare the latent factor structure of SR at the 4 time points split by gender. Notably, there was an increase in Heywood cases (females: baseline and BrAC of 20 mg%; males: BrAC of 40mg%. and 60mg%) that was likely due to the substantial reduction of our sample size. Lastly, bivariate Pearson's correlations were conducted in SAS University Edition v.9.4 to explore the association between the generated factors and indicators of problematic alcohol use (e.g., AUD symptom count). For the correlations with indicators of problematic alcohol use, a multiple-comparison correction was applied (corrected alpha = 0.017), which is the equivalent of dividing the alpha level of $p = 0.05$ by 3, which is the number of indicators of problematic use examined. Scatter plots were constructed to further examine the association between the resulting factors at the end of the intravenous alcohol administration (i.e., BrAC of 60 mg%) and problematic alcohol use variables.

RESULTS

Sample Characteristics

Participant characteristics are reported in Table 1. In general, participants were young, heavy drinkers, with the majority of the sample meeting criteria for an AUD (57%). Participants reported drinking over half of the days in the previous month and drank an average of 5.3 drinks on a drinking day.

Subjective Response Measure Correlations

An example of the correlations between the subjective response measures at each time point is presented in Table 2 (the full set of correlations at each time point can be found in the Table S1). Generally, across time points, BAES stimulation was positively correlated with SEAS high arousal positive, POMS-positive mood, and AUQ, and negatively correlated with POMS-negative mood. BAES sedation was positively correlated with SHAS, SEAS low arousal negative, and POMS-negative mood, and negatively correlated with SEAS high arousal positive and POMS-positive mood. SHAS was positively correlated with SEAS high arousal negative and POMS-negative mood. SEAS high arousal positive was positively correlated with SEAS low arousal positive and POMS-positive mood, and negatively correlated with POMS-negative mood. SEAS low arousal positive was positively associated with POMS-positive mood and negatively correlated with POMS-negative mood. SEAS low arousal negative was positively associated with POMS-negative mood. POMS-positive mood was negatively correlated with POMS-negative mood. SEAS high arousal negative did not display a consistent pattern of correlations.

Table 1. Demographic and Clinical Sample Characteristics

Characteristic	Mean + SD	Range
Age	29.09 ± 6.56	21 to 45
Sex (M/F)	36/31	-
AUD Severity (None/Mild/ Moderate/Severe)	29/15/16/7	-
AUD Symptoms	2.43 ± 2.07	0 to 8
AUDIT Score	13.43 ± 5.80	4 to 33
PACS Score	9.75 ± 5.76	0 to 26
Total Drinks (30 Days)	94.47 ± 56.11	28.76 to 375.84
Drinking Days (30 Days)	18.18 ± 6.40	7 to 30
Drinks Per Drinking Day (30 Days)	5.30 ± 2.54	2.07 to 13.81
Binge Drinking Days (30 Days)	8.67 ± 6.65	0 to 29

Factor Analysis

Both the scree plot and the maximum likelihood estimation analyses agreed on a 3-factor solution (see Table S2). The factor solution was consistent across all BrAC levels. Examination of eigenvalues also agreed with a 3-factor solution. For example, at BrAC of 60mg%, Factor 1 had an eigenvalue of 3.29 which accounted for 52% of the variance. Factor 2 had an eigenvalue of 2.10, accounting for 33% of the variance, and Factor 3 had an eigenvalue of 1.02, accounting for 16% of the variance.

As shown in Table 3, Factor 1 was comprised of BAES stimulation, SEAS high arousal positive, and POMS-positive mood, suggesting this factor represents the stimulating and hedonic aspects of alcohol response. BAES sedation, SHAS, and SEAS low arousal negative loaded onto Factor 2, indicating that this factor represents the sedative and aversive aspects of the subjective response to alcohol. Finally, Factor 3 was comprised of SEAS low arousal positive and POMS-negative mood, inversely related, suggesting that this factor captures the calming and tension-reducing aspects of the subjective response to alcohol. The loadings for Factor 3 differed between baseline and during alcohol administration, such that at baseline, the factor reflected negative mood, with low arousal positive negatively loading onto this factor. Additionally, at baseline AUQ loaded onto this factor, suggesting that craving and negative mood were high at baseline prior to the administration of alcohol. Conversely, during rising breath alcohol concentrations, low arousal positive loaded positively onto the factor and negative mood loaded negatively onto the factor. Similar factors were obtained when the study sample was split by gender (see Table S3). Interfactor correlations can be found in Table S4.

Correlations Between SR Factors and Clinical Variables

Associations between subjective response factors and clinical variables reflecting problematic alcohol use are presented in Table 4. Factor 1, which captured stimulation and reward, was only significantly associated with number of drinking days in the past 30 days and only at BrAC of 20mg%. This indicates that individuals who reported greater alcohol-induced stimulation also reported drinking more frequently over the past month. Factor 2, which represents sedation and aversive response, was significantly correlated with number of AUD symptoms. Specifically, individuals who reported more sedation at baseline were more likely to endorse more

Table 2. Correlations between Subjective Response Measures at BrAC = 60 mg%

	BrAC = 60mg%									
	Stim	Sed	SHAS	HP	HN	LP	LN	POMS+	POMS-	AUQ
Stim	1									
Sed	**−0.27**	1								
SHAS	0.16	**0.60**	1							
HP	**0.86**	**−0.41**	−0.01	1						
HN	0.17	0.05	0.20	0.12	1					
LP	**0.33**	−0.09	0.001	**0.33**	−0.17	1				
LN	0.18	**0.33**	**0.74**	0.15	0.12	0.03	1			
POMS+	**0.88**	**−0.39**	−0.02	**0.86**	0.21	**0.43**	0.05	1		
POMS-	**−0.28**	**0.31**	**0.26**	**−0.31**	0.05	**−0.64**	0.16	**−0.46**	1	
AUQ	**0.35**	−0.001	**0.27**	**0.32**	0.10	−0.09	0.15	0.22	0.23	1

Stim = BAES stimulation; Sed = BAES sedation; HP = SEAS high arousal positive; HN = SEAS high arousal negative; LP = SEAS low arousal positive, LN = SEAS low arousal negative; POMS+ = POMS-positive mood; POMS- = POMS-negative mood.
Bold typeface indicates significant correlations ($p < 0.05$).

Table 3. Factor Loadings

	Baseline			BrAC = 20mg%			BrAC = 40mg%			BrAC = 60mg%		
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3.	Factor 1	Factor 2	Factor 3
Stim	**0.85**	−0.06	0.13	**0.86**	0.15	−0.04	**0.88**	0.14	0.01	**0.92**	0.09	0.04
Sed	−0.34	**0.56**	−0.04	−0.28	**0.74**	0.19	−0.36	**0.61**	0.11	−0.36	**0.62**	0.03
SHAS	−0.01	**0.94**	−0.01	0.09	**0.91**	−0.01	0.14	**0.97**	0.04	0.10	**1.02**	0.02
HP	**0.81**	−0.01	−0.07	**0.85**	0.01	0.09	**0.90**	−0.09	0.05	**0.92**	−0.07	0.02
HN	0.26	0.21	0.12	0.27	0.21	−0.08	0.33	0.28	−0.08	0.26	0.11	−0.19
LP	0.16	0.11	**−0.86**	−0.01	0.13	**0.98**	−0.04	0.13	**0.95**	−0.03	0.16	**0.85**
LN	0.09	**0.60**	0.30	0.24	**0.72**	−0.17	0.32	**0.70**	−0.12	0.16	**0.69**	0.03
POMS+	**0.96**	0.05	−0.06	**0.84**	−0.16	0.15	**0.88**	−0.09	0.12	**0.85**	−0.06	0.19
POMS-	−0.07	0.19	**0.76**	−0.05	0.22	**−0.67**	−0.12	0.18	**−0.68**	0.03	0.12	**−0.82**
AUQ	0.19	0.14	**0.44**	0.31	0.03	−0.5	0.29	0.13	−0.4	**0.50**	0.13	−0.36

Stim = BAES stimulation; Sed = BAES sedation; HP = SEAS high arousal positive; HN = SEAS high arousal negative; LP = SEAS low arousal positive, LN = SEAS low arousal negative; POMS+ = POMS-positive mood; POMS- = POMS-negative mood.
Bold typeface indicates measures which loaded significantly onto each factor.

symptoms of AUD. Factor 3, representing tension reduction, was negatively associated with AUD severity (AUDIT score and number of AUD symptoms) measures at higher BrAC levels (40 and 60mg%). Specifically, individuals who reported greater alcohol-induced relaxation had lower AUDIT scores and endorsed fewer AUD symptoms. At baseline, where Factor 3 represents negative mood and craving, this factor was positively associated with AUD severity, such that individuals who reported greater negative mood pre–alcohol infusion endorsed more AUD symptoms. Scatter plots of the correlations between SR factors at BrAC of 60mg% and clinical variables are shown in the Fig. S1. An examination of normality indicators (e.g., skew, kurtosis, outliers, and z-scores) revealed all variables included in the correlations were approximately normally distributed. Scatter plots revealed a few noticeable outliers particularly for Factor 3 (tension reduction).

Table 4. Correlations between SR Factors and AUD Clinical Variables

	AUDIT	AUD Symptoms	Drinking Days
Factor 1—Stimulation			
Baseline	−0.12	−0.21	0.07
BrAC = 20mg%	−0.09	0.06	**0.32**
BrAC = 40mg%	−0.18	0.04	0.21
BrAC = 60mg%	−0.09	0.08	0.18
Factor 2—Sedation			
Baseline	0.22	**0.46**	0.15
BrAC = 20mg%	0.26	0.25	−0.04
BrAC = 40mg%	0.22	0.24	0.07
BrAC = 60mg%	0.22	0.19	0.06
Factor 3—Tension Reduction			
Baseline	0.14	**0.35**	0.09
BrAC = 20mg%	−0.09	−0.08	0.16
BrAC = 40mg%	**−0.28**	−0.28	0.01
BrAC = 60mg%	**−0.36**	**−0.36**	−0.08

Significant correlations ($p < 0.017$) are presented in bold typeface.

DISCUSSION

The goal of this study was to evaluate the factor structure of measures of subjective response to alcohol alongside measures of mood and alcohol craving. The focus of this analysis was to investigate how the dimensions evaluated in the SEAS (high/low arousal positive/negative) loaded with

traditional subjective response measures (e.g., stimulation and sedation). We hypothesized the emergence of 4 factors, reflecting dimensions of stimulation, sedation, negative mood, and alcohol craving. Contrary to our initial hypothesis, results of the factor analyses indicated a 3-factor solution from baseline across rising breath alcohol concentrations. The consistency of this solution across BrAC levels is important in evaluating the reliability of these findings. Factor 1 captured feelings of stimulation and positive mood and was comprised on BAES stimulation, SEAS high arousal positive, and POMS-positive mood. Factor 2 captured feelings of sedation and aversive responses and was comprised of BAES sedation, SHAS, and SEAS low arousal negative. Factor 3 captured a negative mood and craving state pre–alcohol administration (positive loading of POMS-negative mood and AUQ and negative loading of SEAS low arousal positive) and feelings of calm and relaxation at rising breath alcohol concentrations (positive loading of SEAS low arousal positive and negative loading of POMS-negative mood). The stimulation/hedonic factor (Factor 1) was associated with drinking frequency, while the sedation (Factor 2) and tension reduction (Factor 3) factors were associated with AUD severity. Overall, this study demonstrates that the SEAS does provide novel information not assessed in the BAES, SHAS, or POMS measures; specifically, through the low arousal positive domain, which loaded onto a tension reduction factor inversely with POMS-negative mood. Yet, the SEAS high arousal positive loaded with the BAES stimulation and the low arousal negative loaded with BAES sedation as SHAS as predicted.

Early theories conceptualized the subjective effects of alcohol into 2 broad domains: stimulation, representing the hedonic and reinforcing effects of alcohol, and sedation, representing the depressant and aversive effects of alcohol. More recent work has expanded on these domains, through the addition of craving/motivation and the separation of negative affect from sedation (Bujarski et al., 2015; Ray et al., 2009) and through the addition of high arousal negative, thought to capture the subjective response of aggression, and low arousal positive, theorized to depict the calming and relaxing feelings associated with alcohol ingestion (Morean et al., 2013). Our findings provide partial support for the novel domains of the SEAS. Specifically, we found that low arousal positive loaded onto a separate factor from low arousal negative, which was grouped with BAES sedation and SHAS. Low arousal positive loaded inversely with POMS-negative mood, indicating that those who felt the calming effects of alcohol also reported lower levels of negative mood states. Interestingly, pre–alcohol administration, POMS-negative mood, and AUQ loaded positively onto the factor, while low arousal positive loaded negatively. This suggests that at baseline, when participants were not receiving alcohol (and were required to abstain prior to the visit to begin the study at a BrAC of 0mg%), participants reported negative mood and experienced craving, potentially reflecting a baseline dysphoric state. This provides indirect support for the "dark side of addiction" theory, where negative mood states and withdrawal symptoms are the main driver of drinking (Koob and Volkow, 2016). After alcohol was administered, the factor loadings changed, such that SEAS low arousal positive loaded positively and POMS-negative mood loaded negatively onto the factor, indicating that alcohol may have relieved these negative mood symptoms. These findings provide support for the tension reduction and stress reduction models (Levenson et al., 1980; Sher and Levenson, 1982), which suggest that individuals drink alcohol due to its ability to reduce tension and responses to stress. It has been suggested that individual variability in personality, for example, hostility (Zeichner et al., 1995), anxiety and negative urgency (Menary et al., 2015), as well as genetic variability in HPA axis genes (Clarke et al., 2008), may play an important role in the interaction between alcohol and tension/stress. However, it must be noted that this study was unable to test the longitudinal relationship between factor loadings and rising breath alcohol concentrations, as we applied an exploratory factor analysis approach. Therefore, it is not possible to definitively conclude the directional changes in factor loadings are due to alcohol administration. Future studies should employ a confirmatory factor analysis approach to evaluate this important relationship. Furthermore, based on a previous study (Bujarski et al., 2015), we hypothesized that craving would arise as a separate factor from stimulation, sedation, and tension relief. Contrary to this hypothesis, we found that craving did not load onto a separate factor at baseline or at any breath alcohol concentration. This difference may be due to sample size, the inclusion of different SR and craving measures, and/or the use of different data analytic strategies. Bujarski and colleagues (2015) enrolled a larger sample than the current study, included measures of alcohol liking and wanting in addition to the AUQ craving measure, and combined SR measures across the ascending limb.

This study did not find evidence to support the SEAS domain of high arousal negative as adding to the SR factor structure. SEAS high arousal negative did not load onto the 3 factors at any stage of alcohol administration, with the highest factor loading being 0.27 onto the stimulation factor at BrAC of 20mg%. This lack of an effect may be driven by the unreliability of this measure in our sample. Cronbach's alpha for SEAS high arousal negative ranged from 0.40 to 0.79, indicating that participants were not consistent in their response to the 3 items making up this subscale (aggressive, demanding, and rude). This is in contrast to Morean and colleagues (2013) who reported reliability estimates of SEAS high arousal negative to be 0.80 and 0.84 for the ascending and descending limb, respectively. The current study design and sample differ from that of Morean and colleagues (2013), which may partially explain these differences. The previous study used an oral alcohol design, was a majority male sample (74%), who drank on average ~ 60 drinks in the past month. This study employed an IV alcohol design, which allows for more control over breath alcohol levels at

the cost of ecological validity. Further, this sample was balanced on gender (54% male) and was heavier drinkers, with participants reporting drinking ~ 95 drinks over the past month. Therefore, the high arousal negative domain may be more valid in studies, which use the oral alcohol paradigm, or may be more prominently found in male drinkers (or individuals at moderate drinking levels).

Our association analyses examining correlations between factor scores and drinking variables did not provide support for the Low Level of Response (LLR) model and only provided partial support for the differentiator model (DM). Regarding the LLR model, we found pre–alcohol associations between Factor 2, which captured sedation (BAES sedation) and unpleasant responses to alcohol (SHAS), and AUD severity, such that at baseline, individuals who reported greater sedation were those that endorsed more AUD symptoms. This is in contrast to previous studies which found that individuals who report less unpleasant effects of alcohol via lower scores on the SHAS are more likely to develop AUD (Schuckit et al., 2004). This study did find an association between the stimulation and hedonic response factor (Factor 1) and drinking frequency (number of past-month drinking days), but only at a BrAC of 20mg %. A large prospective study found that heavy drinking individuals who go on to develop a more severe AUD report heightened stimulating and rewarding effects of alcohol compared to heavy drinking individuals with less severe or no AUD symptoms (King et al., 2016). In brief, these correlations were exploratory and sought to further validate/interpret the resulting factor scores. Nonetheless, the integration of the SEAS in large prospective studies, such as the work of King and colleagues, will ultimately define the interpretation of risk conferred by dimensions of SR that encompass SEAS.

This study should be interpreted based on its strengths and limitations. Study strengths include the collection of multiple measures of subjective response (BAES, SHAS, and SEAS) in combination with mood and craving assessments, and the controlled alcohol administration design. This allows for a direct comparison of the SEAS in relation to prior factor analytic models that did not include this measure in the assessment battery during the alcohol challenge. This work is largely programmatic as our group has examined the factor structure of SR in multiple independent samples. In this study, we expand the factor structure of SR to encompass unique dimensions offered by the SEAS measure. Study limitations include the moderate sample size, the inclusion of only individuals of Caucasian ethnicity, and the relatively low number of participants with moderate-to-severe AUD. The sample size in this study limited our ability to include additional variables of interest such as alcohol liking and wanting, and additional subscales of the POMS. Further, standard error of loadings is expected to be larger when the sample size is small (de Winter et al., 2009); thus, there is a greater risk of artificially high loadings. Future studies with larger, more racially and ethnically diverse samples should include these measures to evaluate their relationship with the SEAS domains. Sample size also limited our ability to conduct a confirmatory factor analysis, which would have provided information regarding the stability of the factors over rising breath alcohol levels and differences by gender. Future studies should employ a CFA approach to examine the measurement invariance of these factors during alcohol administration. Additionally, all study participants were non–treatment-seeking; therefore, it is unknown if the factors captured in this sample will generalize to a treatment-seeking population. As with all IV alcohol studies, this study compromised ecological validity to gain tight control over breath alcohol concentrations. The exclusion of alcohol cues, both taste and sight, may have limited our ability to assess the full range of the subjective response to alcohol (Cyders et al., 2020). Further, this study only administered alcohol to a target BrAC of 60mg%. As heavy drinkers and individuals with AUD commonly report tolerance to alcohol, administering alcohol to higher breath alcohol concentrations may reveal a different set of SR factors.

In conclusion, this study extends the literature evaluating the biobehavioral effects of alcohol in heavy drinkers by examining a novel combination of subjective response to alcohol measures alongside measures of mood and craving. A "back-to-basics" approach was taken by allowing the SEAS to inform the factor structure of SR in the context of alcohol administrations, alongside more widely used measures of SR. This was under the assumption that the SEAS provides unique dimensions of SR and may contribute unique variance to this multifaceted phenotype. The data were best represented by a 3-factor solution. Factor 1 captured the stimulating and hedonic effects of alcohol. Factor 2 captured the sedative and aversive effects of alcohol. Factor 3 captured negative mood and craving experienced by individuals prior to alcohol administration and depicted tension-reducing effects upon alcohol administration. This study demonstrates that the SEAS low arousal positive domain provides novel information not captured by the BAES or SHAS measures, as this domain loaded independently from these measures. These findings suggest that the underlying phenomenology of subjective response to alcohol is best captured by dimensions of positive/stimulant effects, negative/aversive effects, and tension reduction effects. Going forward, studies of alcohol's subjective effects should continue to use this dimensional approach to reduce multiple comparisons across a wide range of scales and to build a systematic literature grounded on the underlying structure of subjective response as a translational phenotype for AUD.

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CONFLICTS OF INTEREST

None of the authors have conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Correlations between subjective response measures at each timepoint.

Table S2. Maximum likelihood (ML) factor analysis.

Table S3. Factor loadings split by gender.

Table S4. Inter-factor correlations.

Fig. S1. Scatter plots of BrAC = 60mg% and AUD clinical variables.