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Moderation of Alcohol Craving Reactivity to Drinking-Related Contexts by Individual Differences in Alcohol Sensitivity: An Ecological Investigation

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Abstract

Laboratory cue exposure investigations have demonstrated that, relative to drinkers who report a high sensitivity to the pharmacologic effects of alcohol, low sensitivity (LS) drinkers show exaggerated neurocognitive and behavioral reactivity to alcohol-related stimuli. The current study extends this line of work by testing whether LS drinkers report stronger cravings for alcohol in daily life. Data were from an ecological momentary assessment (EMA) study in which participants (N = 403 frequent drinkers) carried a palmtop computer for 21 days and responded to questions regarding drinking behavior, alcohol craving, mood states, and situational context. Initial analyses identified subjective states (positive and negative mood, cigarette craving) and contextual factors (bar/restaurant location, weekend, time of day, presence of friend, recent smoking) associated with elevated craving states during non-drinking moments. Effects for nearly all of these craving correlates were moderated by individual differences in alcohol sensitivity, such that the associations between situational factors and current alcohol craving were larger among LS individuals (as determined by a questionnaire administered at baseline). Complementary idiographic analyses indicated that self-reported craving increased when the constellation of situational factors more closely resembled an individual's observed drinking situations. Again, this effect was moderated by alcohol sensitivity, with greater craving response increases among LS drinkers. The findings align with predictions generated from theory and laboratory cue exposure investigations and should encourage further study of craving and incentive processes in LS drinkers.

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Keywords

alcohol; alcohol sensitivity; craving; ecological momentary assessment; incentive salience

Individual drinkers differ markedly with respect to their sensitivity to the pharmacologic effects of alcohol (Li, 2000). A great deal of evidence now indicates that a low sensitivity (LS) or blunted response to alcohol is an important risk factor for alcohol use disorder (AUD; Ray, Bujarski, & Roche, 2016; Schuckit, 1980; Schuckit & Smith, 1996; Trim, Schuckit, & Smith, 2009). LS drinkers must consume more alcohol in order to achieve desired psychological effects of drinking (Schuckit, 1994; Trela, Piasecki, Bartholow, Heath, & Sher, 2016). This heavy drinking style is thought to promote problematic alcohol involvement directly and also indirectly by fostering acquisition of coping motives for drinking, biasing alcohol outcome expectancies to be more positive, and promoting affiliations with heavy-drinking peers (Schuckit, Smith, Anderson, & Brown, 2004; Schuckit et al., 2008). However, the mechanisms through which LS risk is translated into problematic drinking outcomes remain to be fully elucidated.

Theorists have long considered craving – an appetitive motivational state associated with an acute desire to approach and use a drug – to be an important feature of problematic substance use (e.g., Baker, Morse, & Sherman, 1987; Drummond, 2001; Sayette, 2016). A recent influential model, Incentive Sensitization Theory (IST; Robinson & Berridge, 1993) identifies amplification of this drug-wanting process as a central mechanism in transition from casual drug use into addiction. Specifically, IST posits that neural systems that regulate drug wanting can become sensitized through repeated use of drugs such that cues associated with drug use become imbued with exaggerated incentive salience. Through this process, previously neutral drug-related stimuli can be transformed into “motivational magnets” that command attention, excite drug ‘wanting’ and impel drug use (Berridge & Robinson, 2003).

Motivated by IST, an emerging line of research indicates that LS drinkers show stronger incentive motivational responses to alcohol-related cues relative to their higher-sensitivity (HS) peers. The amplitude of the P3 event-related potential (ERP) component is modulated by the motivational significance (Nieuwenhuis, Aston-Jones, & Cohen, 2005; Schupp, et al., 2000; Weinberg & Hajcak, 2010) or incentive value (Begleiter, Porjesz, Chou, & Aunon, 1983) of the eliciting stimulus, and therefore can be used to investigate the motivational salience of target stimuli. Compared to HS drinkers, LS individuals show exaggerated P3 ERPs in response to alcohol images (Bartholow, Henry, & Lust, 2007). This sensitivity-related difference in neural response is specific to alcohol cues and is not observed in response to other classes of emotionally arousing stimuli (Bartholow, Lust, & Tragesser, 2010). LS risk has also been linked to attentional biases toward alcohol cues (Bailey & Bartholow, 2016; Shin, Hopfinger, Lust, Henry, & Bartholow, 2010), and a behavioral approach bias to alcohol images (Fleming & Bartholow, 2014). Taken together, these findings suggest that LS drinkers may be more motivationally reactive to environmental alcohol-related cues, perhaps resulting in greater craving reactivity that promotes alcohol use.

Trela, et al. (2016) recently investigated how individual differences in self-reported alcohol sensitivity were related to subjective responses to alcohol during ecologically assessed drinking episodes. Findings indicated that alcohol sensitivity moderated the association between momentary estimated blood alcohol concentration (eBAC) and intoxication responses (e.g., ratings of buzz, dizziness). As anticipated, LS drinkers showed blunted intoxication responses compared to their high-sensitivity peers. Based on prior laboratory cue exposure studies, Trela, et al. (2016) tentatively hypothesized that LS would be associated with greater craving intensity during drinking episodes, which perforce entail exposure to interoceptive and exteroceptive alcohol cues. Contrary to predictions, alcohol sensitivity was not related to craving intensity and did not moderate the relation between eBAC level and craving.

In the current article, we present additional tests of the working hypothesis that alcohol sensitivity moderates craving reactivity in the natural environment. Data come from the same sample used by Trela, et al. (2016), but the current investigation extends the prior work in two important ways. First, we focus here on data from moments recorded when participants were *not* actively drinking. Examining reports collected during active drinking potentially conflates the contributions of direct pharmacologic effects of alcohol and cue reactivity to craving experience. A focus on non-drinking experiences may better isolate craving reactivity effects. Additionally, some theoretical models posit that conscious cravings are most likely to be experienced when drug-related cue complexes are encountered but automatized self-administration behavioral routines are blocked or resisted (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Tiffany, 1990; Tiffany & Conklin, 2000). Notably, the existing laboratory evidence documenting greater incentive reactivity among LS drinkers has been obtained from participants in a sober state. Second, whereas our prior work was focused on the subjective effects associated with various eBAC levels, the current analyses specifically test whether LS moderates the associations between various *craving- and alcohol-related contexts* and craving for alcohol. This focus on potential LS moderation of craving reports under differing drinking-related stimulus conditions is more directly aligned with the designs of cue exposure investigations and the central tenets of IST.

Because direct assessments of exposure to alcohol cues were not incorporated into the electronic diary assessments, we used two indirect strategies to address the central hypothesis. First, we identified contexts and subjective states that prior research and theory indicate might be considered triggers for craving and that were empirically associated with elevated momentary craving during non-drinking moments. We then tested whether any of the significant context-craving associations were moderated by individual differences in alcohol sensitivity. In a complementary idiographic approach, we used within-subjects logistic regression analyses to predict the occurrence of drinking from the same set of contextual factors and subjective states. Predicted values from these models yielded, for every diary record, an index of the degree to which the constellation of momentary ratings resembled that individual’s drinking context. We then conducted analyses, limited to non-drinking moments, testing whether higher predicted values (indexing a greater match between the current situation and that participant’s observed drinking situations) were associated with elevated craving and whether this effect was moderated by alcohol sensitivity. Based on the existing laboratory cue exposure studies (e.g., Bartholow et al., 2007, 2010; Fleming & Bartholow, 2014), we expected that drinkers with lower self-reported alcohol sensitivity would show relatively greater reactivity to empirical antecedents of craving and in situations that more closely resembled their recorded drinking occasions.

Method

Participants

Participants were current drinkers (defined as self-report of ≥ 4 drinking occasions in the past 30 days) who were recruited through an email listserv maintained by the University of Missouri that included students, faculty, and staff, and also via flyers posted in the community and print commercial circulars to recruit individuals who were unaffiliated with the university. Participants were compensated up to $150 for their full participation in the study, including attendance at study visits and return of the electronic-diary (ED) used in the field. The study intentionally oversampled current cigarette smokers because a major aim of the larger EMA project was to examine alcohol and tobacco co-use (Piasecki, et al., 2011). Because of this goal of the overarching study, the threshold to be considered a current smoker was low: self-report of smoking at least one cigarette per week at screening. Of the 418 subjects who completed informed consent, 403 attended a diary training session and actively recorded data in the field using a study-issued electronic diary (ED) and were included in the current analyses. Participants ranged in age, but the majority were young adults (M = 23.3 years, SD =7.2, Mdn = 21; range = 18 to 70, 75% ages 18-22). The sample was balanced with respect to gender (n = 202 female, 50.1%). At baseline, participants reported consuming an average of 19.4 drinks per week in the past 30 days (SD = 15.6, Mdn = 15.1). A total of 258 participants (64.0%) were current smokers, of whom 184 (71.3%) reported smoking on a daily basis. At baseline, smokers reported consuming an average of 57.3 cigarettes per week over the past 30 days (SD = 72.3, Mdn = 45.2). Other data from this study have been presented in prior reports (Epler, et al., 2014; Piasecki, et al., 2011; Piasecki et al., 2012a; Piasecki, Wood, Shiffman, Sher, & Heath, 2012b; Piasecki, et al., 2014; Robertson, et al., 2012; Tarantola, Heath, Sher, & Piasecki, 2017; Trela, et al., 2016; Treloar, Piasecki, McCarthy, Sher, & Heath, 2015), but this article is the first to examine alcohol craving reactivity as a function of individual differences in alcohol sensitivity during non-drinking moments. Data were collected between January, 2007 and November, 2008. All participants provided informed consent and the protocol was approved by the Institutional Review Boards of the University of Missouri and Washington University School of Medicine.

Procedure

Each participant attended two laboratory visits prior to the recording phase of the study. At the first session, participants completed a battery of questionnaires, including the self-report measure of alcohol sensitivity. Participants returned for a second training session during which they were instructed on how to initiate and complete reports on the ED. The recording phase of the study lasted 21 days beginning immediately following the end of the training session. During the recording phase, participants returned to the lab on 4 occasions to review compliance and troubleshoot any technical issues.

Diary Device and Protocol

The ED was implemented on palmtop computers (Palm m500, Palm Inc., Sunnyvale, CA) using customized software designed for the project by invivodata, Inc. (Pittsburgh, PA). During the recording phase participants made five types of reports. *Morning Reports* (MR; *n* = 7,424) were completed once daily soon after awakening. The EDs doubled as alarm clocks, with participants being able to program their device to deliver a wake-up alarm that also triggered the MR. Participants were prevented from programming the wake-up alarm to occur after 12pm, and were also unable to access morning reports regardless of the scheduled wake-up time after noon (i.e., participants who slept through the alarm could not make up the morning report late in the day). Each participant received up to 5 additional audible prompts on a random schedule each day to complete a report. These *Random Prompts* (RP; *n* = 26,933) could occur as soon as the morning report was completed (or noon in cases where a morning report was not completed) and were able to trigger until the participant indicated they were retiring to sleep for the evening. Participants who were current smokers at the initial laboratory session were instructed to log a *Cigarette Report* (CR) following each cigarette smoked in the course of the day. To prevent excessive assessment burden for heavy smokers, the ED administered questionnaires only for the first cigarette within a 6-hour block of time. Subsequent CRs within that time period returned a note that the cigarette had been logged and thanked the participant prior to reverting to the home screen of the ED. The current analyses include data from 6,605 CRs that were followed by full set of diary items. When participants completed the first drink of alcohol in a drinking episode, they were asked to log a *Drink Report* (DR; *n* = 2,108). An automated set of prompted *Drinking Follow-Ups* (DFU; *n* = 8,435) oversampled experiences in the aftermath of drinking.

The current analyses chiefly focus on data collected during non-drinking moments (RP, MR, and CR, *n* = 39,774). Morning reports were assumed to be non-drinking moments. In RP and CR reports, participants were asked whether they had consumed any alcohol since making their last report. If they answered this question affirmatively the report was reclassified as a drinking moment and triggered the drink report follow-ups described above. A total of 3,296 *Drink Initiation* moments (DI) occurred in the study (the sum of 2,108 DR and 1,188 reclassified reports). These DI reports were used in the idiographic analyses to identify drinking-like situations for each individual. DFUs were used in descriptive analyses.

Measures

Alcohol Sensitivity—The Self-Rating of the Effects of Alcohol (SRE; Schuckit, Smith, & Tipp, 1997a; Schuckit, Tipp, Smith, Wiesbeck & Kalmijn, 1997b) form was administered to evaluate individual differences in sensitivity to alcohol. The SRE queries the number of drinks respondents require before they begin to feel different (i.e., experience any effect of alcohol), to feel dizzy or begin slurring speech, to begin stumbling or walking in an uncoordinated manner, and to pass out. These effects are assessed for three distinct time periods: the first five lifetime drinking episodes, the most recent period of drinking on a monthly basis for three months, and the heaviest lifetime period of drinking. Responses across all effects and time periods can be averaged to compute an overall SRE score (Schuckit et al. 1997b; Ray, Hart, & Chin, 2011). Higher SRE scores indicate lower alcohol sensitivity (i.e., a higher number of drinks required to experience measured alcohol effects). Previous research has established the validity of the SRE, demonstrating that self-reported sensitivity is associated with subjective responses to alcohol challenge in controlled laboratory studies (Fleming et al., 2016; Schuckit et al., 1997a; Schuckit et al., 1997b).

For the current analyses, we scored the SRE using a standardized person-mean imputation method (Lee, Bartholow, McCarthy, Pedersen, & Sher, 2015) in order to produce a less biased estimate of sensitivity by accounting for the relationship between missing data (typically occurring when an individual has never experienced a queried alcohol effect) and overall SRE score. There was a significant difference between male ($M = 8.84$, $SD = 3.02$) and female ($M = 6.57$, $SD = 2.16$) raw SRE scores, $t_{(401)} = 8.69$, $p < .001$. SRE scores were standardized within sex to avoid conflating sex differences and alcohol sensitivity. The resulting score indexes each participant's alcohol sensitivity relative to same-sex peers, with each 1-point change corresponding to a standard deviation increment.

State and Contextual Predictors of Craving—Because the diary protocol did not directly assess participants' exposure to alcohol cues during non-drinking moments, we selected a number of diary-derived measures as possible craving triggers on the basis of existing research and theory. *Bar/restaurant location* was selected because these settings are likely to resemble drinking venues, and some of these will have contained alcohol cues or served alcohol. *Time of day* and *weekend* (vs. weekday) were selected because they tend to be strongly related to alcohol consumption (Piasecki, McCarthy, Fiore, & Baker, 2008, Reich, Cummings, Greenbaum, Moltisanti, & Goldman, 2015; Wood, Sher, & Rutledge, 2007). *Positive* and *negative affect* were selected based on theories suggesting drug cravings are embedded in schematic networks organized around prototypic emotions and can be triggered by schema-congruent emotional states (Baker, et al., 1987; Baker, et al., 2004). Presence of a *friend* has been associated with alcohol use in ecological studies (Aan Het Rot, Russell, Moskowitz, & Young, 2008; Piasecki, et al., 2008) and socializing is a major motive for drinking (Cooper, 1994). Finally, *recent cigarette use* and *craving for cigarettes* were selected in light of the frequent co-use of alcohol and tobacco (Piasecki, et al., 2008; Piasecki, et al., 2011; Shiffman & Paty, 2006).

Diary Measures of Subjective States—The ED assessed a variety of subjective states using a common stem ("In the PAST 15 MINUTES, did you feel …?") at each report. These items were rated on a 5-point Likert scale (1 = "not at all" to 5 = "extremely"). One item assessed *alcohol craving*, completing the item stem with "crave a drink." This was used as the primary outcome variable. Responses to three items (enthusiasm, happy, excited) were averaged to create a *positive affect* variable ($\alpha = 0.96$), and two items (sad, distressed) were averaged to form a *negative affect* composite ($\alpha = 0.88$). Current smokers also completed a single item assessing *cigarette craving* over the past 15 minutes in every report.

Diary Measures of Contextual Features—In all ED assessments, participants were asked to report their current location by checking all applicable options from a list of possible locations (school, work, bar/restaurant, primary residence, outside, vehicle, and other). Responses were recoded to create a binary variables indicating endorsement (scored 1) or non-endorsement (0) of the bar/restaurant location. Similarly, a checklist item asking who the participant had been with in the past 15 minutes was recoded to form a binary variable indicate the presence or absence of friend.

All reports were date and time stamped automatically by the ED. We used this information to create a set of 3-hour blocks (e.g., midnight to 3am) to represent time of day and to code each report as having occurred on a weekday or weekend. We defined weekend liberally as spanning from 5pm on Thursday to 3pm Sunday because prior literature has suggested that drinking is heightened in this timeframe relative to the rest of the week for college age individuals (Del Boca, Darkes, Greenbaum & Goldman, 2004; Wood, et al., 2007), an age range containing the bulk of the current sample.

For current smokers, cigarette use in proximity to each diary entry was determined using a combination of assessments varying by record type. CRs were, by definition, assumed to occur after smoking. In RPs and DRs, participants were asked a yes/no question as to whether they had smoked a cigarette in the past 15 minutes. MRs included a similar item, but used a different time referent ("since wakeup"). A binary current smoking variable was created, with smoking coded as having occurred if: (a) the report was a CR, or (b) if the report was a RP, DR, or MR and the participants answered the recent smoking question affirmatively.

Additional Covariates—In order to more effectively isolate effects associated with individual differences in alcohol sensitivity, we covaried several additional person-level variables assessed in the baseline questionnaire battery. Impulsivity was assessed using the total score on the Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, & Barratt, 1995). Family history of alcohol use disorder measured by a modified paternal (F-SMAST) and maternal (M-SMAST) versions of the Short Michigan Alcoholism Screening Test (Crews & Sher, 1992; Selzer, Vinokur, & van Rooijen, 1975). Participants were considered to be positive for family history if the F-SMAST or M-SMAST score was 5 or higher (Crews & Sher, 1992). Typical alcohol consumption patterns were represented using the AUDIT-C (Bush, Kivlahan, McDonnell, Fihn, & Bradley, 1998), a set of three items from the Alcohol Use Disorder Identification Test (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001) assessing frequency of drinking, number of drinks per drinking occasion, and frequency of consuming 6 or more drinks per occasion.

Statistical Analysis—Diary data were analyzed using 3-level mixed regression analyses (Level 1 = moment, Level 2 = day in study, Level 3 = participant) with random intercepts at day and participant levels. Participant records that did not include reports of all relevant independent and dependent variables were excluded in a case-wise fashion.

One set of analyses used a nomothetic approach to (a) identify contextual and subjective features that were associated with elevated drinking craving across participants, and (b) determine whether these effects were moderated by individual differences in alcohol sensitivity. These analyses were limited to diary data collected from non-drinking moments. First, a multivariate mixed regression analysis predicted current alcohol craving from six selected measures Level-1 variables (positive affect, negative affect, weekend, time of day, presence of a friend, and bar/restaurant location), and covariates at Level-2 (whether any drinking occurred on that day) and Level-3 (impulsivity, typical alcohol consumption, family history status). A series of follow-up models were then estimated. Each included main effects for all of the predictors in the initial model, but tested a single Level-1 predictor × SRE interaction.

Momentary craving for cigarettes and recent smoking were only assessed in the subsample of current smokers. Consequently, we repeated the nomothetic analyses after limiting the data to reports from current smokers, adding cigarette craving and recent smoking as additional predictors of alcohol craving.

Another set of analyses used an idiographic approach (cf., Shiffman, Dunbar, & Ferguson, 2015; Shiffman & Paty, 2006). The first step used diary data from both non-drinking and DI moments. For each participant, we conducted a multivariate logistic regression analysis in which the dependent measure was whether the record was a DI record (scored 1) or not (0). All subjective and contextual predictors tested in the nomothetic analyses were included in these logistic models. Predicted values from the logistic models were saved. These values indicate the model-predicted probability that a given moment is a drinking occasion based on the configuration of immediate subjective and contextual features. Note that the use of single-subject logistic regression analyses means that the importance of particular predictors of drinking can vary across individuals. In the next step, we limited data to non-drinking moments and conducted a pooled multilevel regression analysis in which ratings of alcohol craving were predicted from selected covariates (drinking day, AUDIT-C, impulsivity, and family history), the idiographic model-predicted values (i.e., resemblance of the current moment to the participant's observed drinking occasions), SRE scores, and the interaction between SRE and drinking occasion resemblance. Again, this idiographic approach was repeated in the subsample of current smokers, including cigarette craving and recent smoking as additional predictors.

Results

Descriptive Analyses

Standardized SRE scores were strongly correlated with AUDIT-C ($r = .52$, $p < .001$) indicating that lower sensitivity individuals were heavier drinkers at study baseline. SRE was negatively correlated with participant age ($r = -.18$, $p < .001$), indicating that older participants tended to be more sensitive to the effects of alcohol. Family history of AUD, impulsivity, smoking status, sex, and proportion of drinking and smoking days during the diary monitoring period were not significantly correlated with SRE (rs ≤ |.06|, ps ≥ .22).

Nomothetic Approach

Results from the initial multivariate models predicting alcohol craving from subjective and contextual factors are presented in Table 1. In the full analytic sample, all Level-1 predictors were simultaneously associated with current reports of craving for alcohol. Specifically, craving was higher when positive and negative affect were elevated, on the weekends relative to weekdays, in the presence of a friend, and when in a bar/restaurant location. Craving also varied significantly over time of day. Among current smokers, the same pattern of results was observed. Additionally, craving for alcohol was positively related to current levels of cigarette craving and lower when recent smoking was reported.[1] Craving for alcohol was also stronger on days when drinking ultimately occurred. Of the Level-3 covariates, only AUDIT-C was significant, indicating heavier drinkers tended to report higher levels of craving.

Table 2 summarizes tests of interactions between alcohol sensitivity and particular subjective and contextual features. In the full sample, alcohol sensitivity significantly moderated the effects of all state and contextual predictors of craving. In current smokers, alcohol sensitivity moderated the association between current cigarette craving and alcohol craving but did not interact with recent smoking. Figure 1 illustrates the significant interactions by plotting marginal model-estimated means for alcohol craving for low- and high-sensitivity drinkers under varying contextual and subjective conditions. As predicted, the associations between state and contextual predictors and current alcohol craving were stronger among drinkers with lower alcohol sensitivity. The effects of situational factors and the moderating effects of alcohol sensitivity tended to be modest in magnitude. Elevated craving (i.e., a score > than 1, the value associated with the "not at all" anchor point) was present approximately 25% of all records, and mean levels of current craving for alcohol tended to be low overall (approximately 1.5 to 2.0 on a 1-5 scale)[2].

As noted above, craving was elevated on days when drinking ultimately occurred (Table 1). We conducted supplementary analyses incorporating 3-way alcohol sensitivity × state/context × drinking day interaction terms to explore whether the effects in Table 2 were further moderated by day-level alcohol use outcomes. Findings revealed significant 3-way interactions involving numerous states and contexts (Positive Affect: interaction $b = .025$, $p < .001$; Negative Affect: interaction $b = .037$, $p < .001$; Friend: interaction $b = .080$, $p < .001$; Smoked: interaction $b = .071$, $p = .019$; Crave Cigarette: interaction $b = .032$, $p < .001$; Time of Day, omnibus interaction $F(8, 28635.36) = 3.890$, $p < .001$). To characterize these effects, we conducted separate analyses stratified by day-level drinking outcome. Findings indicated that the two-way interactions between alcohol sensitivity and various craving-related states and contexts were primarily observed on days when drinking ultimately occurred (Table 3).

Idiographic Approach

Inspection of the distribution of predicted probabilities (i.e., drinking occasion resemblance) in non-drinking diary records generated from the single-subject logistic regression analyses indicated that these values were low overall ($M = .037$, SD = .101, 98.6% of estimates < .50) with a modal value of zero (67.6% of nondrinking moments in the full sample). This was partly attributable to the strong association between time of day and drinking (Piasecki, et al., 2011). Panel A of Figure 2 shows the frequency distributions for nondrinking and

[1]Reports of cigarette craving were significantly higher when recent smoking was reported ($b = .482$, $p < .001$). If momentary cigarette craving is omitted from the predictor set in the multivariate nomothetic model, recent smoking is positively associated with alcohol craving ($b = .023$, $p = .03$).

[2]A similar pattern of interaction effects was obtained when gamma regression analyses were performed using generalized linear mixed models for skewed outcomes (e.g., Neal & Simons, 2007). The only difference was the SRE × cigarette craving interaction was not significant ($p = .09$).

drinking diary records by time of day in the full sample, illustrating the virtual absence of drinking records between 3 a.m. and 3 p.m. (the unshaded area). As would be expected, the mean model-predicted probabilities hover very close to zero in this time window, but track higher between 3 p.m. and 3 a.m. when both non-drinking and drinking records were observed (shaded area, Panel B). Panel C shows that mean levels of alcohol craving in nondrinking moments were also elevated primarily at times of day when drinking records were common. In light of these patterns, the primary idiographic analyses predicting craving were limited to 20,607 non-drinking diary records logged between 3 p.m. and 3 a.m., a period that is most clinically and practically relevant (i.e., drinking is plausible and craving is more pronounced). Exploratory analyses indicated that temporal patterns of craving level and drinking resemblance were consistent across weekdays and weekends (profile *r*s ≥ .79).

In both the full sample and subsample of current smokers, drinking occasion resemblance was robustly related to contemporaneous reports of alcohol craving (Table 4). As the resemblance between the profile of immediate contextual and subjective conditions to those observed in drinking events increased, drinkers reported experiencing higher levels of desire to drink. These effects were moderated by individual differences in alcohol sensitivity, with lower-sensitivity drinkers showing a stronger relationship between craving and drinking-resembling situations. Figure 3 illustrates these effects. When the analyses were expanded to include data from all non-drinking moments, similar findings were obtained (Table 4).

We again conducted supplementary analyses examining whether these 2-way interaction were further moderated by day-level drinking occurrence. Using the records from the primary 3 p.m. to 3 a.m. time period, the 3-way alcohol sensitivity × drinking resemblance × drinking day interactions was not significant in the full sample ($b = .052$, $p = .677$). The corresponding 3-way interaction was significant in the smoker subsample ($b = .492$, $p = .012$). Analyses of the smokers stratified by day-level drinking outcome indicated that alcohol sensitivity moderated the effect of drinking resemblance on craving on days when drinking occurred ($b = .298$, $p = .001$) but not on non-drinking days ($b = .030$, $p = .869$). Results were similar when records from all non-drinking moments were analyzed.

Discussion

Findings from this study complement evidence from prior laboratory cue exposure investigations indicating that LS drinkers show enhanced neurophysiological and behavioral reactivity to alcohol-related cues (Bartholow, et al., 2007, 2010; Fleming & Bartholow, 2014; Shin, et al., 2010), and extend those findings by demonstrating that LS drinkers show greater alcohol craving reactivity to drinking- and craving-related settings in the natural environment. This line of inquiry has drawn from incentive sensitization theory, which posits that drugs of abuse like alcohol can sensitize neural circuitry responsible for imbuing reward-predicting cues with motivational salience (Robinson & Berridge, 1993, 2003, 2008). With repeated use, previously neutral cues associated with drug self-administration become attractive targets that may elicit behavioral approach accompanied by the subjective experience of wanting or craving (Berridge & Robinson, 2003). From this theoretical perspective, the current findings suggest that the development of a pathologically amplified, alcohol-focused wanting process may be an important mechanism through which LS confers risk for problematic drinking outcomes.

Preclinical studies have revealed that there are substantial individual differences in the susceptibility to sensitization of incentive motivation for reward-paired cues (Flagel, Akil, & Robinson, 2009). These findings suggest that there may be multiple pathways to addiction, with perhaps only a subset of cases attributable to sensitized drug wanting and exaggerated cue reactivity (Robinson, Yager, Cogan, & Saunders, 2014). Bartholow, et al. (2010) found that LS status moderated the P3 amplitude to alcohol cue exposure when controlling for other AUD risk factors such as impulsivity and familial alcoholism. In a cue exposure study involving young adult smokers, individual differences in the severity of tobacco dependence did not moderate P3 responses to smoking images (Piasecki, Fleming, Trela, & Bartholow, 2017). However, in this same study, smokers who reported lower alcohol sensitivity showed larger neural responses to smoking images compared to their higher-sensitivity peers. Taken together, such findings suggest exaggerated incentive salience is not an essential or inevitable concomitant of addiction or addiction risk and indicate that a low subjective response to alcohol may be a trait marker that identifies ‘cue reactors.’ Interestingly, mesolimbic dopaminergic systems have been implicated in both incentive learning (Saunders & Robinson, 2012) and subjective response to alcohol (Setiawan, et al., 2014). The possibility that LS risk and pathological drug ‘wanting’ have overlapping neural underpinnings merits focused investigation in future research.

A prior analysis of data collected during active drinking episodes from the same sample focused on prediction of craving and other subjective states as a function of momentary eBAC level (Trela, et al., 2016). Findings indicated that momentary eBAC was not related to craving intensity. Furthermore, individual differences in alcohol sensitivity did not moderate the association between craving and eBAC (Trela, et al., 2016). The current analyses focused more squarely on how craving responses were related to *environmental and subjective setting conditions* associated with craving and drinking. This focus on situational factors that may serve as learned triggers for craving (vs. alcohol dose) more clearly aligns with the tenets of IST upon that motivated prior cue exposure studies examining moderating effects of LS risk (e.g., Bartholow et al., 2007; Bartholow et al., 2010). This may account for the greater correspondence of the current findings with predictions extrapolated from the laboratory investigations (e.g., Fleming & Bartholow, 2014; Trela et al., 2016). It is also possible that the craving reactivity and effects of trait moderators of such reactivity are more evident when alcohol has not been consumed (e.g., Baker, et al., 2004; Tiffany, 1990). However, analyses focused on reactivity to discrete situational features during active alcohol use might show effects similar to those found here.

The strength of the moderating effect that alcohol sensitivity had on the relationship between the state and contextual predictors of craving depended in part on whether drinking ultimately occurred on a given day. The meaning of these effects is uncertain on present evidence. One possibility is that cravings triggered by environmental contexts or internal states sometimes impel individuals to initiate drinking, and this this process may be more prominent in LS drinkers. If so, limiting analyses to days on which drinking occurred would tend to reveal an excess of state/context craving reactivity in LS drinkers compared to their higher-sensitivity peers, for whom other factors may be more influential in drink initiation. A second possibility is that planned drinking later in the day (e.g., happy hour following work) might elicit anticipatory craving that operates differentially based on one's alcohol sensitivity. Unfortunately, the present data do not allow us to fully evaluate these alternative explanations.

Although these ‘real world’ observations generally accord with our prior laboratory findings, several caveats must be noted. Chief among these is that due to observational design, we cannot definitively state that increases in craving were caused by exposure to the putative situational triggers. It is theoretically possible that the increases in craving observed in the study were caused by a variable(s) that we did not measure via the ED or at the participants' baseline laboratory visit. In addition, average levels of self-reported craving for alcohol were low during nondrinking moments. Furthermore, the effects of drinking- and craving-related settings and their moderation by LS on craving tended to be modest in magnitude. These observations appear incongruent with the theoretical expectation that drug-related cues become powerful ‘motivational magnets’ that are pathologically wanted, and potentially question the clinical relevance of the findings. On the other hand, incentive sensitization theory recognizes that under differing conditions, mesolimbic drug ‘wanting’ responses may be evident at various levels of awareness, ranging from subtle unconscious biasing of attention and motivation to more intense desire with explicit awareness of craving experience (Berridge & Robinson, 2016). From this perspective, even low levels of self-reported craving may be theoretically interesting, tapping a comparatively high threshold on the continuum of possible incentive salience ‘wanting’ outcomes. However, such distinctions also suggest that self-reported craving ratings may represent rather blunt instruments for investigating incentive salience effects in ecological studies. In future work, it would be valuable to incorporate additional ambulatory measures that may be more sensitive to subtler effects, such as mobile visual dot-probe or Stroop tasks (Kerst & Waters, 2014; Marhe, Waters, van de Wetering, & Franken, 2013).

A second important caveat is that the diary protocol did not incorporate direct assessments of exposure to alcohol cues per se. We used both a theory-based nomothetic approach and an empirically derived idiographic method to identify states and settings that were associated with craving and alcohol use occasions. Findings from both approaches provide evidence linking LS risk with a general craving reactivity in the natural environment, but they cannot directly establish that these effects arise as a result of incentive sensitization or associative learning. Of the contexts examined here, the bar/restaurant location is the likely the best indirect proxy for exposure to discrete environmental alcohol-related cues. However, our brief assessment of physical locations did not allow us to determine which of these situations actually contained such cues. It is possible that alcohol cues were absent in a large subset of occasions for which bar/restaurant was endorsed (e.g., fast food outlets). The theoretical relevance of other of the correlates of craving to IST can be questioned. For example, positive and negative affect were tested on the assumption that they produce interoceptive cues that may become associated with drinking through associative learning (Baker, et al., 1987; Baker, et al., 2004). The intensities of these affective states were empirically associated with elevated craving, but it is possible that this is not attributable to their having acted as conditioned alcohol cues. A lower subjective response to alcohol is hypothesized to foster acquisition of coping motives for drinking (Schuckit, et al., 2004), which might explain why negative affect is accompanied by an elevated desire to drink in LS individuals. Similarly, the presence of a friend could be associated with higher craving through mechanisms that have little to do with associative learning. LS individuals are expected to selectively affiliate with heavy drinking peers (Schuckit, et al., 2004). If so, their friends may be more likely to directly invite or pressure them to drink compared to the company kept by higher sensitivity drinkers. Future ecological studies are needed to more strictly probe incentive sensitization mechanisms in LS drinkers. It will be important to determine whether similar findings are observed when participants explicitly report noticing alcohol cues (e.g., Begh, et al., 2016) or when cue presentations are manipulated directly via the mobile device (e.g., Wray, Godleski, & Tiffany, 2011).

The current study did not formally investigate whether individual differences in craving reactivity were associated with problematic drinking outcomes. Prior reports from this sample indicated that individual differences in alcohol sensitivity were not associated with drinking frequency (Piasecki et al., 2012a). However, relative to their high-sensitivity peers, LS drinkers had steeper rising slopes of estimated blood alcohol concentration when drinking (Trela, et al., 2016) and were more likely to report hangovers the morning after drinking (Piasecki et al., 2012a). Indirectly, such findings suggest craving reactivity in non-drinking moments might be more related to the speed, quantity, or consequences of consumption than to the likelihood of alcohol use initiation. This remains to be tested formally in future studies. Although these downstream consequences require additional investigation, documenting a relation between LS risk and real-world craving responses is itself significant given the inclusion of craving as an AUD diagnostic criterion in DSM-5 (Hasin, et al., 2013).

The models included a number of covariates at the day- and person-levels in an attempt to isolate effects uniquely associated with alcohol sensitivity. It is possible that these covariate controls were overly stringent (Meehl, 1971). For example, a pattern of heavy alcohol consumption, such as captured by the AUDIT-C, might be considered to represent a fundamental expression of LS risk, potentially playing an important causal role in translating a latent vulnerability into an active craving reactivity phenotype. If so, the current findings might understate the true relation between alcohol sensitivity and craving response in daily life.

A final caveat is that the participants in the current study were not administered the neurocognitive and behavioral tasks used to identify incentive salience effects in our prior laboratory studies (Bartholow, et al., 2007; Bartholow, et al., 2010, Fleming & Bartholow, 2014; Shin, et al., 2010). Thus, it remains to be empirically established that responses on such tasks are associated with self-reported cravings for alcohol in the natural environment. Comprehensive, multimethod studies are needed to confirm that various putative indicators of incentive salience that have been associated with LS risk indeed tap a common psychological process.

In summary, drinkers who report a lower level of sensitivity to alcohol report larger changes in craving when encountering craving- and drinking-related states and contexts. The findings align with predictions generated from theory and laboratory cue exposure investigations and should encourage further study of craving processes in LS drinkers. Theoretical inferences are constrained by several important caveats arising from limitations in the assessment protocol. Future investigations with specialized assessments are needed to more sensitively probe whether the kinds of craving effects seen here are largely attributable to heightened reactivity to alcohol-related cues in the manner anticipated by IST. Importantly, the current study had the potential to produce evidence disconfirming the basic assertion that LS drinkers show greater craving reactivity, which could have cast doubt on the tenability of our hypothesis. This initial evidence provides a foundation for more rigorous and probative follow-on studies of incentive salience wanting and low subjective response to alcohol.

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Public Significance Statement

This study extends prior laboratory based work demonstrating that an individual's level of alcohol sensitivity is related to the degree of craving reported when exposed to alcohol cues. Here we provide evidence that the craving reactivity previously observed in highly controlled laboratory environments exists and functions similarly in the "real world."

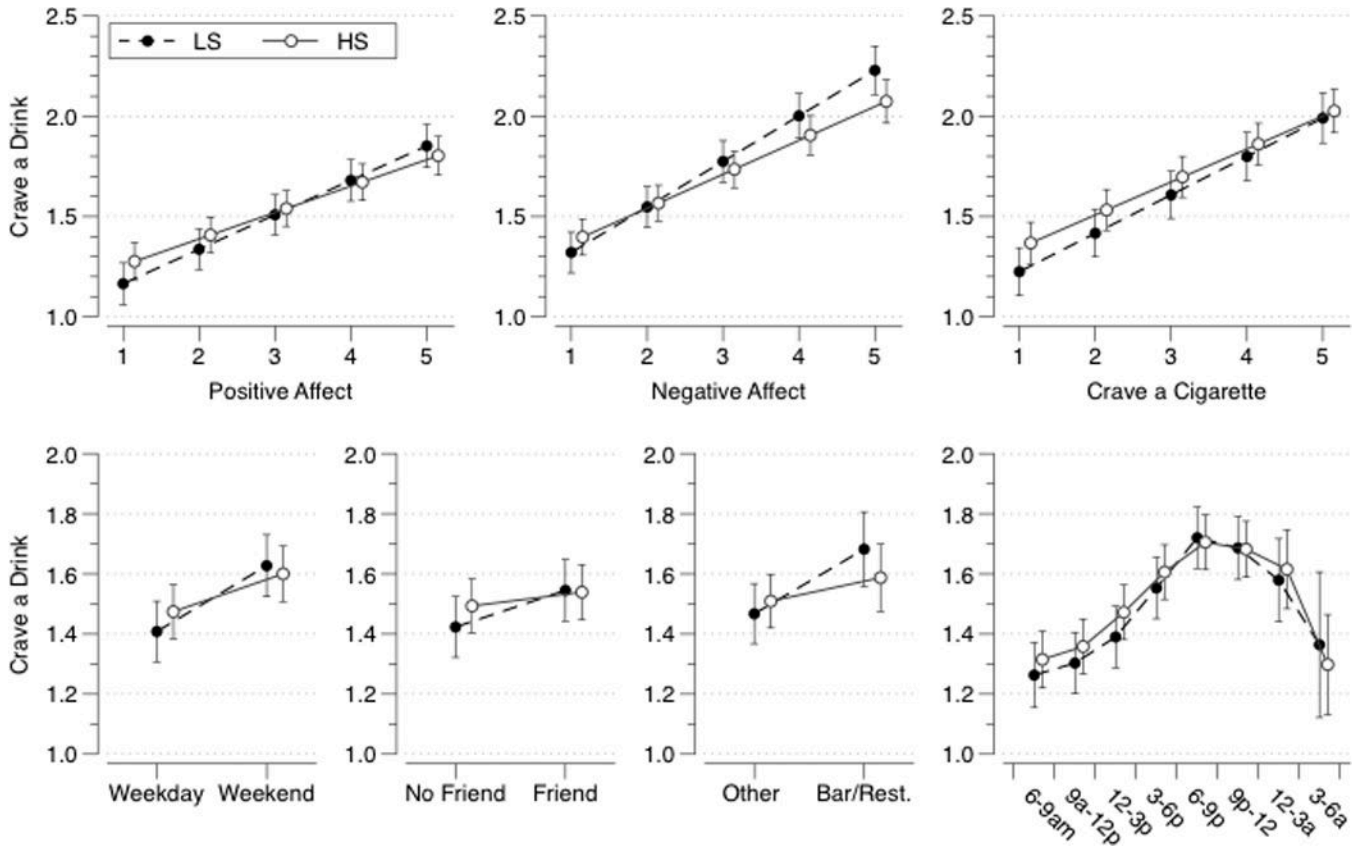

Figure 1.

Model-predicted means and associated 95% confidence intervals illustrating significant interaction effects involving state/contextual features and alcohol sensitivity in nomothetic models. Lines are plotted at the mean of the top (LS) and bottom (HS) quartiles of the distribution of standardized person-mean imputed SRE scores (pooled across sexes) to illustrate sensitivity-related effects and at the mean level of all other covariates. LS = Low Sensitivity, HS = High Sensitivity, Rest = Restaurant, SRE = Self-Rating of the Effects of Alcohol

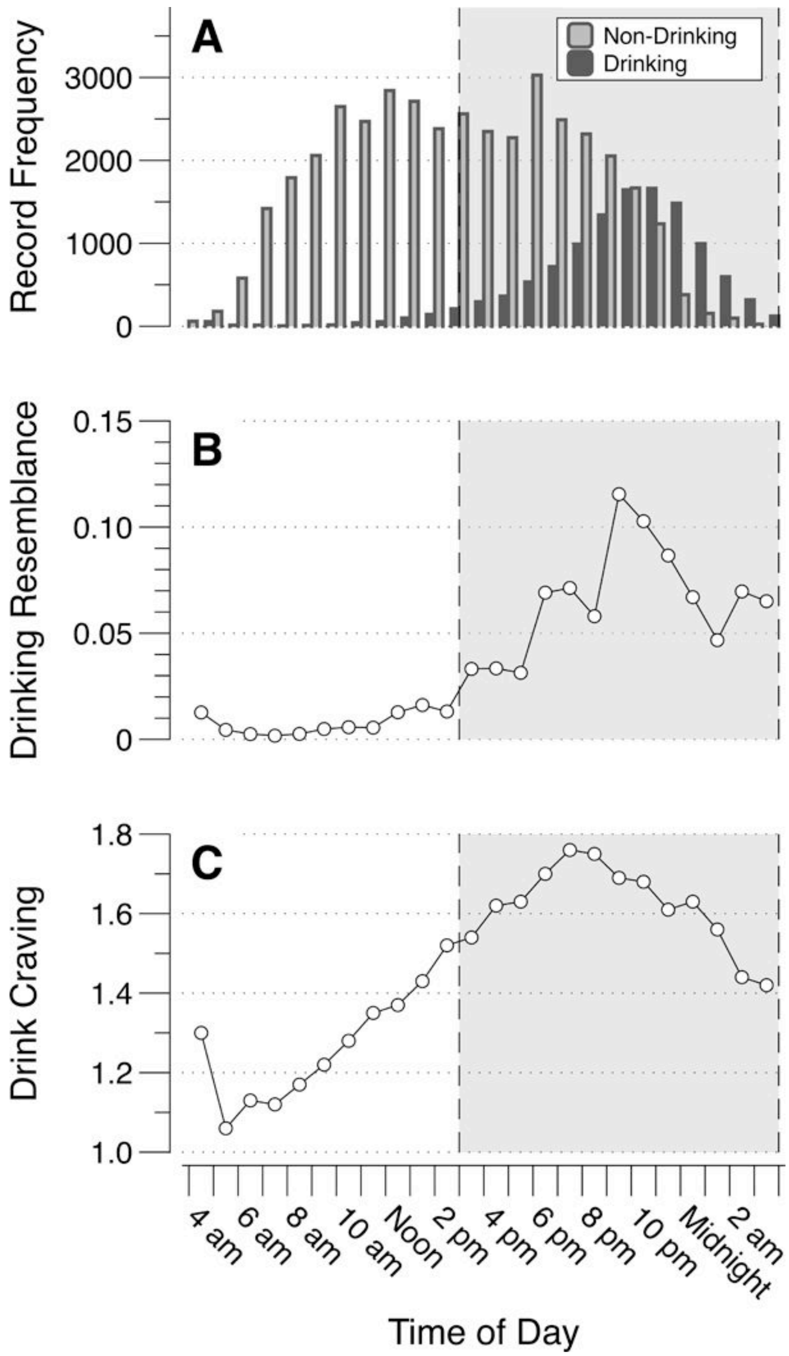

Figure 2.

(A) Frequency distributions of non-drinking and drinking (both drink initiation records and drinking follow-ups) diary records as a function of time of day. (B) Mean predicted values (i.e., drinking occasion resemblance) from participant-stratified logistic regression analyses in the full sample by time of day. (C) Mean ratings of alcohol craving in the full sample by time of day. The shaded area (3 p.m. to 3 a.m.) was selected as the focus of primary idiographic analyses.

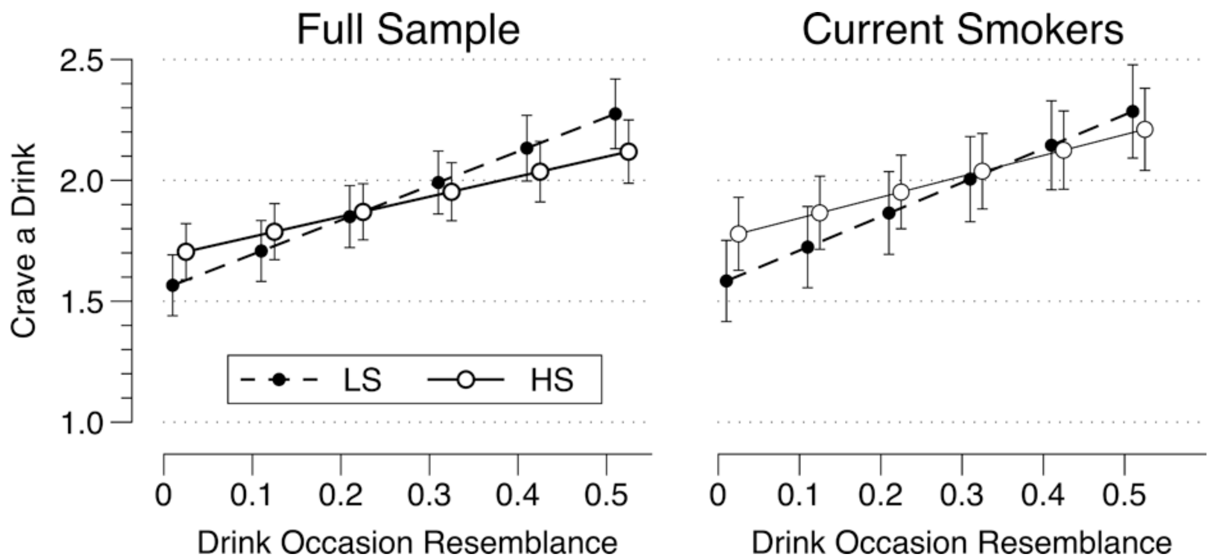

Figure 3.

Model-predicted mean ratings of momentary alcohol craving and associated 95% confidence intervals illustrating alcohol sensitivity × contextual resemblance to drinking situations interactions from idiographic models, using records occurring between 3 p.m. and 3 a.m. Lines are plotted at the mean of the top (LS) and bottom (HS) quartiles of the distribution of standardized person-mean imputed SRE scores (pooled across sexes) to illustrate sensitivity-related effects and at the mean level of all other covariates. LS = Low Sensitivity, HS = High Sensitivity, SRE = Self-Rating of the Effects of Alcohol

Table 1

Fixed effects from multilevel regression analyses predicting momentary alcohol craving from diary-measured contextual and subjective factors.

Predictor	Full Sample (n = 403)			Current Smokers (n = 258)		
	Estimate	SE	*p*	Estimate	SE	*p*
Level-1						
Positive Affect	0.151	0.006	< .001	0.116	0.007	<. 001
Negative Affect	0.197	0.006	< .001	0.159	0.007	< .001
Weekend	0.169	0.011	< .001	0.157	0.013	< .001
Time of Day[a]						
09:00-12:00	(Ref)			(Ref)		
12:00-15:00	0.101	0.012	< .001	0.097	0.014	< .001
15:00-18:00	0.249	0.012	< .001	0.252	0.015	< .001
18:00-21:00	0.380	0.012	< .001	0.387	0.015	< .001
21:00-00:00	0.351	0.014	< .001	0.366	0.017	< .001
00:00-03:00	0.265	0.031	< .001	0.248	0.033	< .001
03:00-06:00	−0.016	0.047	.732	−0.048	0.053	.373
06:00-09:00	−0.041	0.015	.006	−0.042	0.018	.020
Friend	0.083	0.009	< .001	0.096	0.012	< .001
Bar/Restaurant	0.144	0.012	< .001	0.138	0.029	< .001
Recent Smoking				−0.048	0.010	<.001
Crave Cigarette				0.167	0.005	< .001
Level-2						
Drinking Day	0.173	0.014	< .001	0.114	0.017	< .001
Level-3						
AUDIT-C	0.047	0.012	< .001	0.056	0.014	< 0.001
Impulsivity	0.003	0.002	.142	0.003	0.003	.314
Family History	−0.055	0.068	.417	−0.057	0.076	.450

[a]Omnibus test for Time, Full Analytic Sample: $F(7, 35609.06) = 230.47$, $p < .001$; Current Smokers: $F(7, 25084.58) = 165.18$, $p < .001$. AUDIT-C = Alcohol Use Disorder Identification Test - Consumption items; (Ref) = referent.

Table 2

State/contextual feature × alcohol sensitivity interaction fixed effects from multilevel regression analyses predicting alcohol craving.

Sample/State/Context × SRE Interaction	Estimate	SE	*p*
Full Sample (*n* = 403)			
Positive Affect	0.020	0.006	.002
Negative Affect	0.029	0.008	< .001
Weekend	0.047	0.014	.001
Time of Day[a]			
09:00-12:00	(Ref)		
12:00-15:00	−0.013	0.015	.379
15:00-18:00	0.001	0.015	.930
18:00-21:00	0.036	0.015	.019
21:00-00:00	0.030	0.017	.085
00:00-03:00	0.010	0.042	.812
03:00-06:00	0.061	0.081	.450
06:00-09:00	0.002	0.020	.923
Friend	0.039	0.012	.001
Bar/Restaurant	0.069	0.029	.018
Current Smokers (*n* = 258)			
Recent Smoking	−0.022	0.014	.111
Crave Cigarette	0.014	0.006	.017

Note: Each model included a single State/Context × SRE interaction term and included main effects for all Predictors in Table 1. SRE = Self-Rating of the Effects of Alcohol; (Ref) = referent

[a]Omnibus test for SRE × Time, $F(7, 35516.22) = 2.12$, $p = .038$.

Table 3

State/context × alcohol sensitivity interactions from analyses predicting alcohol craving, stratified by day-level drinking outcomes.

	Drinking Days			Non-Drinking Days		
Sample/SRE × State/Context	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***
Full Sample ($n = 403$)						
Positive Affect	0.031	0.009	< .001	0.005	0.009	.563
Negative Affect	0.037	0.011	< .001	0.020	0.011	.066
Weekend	0.037	0.019	.053	0.038	0.021	.067
Time of Day[a]						
09:00-12:00	(Ref)			(Ref)		
12:00-15:00	−0.008	0.021	.685	−0.014	0.021	.520
15:00-18:00	0.019	0.022	.383	−0.020	0.021	.331
18:00-21:00	0.068	0.021	.001	−0.003	0.021	.905
21:00-00:00	0.023	0.026	.380	0.035	0.022	.107
00:00-03:00	−0.022	0.050	.656	0.154	0.082	.058
03:00-06:00	0.011	0.107	.917	0.01	0.125	.939
06:00-09:00	0.001	0.027	.985	−0.017	0.028	.552
Friend	0.074	0.017	< .001	0.001	0.015	.933
Bar/Restaurant	0.078	0.038	.040	0.05	0.045	.264
Current Smokers ($n = 258$)						
Recent Smoking	−0.016	0.015	.283	−0.079	0.029	.006
Crave Cigarette	0.01	0.007	.119	0.003	0.01	.757

Note: Each model included a single State/Context × SRE interaction term and included main effects for all Predictors in Table 1. SRE = Self-Rating of the Effects of Alcohol; (Ref) = referent

[a]Omnibus test for SRE × Time on drinking days, $F(7, 21100.47) = 2.57$, $p = .012$. Omnibus test for SRE × Time on non-drinking days, $F(7, 14368.72) = 1.67$, $p = .112$.

Table 4

Fixed effects from idiographic models predicting alcohol craving.

Model/Predictor	Full Sample (n = 403)			Current Smokers (n = 258)		
	Estimate	SE	*p*	Estimate	SE	*p*
Limited to 3 pm – 3 am						
Intercept	0.512	0.229	.026	0.431	0.303	.156
Drinking Day	0.307	0.021	< .001	0.242	0.027	< .001
AUDIT-C	0.073	0.018	< .001	0.086	0.023	< .001
Impulsivity	0.007	0.003	.031	0.007	0.004	.078
Family History	−0.097	0.089	.280	−0.065	0.111	.556
SRE	−0.070	.051	.173	−0.099	0.068	.147
Drink Occasion Resemblance	1.106	.049	< .001	1.116	0.062	< .001
SRE × Predicted Value	0.298	0.064	< .001	0.272	0.082	.001
All Records						
Intercept	0.611	0.192	.002	0.519	0.245	.035
Drinking Day	0.172	0.014	< .001	0.139	0.018	< .001
AUDIT-C	0.055	0.015	< .001	0.067	0.019	< .001
Impulsivity	0.005	0.003	.030	0.006	0.003	.063
Family History	−0.065	0.075	.388	−0.044	0.090	.627
SRE	−0.035	0.043	.410	−0.068	0.055	.215
Drink Occasion Resemblance	1.765	0.040	< .001	1.842	0.051	< .001
SRE × Drink Occasion Resemblance	0.192	0.052	< .001	0.164	0.068	.015

Note: SRE = Self –Rating of the Effects of Alcohol form; AUDIT-C = Alcohol Use Disorder Identification Test - Consumption items.