INDIVIDUAL DIFFERENCES IN ALCOHOL SENSITIVITY AND THEIR EFFECTS ON SUBJECTIVE STATE AND CRAVING IN NATURALISTIC ENVIRONMENTS

A Thesis

presented to

the Faculty of the Graduate School

at the University of Missouri-Columbia

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

by

CONSTANTINE TRELÀ

Dr. Thomas Piasecki, Thesis Supervisor

MAY 2014
The undersigned, appointed by the dean of the Graduate School, have examined the thesis entitled

INDIVIDUAL DIFFERENCES IN ALCOHOL SENSITIVITY AND THEIR EFFECTS ON SUBJECTIVE STATE AND CRAVING IN NATURALISTIC ENVIRONMENTS

presented by Constantine Trela, a candidate for the degree of master of psychology, and hereby certify that, in their opinion, it is worthy of acceptance.

___________________________________________
Professor Thomas Piasecki

___________________________________________
Professor Bruce Bartholow

___________________________________________
Professor Matthew Martens
DEDICATION

This work is dedicated to Constantine Trela Sr., my grandfather, who taught me that perseverance is all one truly needs in life.
ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. Thomas Piasecki, for his dedication to this project and more generally giving me every opportunity to be successful in the program thus far. It has truly been an honor and a privilege to work with him.

I would also like to thank the other members of my committee, Drs. Bruce Bartholow and Matthew Martens, for their thoughtful comments and feedback on this work.
# TABLE OF CONTENTS

ACKNOWLEDGEMENTS ........................................................................................................ ii

LIST OF TABLES ............................................................................................................... iv

ABSTRACT ........................................................................................................................ v

Chapter

1. INTRODUCTION ........................................................................................................ 1

   Aims of the research

2. METHODS .................................................................................................................. 9

3. RESULTS ................................................................................................................... 17

4. DISCUSSION ............................................................................................................. 21

REFERENCES .................................................................................................................. 28

APPENDIX

1. TABLES OF RESULTS .......................................................................................... 35
LIST OF TABLES

Table                                           Page

1. Effects of Alcohol Sensitivity, Drinking Moments, and their Interaction Relative to Proximal Random Prompts ..........................................................35


3. Descending Limb: Effects of Alcohol Sensitivity, eBAC, Interaction, and Peak eBAC ........................................................................................................37
INDIVIDUAL DIFFERENCES IN ALCOHOL SENSITIVITY AND THEIR EFFECTS ON SUBJECTIVE STATE AND CRAVING IN NATURALISTIC ENVIRONMENTS

Constantine Trela
Dr. Thomas Piasecki, Thesis Supervisor

ABSTRACT

Sensitivity to the effects of alcohol has long been studied as a risk factor for developing an alcohol use disorder. Several theories exist regarding the profile of subjective responses that constitute the highest risk: Two of the most prominent are the Low Level of Response and Differentiator Models. A newer model focused on craving for alcohol, the Dual Process Model, suggests that craving may be correlated to the risky patterns of response predicted by the Low Level of Response and Differentiator Models. Relatively little research up to this point has focused on whether the responses predicted by these models generalize beyond the laboratory. The present study focuses on how individual differences in response to alcohol during the course of naturalistic drinking episodes map onto those laboratory-based theories. Participants from Project Six of the Midwest Alcoholism Research Center recorded their responses to alcohol and when randomly prompted by an electronic diary for 21 days. Three sets of analyses were conducted: examining responses following the first drink of an episode relative to a random prompt, as well as while estimated blood alcohol content was ascending and descending. The Low Level of Response Model enjoyed the highest degree of support in the data. The observed pattern of craving responses did not clearly match either the Low Level of Response or Differentiator Models.
**Introduction**

The costs of alcohol use disorders (AUD) are alarming. Worldwide, 3.8% of deaths are directly linked to AUD, and economic costs from medical bills to lost productivity frequently exceed 1% of gross national product in highly developed nations (Rehm et al., 2009). Despite the human and economic effects of AUD, their development is not fully understood.

Because alcohol consumption is the *sine qua non* of AUD, investigators have long been drawn to examining whether alcohol has distinctive effects in individuals at high risk for AUD, as inferred from a family history of alcoholism, compared to those with no known familial risk. This line of inquiry has culminated in the identification of a diminished subjective response to alcohol (SR) as an important AUD risk factor (Morean & Corbin, 2010; Quinn & Fromme, 2011). The bulk of existing research into individual differences in SR has been informed by two theoretical models: The low level of response model (LLRM; Schuckit, 1980) and the differentiator model (DM; Newlin & Thomson, 1990). There is both considerable evidence for each model and debate over which best characterizes AUD risk (Morean & Corbin, 2010).

More recently, drawing from dual process cognitive models (e.g., Weirs, et al., 2007) and the incentive-sensitization theory of addiction (Robinson & Berridge, 1993), researchers have begun to investigate how individual differences in SR are related to the neural processing of alcohol cues. This work demonstrates that at-risk drinkers show enhanced late positive electrocortical potentials during alcohol cue exposure, suggesting amplified approach motivation that may be experienced as craving. A better
understanding of SR (including craving) will allow for better identification of at-risk drinkers and potentially lessen the societal, family, and personal burdens of AUDs.

**Low level of response model**

The LLRM grew out of Schuckit’s work with sons of alcoholics. Schuckit (1980) found that young men with a family history of alcoholism (FH+) reported less SR on the Subjective High Assessment Scale (SHAS; Judd, Hubbard, Janowsky, Huey, & Attewell, 1977) at peak BAC and later time points compared to matched-controls without a family history of alcoholism (FH-). The FH+ participants also estimated that they had a lower BAC than FH- participants despite a non-significant difference in BAC between groups. Schuckit replicated the original findings (Schuckit, 1980) in a placebo controlled study (Schuckit, 1984). The results from Schuckit (1980) were also later replicated in a sample of FH+ and FH- females (Eng, Schuckit, & Smith, 2005). A follow-up study conducted with participants from Schuckit (1980) found that among FH+ participants, 56% of those in the lowest pentile of SR had developed an AUD compared to only 14% in the highest pentile (Schuckit, 1994). A key turning point in the LLRM was an investigation by Schuckit and Smith (1996). In this study, Schuckit and Smith conducted an analysis based upon level of sensitivity that combined both FH+ and FH- participants. The results indicated that low sensitivity (LS) to alcohol’s effects was a predictor of developing an AUD even after statistically controlling for the effects of family history status. Previously, the LLRM applied to a subset of FH+ drinkers, but Schuckit and Smith (1996) indicated that the theory ought to be applied more broadly.
In a follow-up study to Schuckit and Smith (1996), LS remained a predictor of AUD independent of family history status, but also remained significant with the inclusion of additional factors believed to be related to developing an AUD, including impulsivity, alcohol expectancies, and several others (Schuckit & Smith, 2001). The implication of Schuckit and Smith (2001) was that LS was a true predictor of risk for developing an AUD in and of itself, and not merely a marker of a separate risk. The exact mechanisms of how LS fosters an increase in risk for developing an AUD are not definitively clear. Schuckit and colleagues have suggested that LS drinkers lack warning signs of increasing intoxication that normative drinkers have, leading to greater consumption of alcohol (Schuckit, 1994; Schuckit & Smith, 2001). In turn, heavier drinking encourages more associations with other heavier drinkers, potentially altering beliefs about alcohol’s effects and normative drinking behaviors (Schuckit, 2009). Trim, Schuckit, and Smith (2009), however, have suggested that the relationship between LS and AUD is much more complicated that merely increasing alcohol consumption.

Despite evidence in support of the LLRM, there are several methodological and psychometric limitations. The protocol for many of Schuckit’s studies involved beginning drinking in the morning, between the hours of 7 and 9 am (Schuckit, 1980; Schuckit, 1984); this represents a non-normative time for drinking that Jones (1974) suggests can have an impact on drinking experiences. The primary measure of response examined in studies supporting the LLRM, the SHAS, was not developed specifically as a measure of alcohol response, and evaluates primarily negative effects (Judd et al., 1977) that do not frequently occur while BAC is rising. Furthermore, Schuckit and colleagues
rarely examine level of response throughout the entire range of BAC, and the reports that exist lack adequate description of study methodology (e.g. rate of alcohol administration as in Schuckit & Gold, 1988) or use inappropriate statistical corrections to data (e.g. BAC level in Schuckit, Tsuang, Anthenelli, Tipp, & Nurnberg Jr., 1996) making conclusions regarding level of response on the ascending limb of the BAC unclear.

**Differentiator Model**

In the decade following the publication of Schuckit (1980), a number of research groups found heightened effects of alcohol relative to baseline on the ascending limb in young adult, male social drinkers both with and without a family history of alcoholism (Babor, Berglas, Mendelson, Ellingboe, & Miller, 1983; Lukas, Mendelson, & Benedikt, 1986a; Lukas, Mendelson, Benedikt, & Jones, 1986b; Kaplan, Hesselbrock, O’Connor, & DePalma, 1988). Newlin and Thomson (1990) synthesized findings regarding increased perceived intoxication and heightened pleasurable/positive effects on the ascending limb and suggested a different profile of response as compared to the LLRM. The DM proposed by Newlin and Thomson (1990) suggests that FH+ individuals show increased positive SR to alcohol while BAC is ascending and lower SR to effects that occur while BAC was descending. The DM proposes that it is the imbalance in the experience of effects and feedback that constitutes the increased risk for AUD. The development of the Biphasic Alcohol Effects Scale (BAES; Martin, Earleywine, Musty, & Perrine, 1993), a measure of subjective response with both positive and negative items, facilitated better testing of the hypotheses of the DM. The DM was expanded to include heavy drinkers independent of family history (Holdstock, King, & de Wit, 2000; King, Houle, de Wit,
Holdstock, & Schuster, 2002). A recent meta-analysis conducted by Quinn and Fromme (2011) indicated that stimulation increased and sedation decreased across the entire BAC curve among heavier drinkers compared to lighter drinkers. Even more germane to the hypotheses of the DM, heavier drinkers showed increased stimulation particularly on the ascending limb of the BAC curve (Quinn & Fromme, 2011). One component in the body of research supporting the DM that is lacking in comparison to the LLRM is longitudinal studies. To the author’s knowledge, only one longitudinal study has shown that increased positive SR and decreased negative SR are related to development of an AUD in heavy drinkers (King, de Wit, McNamara, & Cao, 2011).

In a similar fashion to the LLRM, there are a variety of theories regarding how heightened responses to alcohol functions as a risk factor for AUD. Unlike the LLRM, however, the theories regarding an increased risk for AUD that operate within the DM framework are more varied. Some propose simple behavioral and motivational mechanisms, as in King et al. (2011) where increased pleasurable effects of alcohol encourage future drinking in order to experience those same effects. Others propose more complex mechanisms, as in Newlin (2002) where alcohol activates neural circuitry involved in basic homeostatic functions and produces a sense of reproductive fitness. The implication of that model is that while alcohol does not produce an actual gain in fitness for reproduction, the individual will learn that drinking alcohol produces the same feeling with a substantially smaller investment of energy.

The DM addressed some of the previously noted limits of the LLRM. In particular, the DM’s emphasis on limb-specific responses encouraged the use of the
BAES and other similar measures to assess both positively and negatively valenced effects of alcohol, an improvement over earlier research practices. Also, the DM and studies in support of the model measure and account for effects of alcohol that are experienced shortly after consumption, while studies in support of the LLRM frequently do not measure those moments, but rather interpolate effects that are observed at peak BAC levels and beyond and applies them to the ascending limb.

**Dual Process Model**

More recently, Bartholow and colleagues (Bartholow, Henry & Lust, 2007; Bartholow, Lust, & Tragesser, 2010; Fleming & Bartholow, 2013; Shin, Hopfinger, Lust, Henry, & Bartholow, 2010) have applied a social-cognitive dual process model (DPM) to understand the nature of LS risk. Broadly, the DPM (Weirs et al. (2007) suggests that AUDs develop as the result of an imbalance between two separate cognitive systems: A fast acting, appetitive system that encourages future use and a slower, more deliberate control system that attempts to inhibit further use. The appetitive system is highly susceptible to sensitization (Robinson and Berridge, 2003), meaning that positive drinking experiences can serve to reinforce drinking behavior in the future. Alternately, the control system is not yet fully developed in adolescence (Dahl, 2004), and even if it were, many adolescent drinkers lack the motivation to control their drinking (Weirs et al., 2007). Using a variety of experimental paradigms, Bartholow and colleagues have applied this framework to studying individual differences in alcohol sensitivity. Results reveal that LS drinkers show increased motivated attention to alcohol cues (Bartholow et al 2007; Bartholow et al., 2010; Shin et al., 2010) and a behavioral bias toward
approaching alcohol cues. This body of findings suggests that LS risk can be profitably conceptualized in terms of exaggerated approach motivation, a state that may be indexed by self-reported craving (Robinson & Berridge, 2003). The LLRM and DM models are both silent with respect to how craving responses might relate to individual differences in alcohol sensitivity.

The various studies that support the LLRM, DM, and the DPM rarely share a standard methodology, but almost all take place in a laboratory setting. In alcohol challenge studies that assess the LLRM and DM, they also exert control over the amount of alcohol consumed and pace of consumption (Morean & Corbin, 2010). As such, one can be reasonably certain of the causal role of alcohol consumption upon the observed effects. A critically lacking component of the research at this time, however, is the generalizability of the results to ad lib drinking episodes in naturalistic environments.

Ecological momentary assessment is a valuable tool in assessing whether effects observed in the laboratory are ecologically valid in the midst of contextual variables like the social environment (Sher, 1985), expectancies, (Mann, Chassin, & Sher, 1987) and pace of consumption (Conrod, Peterson, Pihl, & Mankowski, 1997) that prior research has suggested may play important roles.

Ecological momentary assessment (EMA) is any kind of data collection that occurs in real-time and in a research participant’s natural environment (Shiffman, Stone, & Hufford, 2008). EMA methodologies have been used to assess a wide variety of behaviors (Shiffman et al., 2008), with substance use being an especially apt target (Shiffman, 2009). Indeed, a number of studies utilizing EMA to examine the effects of
alcohol and tobacco co-use (e.g. Piasecki et al. 2011; Piasecki, Wood, Shiffman, Sher, & Heath, 2012b) illustrate how the methodology can effectively examine contextual variables typically unaccounted for in laboratory-based SR research.

In this study, EMA was used to collect data regarding positively and negatively valenced subjective states and craving in moments immediately following consumption of alcohol and throughout drinking episodes in a sample of social drinkers recruited from the community. Individual differences in SR-related risk were indexed using the Self-Rating of the Effects of Alcohol (SRE; Schuckit, Smith, & Tipp, 1997a; Schuckit, Tipp, Smith, Wiesbeck, & Kalmijn, 1997b), a psychometric tool developed and validated in order to determine the level of sensitivity without the need for an alcohol challenge session.

The goals of this research were to investigate how individual differences in SR risk are expressed in subjective states during “real world” drinking episodes. This investigation is informed by each of the three models described above. According to the LLRM, individuals with higher SRE scores (and thus lower alcohol sensitivity) should show a domain-general diminution of alcohol responses. The DM model suggests additional nuances, namely that the effects of SR risk might differ as a function of the valence of the response investigated and the limb of the blood alcohol concentration curve. Neither the LLRM nor DM speaks to craving for alcohol. Existing work conducted from the DPM perspective suggests heightened approach motivation in the presence of alcohol cues could be an important correlate of SR risk (Bartholow et al., 2007; Bartholow et al., 2010). This suggests self-reports of craving for alcohol may be
amplified during drinking episodes (which perforce involve exposure to interoceptive and exteroceptive alcohol cues).

**Methods**

**Participants**

Participants were social drinkers from the Midwest Alcoholism Research Center (MARC) Project 6 dataset that has been the focus of previous investigations (Piasecki et al., 2011; Piasecki et al., 2012a; Piasecki et al., 2012b, Piasecki et al., in press; Robertson, et al., 2012; Epler, et al., in press). Participants were recruited from the community and contained both smokers and non-smokers. The inclusion criteria for participants consisted of (a) drinking alcohol at least 4 times in the past month, (b) being at least 18 years old, (c) being able to read and write English, (d) expressing no interest in seeking AUD related treatment, (e) no report of unsuccessfully cutting down or stopping drinking, (f) no history of alcohol-related legal problems (outside of status offenses), and (g) if female, not currently pregnant or planning to become pregnant. Smokers were oversampled by design (64.1% of the study population) as Project 6 was designed to study alcohol and tobacco co-use. Participants who smoked had to meet the following criteria in addition to those listed above: (a) smoking at least one cigarette per week, (b) not regularly use non-cigarette tobacco products, and (c) expressing no interest in seeking smoking cessation treatment. All participants provided written consent to participate in the study. The research protocol was approved by the University of Missouri and Washington University School of Medicine Institutional Review Boards.
**Procedure**

All participants attended an initial session at which they were weighed using a physician’s scale and completed a series of baseline questionnaires. At a separate session typically completed within 2 days of the initial session, participants completed a training session for their electronic diary device (ED). Training consisted of instructions on how to record smoking events, drinking events, and random prompts on the device. These training sessions lasted 45 minutes and were completed both individually and in groups of up to 10 participants.

**Diary Protocol.** Participants carried the ED for 21 days beginning immediately at completion of the training session. Drinking events were recorded by participants immediately following the first drink of a drinking episode. These events triggered a follow-up protocol which prompted additional responses at 30, 90, 150, and 210 minutes following the first drink record. At each follow-up prompt, the participant was asked whether one or more new drinks were consumed since last report. If one or more additional drinks was reported an additional prompt was scheduled for 60 minutes following the final scheduled prompt (e.g. if a participant reported an additional drink between the first drink report and the 30 minute prompt, an additional prompt would be scheduled for 270 minutes). Participants could report that they were going to bed; in that event all remaining follow-up prompts were canceled. Additionally, participants were randomly prompted to complete a report of subjective state up to 5 times per day. The software pre-empted delivery of random prompts between the first drink report and the end of the drinking follow-up protocol.
In the event that a participant neglected to enter a first drink record, but reported they had consumed alcohol during a random prompt or any other type of record, the drinking follow-up protocol was triggered. These drinks captured through other record types were equivalent to manually entered first drink records with the exception that appraisal of the drink (described below) did not occur. Drinking follow-up records were identical whether triggered by a manually entered first drink or when the first drink was captured through another record type.

**Measures**

**Participant-level covariates.** Participants completed the SRE during the initial session. The SRE asks participants to record the number of drinks required to feel any effect of alcohol, to feel dizzy or begin slurring speech, to begin stumbling or walking in an uncoordinated manner, and to pass out; participants record those number separately based on the first five times they drank, the first time they drank at least monthly for three consecutive months, and for their heaviest period of drinking. A participant’s score on the SRE is the number of drinks required for each endorsed effect across all three time periods divided by the total number of effects endorsed. In the event that a participant has not experienced a particular effect (e.g. if they have never passed out) they are instructed to skip that item and move to the next one. (Schuckit et al., 1997a; Schuckit et al., 1997b). Occasionally, an SRE score is computed using only the first five drinking episodes (see Schuckit et al., 2007 and Schuckit, Smith, Trim, Fukukura, & Allen, 2009 as examples), however the full score was used here since evidence from the development of the SRE suggested the full score method performs best in samples that drink on a
regular basis (Schuckit et al., 1997a). Participants’ SRE were standardized within each sex (ZSRE). This served two purposes: To ensure that sensitivity was not confounded with sex differences, and to improve interpretability such that beta weights corresponded to change per standard deviation.

Participant sex, weight, and age were also recorded during the initial session. Sex was dummy coded such that females served as the reference sex. Weight was measured in pounds. Participant age was also dummy coded into categories of 18-20 years old, 21-30 years old, 31-40 years old, and 41+ years old (the 41+ years old group served as the reference group).

**Episode-level covariates.** All records made in the ED were date and time stamped. Those data were coded into either weekday (after 6 p.m. Sunday and before 6 p.m. Thursday) or weekend (6 p.m. Thursday to 6 p.m. Sunday). Time of day was coded into 4-hour blocks beginning with 12 a.m. to 4 a.m., consistent with previously published work from the lab (Piasecki et al., 2012). Additionally, the latency in hours between the first drink and the most recent pre-drinking random prompt was calculated.

Random prompts and first drink records also asked participants to record their location (work or school, bar or restaurant, home, outside, in a vehicle, and other) and social companionship (alone, with a romantic partner, with friends, with coworkers, with a child, with parents, with other family members, or with other people). A composite “family” episode-level variable was computed from the original “child,” “parent,” and “other family” variables since these three occurred in a minority of cases and were significantly correlated with one another. For both location and social companionship
questions, participants recorded all categories that applied (i.e. participants could select more than one option). Participants were also asked during first drink records and random prompts whether they had smoked a cigarette in the last 15 minutes, and in drinking follow-ups to record the number of cigarettes they had smoked since the last report. To manage assessment burden during drinking episodes, social companionship and participant location were not recorded during drinking follow-ups. As such, these covariates can be assessed at the episode level (specifically the outset of the episode), but cannot be assessed for effects at the moment-to-moment level.

**eBAC.** Participants were assumed to have made first drink reports immediately following finishing the first drink, as this was a focal point of the instruction session. During follow-up records, participants recorded the number of drinks consumed since the last record (none, one, two, three, four, five, or six or more). These data in combination with weight and sex recorded at baseline were used to calculate an eBAC according to a formula that most closely matches *ad libitum* drinking episodes (Mathews & Miller, 1979; Hustad & Carey, 2005). Limb of eBAC curve was coded as ascending if the eBAC was greater than that of the prior record, or descending if less than the prior record. First drink records were always considered to be on the ascending limb, and the first drink was assumed *ad hoc* to have taken 20 minutes. The exact amount of time chosen for the first drink is arbitrary since the eBAC associated with each moment and the magnitude of correlations between eBAC and other variables would be affected equally; rather, 20 minutes was chosen to reflect that it is unlikely that alcohol was absorbed instantaneously, and also since it produced eBACs that seemed reasonable given the raw
number of drinks consumed. There were a total of 44 records (less than 0.5% of all records assessed) where a participant’s momentary eBAC was greater than 0.40%. Given the raw number of drinks reported by any one participant, it seemed unlikely that such dangerously high BACs were achieved.

Each participant’s eBAC also played a vital role in determining whether a drinking follow-up record fell on the ascending or the descending limb of a given episode. Given the *ad libitum* nature of each drinking episode, there is no way to predict when the ascending limb ends and the descending limb begins. Rather, the eBAC at each drinking follow-up record was determined and compared to the most recent preceding report. In the event that the eBAC at a given follow-up record was greater than or equal to the previous record the follow-up was considered to be an ascending limb moment. When the eBAC of a follow-up was less than the previous record that follow-up was considered to be a descending limb moment.

**Subjective state.** Subjective state was measured in all records using 5-point scales (1 = *not at all* to 5 = *extremely*) to assess state over the last 15 minutes. Subjective states that were assessed include composite positive affect (the average of enthusiastic, excited, and happy), composite negative affect (the average of distressed and sad), the individual components of the composite scores, craving for a drink, buzz, dizzy, sluggish, headache, and nausea. Composite positive affect showed good internal consistency for first drink analyses (α = 0.882), ascending limb analyses (α = 0.875) and descending limb analyses (α = 0.879). Composite negative affect also showed adequate-to-good
consistency across first drink ($\alpha = 0.727$), ascending ($\alpha = 0.753$), and descending limb ($\alpha = 0.766$) analyses.

**Appraisal of alcohol effects.** Following first drink records and records of additional drinks during the follow-up protocol, participants rated drinks on a 5-point scale (1 = *not at all* to 5 = *extremely*) for positively reinforcing effects (“Was the last drink pleasurable?”), negatively reinforcing effects (“Did the last drink relieve unpleasant feelings?”), and punishing effects (“Did the last drink make you feel worse?”). These appraisals were only administered when new drinks were recorded; as such there is a relative lack of these ratings on the descending limb versus the ascending limb for at least two reasons. First, in order for a moment to be classified as being on the descending limb it required cessation of drinking, or at least slowing down drinking. This creates an inverse relationship between recording a new drink and being on the descending limb. Second, as described above, participants could log that they were going to bed which canceled any remaining follow-ups. It is reasonable to believe that follow-ups that were canceled for that reason disproportionately fell on the descending limb.

**Analyses.** General mixed linear models were computed using SAS software (SAS version 9.3, SAS Institute Inc., Cary, NC). In testing the hypotheses, three separate models were computed: One where first drink records were compared against the most recent random prompt within one hour of the drink record, an ascending limb model, and a descending limb model. The pairing of the first drink record to a random prompt within one hour prior to the drink record was chosen to create a pseudo-baseline. A true pre-drink baseline record, while certainly more desirable, was not included in this study due
to concerns over subject burden. Periods of 1, 2, 3, and 4 hours prior to the first drink were considered when searching for a temporally proximal random prompt. Naturally, the longer the timeframe considered, the more likely it was that any given first drink would have a temporally proximal random prompt. This was reflected by the total amount of first drink records that could be paired with a random prompt and included in the analyses. A 4 hour window before the drink allowed for use of 74.4% (2,054) of all first drinks (2,760), while periods of 3 hours and 2 hours allowed for 66.7% (1,842) and 42.9% (1,185) respectively. The use of a 1 hour period prior to the first drink only allowed for 16.1% (444) of all first drinks. While the single hour window censored much of the data, the data that remained allowed for the greatest degree of confidence in the assumption that the results observed following the first drink were truly a result of the first drink and not a fluctuation of uncertain causality. For the first drink vs. random prompt models, the main effects of drink record, ZSRE, and the interaction of drink record with ZSRE on subjective states were assessed. For drink appraisals, since there was not a need for a pre-drink baseline, all user initiated drink records (1,812) were considered. In these analyses the main effect of ZSRE was examined, but not drink record or the interaction since these appraisals were only made in drink records. In both types of first drink models, participant-level and episode-level covariates were included as main effects. Both models utilized random intercepts and unstructured covariances.

Ascending and descending limb models were computed separately in order to maximize interpretability of results and ease of calculation. Both were 3-level hierarchical linear mixed models with each momentary assessment nested within an
episode, and with episodes nested within participants. For the ascending model, the main
effects of eBAC and ZSRE, and the eBAC by ZSRE interaction were examined while
also including all episode-level covariates, as well as participant’s age and sex.
Participant weight was not included since the variance due to weight was fully contained
within eBAC. The ascending limb models utilized random intercepts at the episode and
subject level, as well as a random slope for eBAC at each level as well.

The descending limb model differed slightly from the ascending limb model. The
main effects of eBAC and ZSRE, as well as the interaction between the two was still
considered the main outcome measures for subjective state and drink appraisal, but peak
eBAC was also included in order to account for the magnitude of change that occurred
during the descending limb. A further difference between the ascending and descending
limb models was that the slope associated with eBAC was modeled as a fixed effect on
the descending limb. This resulted as an unintended effect of the relative lack of
descending limb moments. Some participants only completed descending limb reports in
a single report, or had only a single descending limb moment across several episodes –
this effectively caused the random effect calculations to be improper since the matrices
involved contained variance components of zero.

Results

First Drink Analyses. A total of 235 participants contributed at least one pair of
a first drink record with a random prompt within the previous 60 minutes in order to
create a pseudo-baseline comparison. These participants were approximately evenly
balanced between males and females (51% male), oversampled for smokers (65%
smokers), and had an average age of 23.37 years old. For subjective state analyses there were 444 valid pairs of first drink and random prompts. The average length of time between the pseudo baseline random prompt and the first drink of an episode was approximately 35 minutes. For the alcohol appraisal analyses all 1,812 user-initiated first drinks were considered. These records were drawn from 398 participants who were evenly split by sex and had an average age of 23.3 years old. The majority (64%) of these participants were current cigarette smokers.

Estimates of subjective state following the first drink, and the appraisals of that drink are presented in Table 1. Most germane to the research aims were the findings on composite negative affect, feeling distressed, dizziness, and craving. There were no significant main effects of alcohol sensitivity or record type on composite negative affect, feeling distressed, or dizziness, but there were significant negative interactions for the three ($b_s = -0.068, -0.116, \text{ and } -0.041$ respectively; all $p_s < 0.05$). There was a positive main effect of record type on craving ($b = 0.179; p < 0.05$), indicating that craving for a drink was higher in the wake of the first drink relative to the temporally relevant random prompt. There was only marginal evidence for an interaction between alcohol sensitivity and record type on craving ($b = -0.120; p = 0.06$). Similarly, there was only marginal evidence for an effect of alcohol sensitivity on ratings of the first drink being pleasurable ($b = 0.069; p = 0.07$).

**Ascending Limb Analyses.** The ascending limb analyses did not require a random prompt in the previous hour; as such, the sample for these analyses was comprised of the 398 participants described above who contributed records to the
appraisal analyses. For the subjective state models there were a total of 8,817 valid records, and a total of 7,250 valid records for drink appraisals.

Ratings of subjective states and drink appraisals are presented in Table 2. There were no main effects of alcohol sensitivity on any of the subjective states. Momentary eBAC had main effects on all subjective states with the exceptions of composite negative affect (and its component states) and craving for a drink. With regards to the research goals, the effects on feeling buzzed and feeling dizzy are the most telling. In addition to the main effect of eBAC on feeling buzzed ($b = 7.319; p < 0.001$), there was also a negative interaction between eBAC and alcohol sensitivity ($b = -1.006, p < 0.01$). This indicated that participants with lower alcohol sensitivity reported relatively less buzz at equivalent levels of eBAC. The results for feeling dizzy were similar. There was a main effect of eBAC on dizziness ($b = 2.644, p < 0.001$) and a negative interaction between eBAC and alcohol sensitivity ($b = -0.629, p < 0.01$).

For the drink appraisal variables, finding additional drinks pleasurable or that additional drinks relieved displeasure did not differ as a function of eBAC, alcohol sensitivity, nor an interaction between the two. There was a significant main effect of eBAC and an interaction between eBAC and alcohol sensitivity on the punishing effects of alcohol (i.e. the additional drink made the participant feel worse). Participants reported higher levels of feeling worse following an additional drink as eBAC increased ($b = 1.227, p < 0.001$), but the negative interaction term indicated that participants with lower alcohol sensitivity were partially protected against this negative consequence ($b = -0.393, p < 0.05$).
As previously noted, ratings of craving for a drink were not significantly affected by eBAC, alcohol sensitivity, or an interaction between the two. While the lack of an effect due to alcohol sensitivity or the interaction parallels the findings from the first drink versus random prompt analyses, the lack of a difference in craving based on eBAC (analogous to the main effect of record type in the previous analyses) did not follow suit. The lack of change in craving over the course of the ascending limb could potentially have resulted from participants being able to manage that craving through having an additional drink, or that the follow-up prompts were too coarsely grained to capture moment-to-moment changes.

**Descending Limb Analyses.** There were 380 participants that reported at least 1 descending limb moment over the course of the study. As with the ascending limb sample, participants were evenly split between males and females, a majority were smokers (63%), and the average age was slightly over 23 years old (23.2 years old). Subjective states were modeled based on 2,735 total records. The results of these models are presented in Table 3. As one would expect, there were negative main effects of momentary eBAC on composite positive affect (and its component states) and craving. The peak eBAC achieved in each episode had a positive effect on each of those states. A similar pattern of results was observed for physiological type results – feeling buzzed, feeling dizzy, feeling sluggish, and feeling nauseous were all significantly affected by momentary eBAC (i.e. at higher eBAC while descending, these states were experienced more acutely). Peak eBAC, however, only significantly affected feeling buzzed.
Alcohol sensitivity had a main effect on feeling happy \( (b = -0.085; \ p < 0.05) \), indicating that over the entirety of the descending limb, regardless of momentary or peak eBAC, lower sensitivity drinkers were less happy than their higher sensitivity peers. There was one significant interaction between momentary eBAC and alcohol sensitivity (feeling sad \( b = 0.710; \ p < 0.05 \)). This suggests that at equivalent levels of eBAC, lower sensitivity drinkers felt more sad than their peers.

**Discussion**

The current study examined responses to alcohol in frequent drinkers in their natural drinking environments. Each drinking episode was intensively sampled, particularly with regard to the ascending limb of the alcohol curve. The findings reported here reflect prior meta-analyses focusing on laboratory based studies of subjective response (Morean & Corbin, 2010; Quinn & Fromme, 2011). Namely, there was evidence for diminished response to alcohol in those with the highest SRE scores (in keeping with the LLRM), but there was also evidence for the enhancement of positively valenced effects while eBAC was ascending (as suggested by the DM). There was also some evidence that craving is enhanced following the initiation of drinking that elucidates how craving may related to several different theoretical models.

Recall that the LLRM suggests that the profile of risk for alcohol use disorders is that of diminished responses to the effects of alcohol regardless of the effect’s valence. The results of this study displayed considerable evidence for the veracity of the model’s predictions. Some effects in the set of analyses that tested first drink records relative to temporally proximal random prompts were straight forward with regard to the Low Level
of Response Model (e.g. the negative interaction between sensitivity and record type for feeling dizzy). Effects that reflect negative reinforcement could be interpreted as evidence for the LLRM. The typical understanding of the LLRM is that consuming alcohol produces a positive effect and that individuals at risk for developing an AUD experience that effect less intensely: In the case when the effect produced by alcohol is negative, as is the case with composite negative affect and distress, the less sensitive participants experienced a differentially greater decrease such that the change from a baseline state was greater, but the overall level was still lower. In the ascending limb models, there was strong evidence for the LLRM. There were negative interactions between eBAC and alcohol sensitivity for several effects that increased as eBAC increased. Even more telling is that these effects (feeling buzzed, feeling dizzy, and that the most recent drink had a punishing effect) have traditionally been thought of as effects that encourage drinkers to “hit the brakes.” The fact that these effects are experienced less intensely in low sensitivity drinkers is a textbook case for not only the predictions of the LLRM, but also one of the potential mechanisms for risk of developing an AUD that is suggested by the model. Evidence for the LLRM on the descending limb was scant, but the significant negative effect of alcohol sensitivity on feeling happy across the full spectrum of eBAC is consistent with the general premise of the LLRM.

Results in this study were less consistent with the predictions of the DM, but still provide some evidence for the model. Composite positive affect and its component states best displayed the limb-specific dynamic effects suggested by that model. As eBAC ascended, these effects similarly increased; once eBAC began to descend, these effects
followed suit. There were not, however, positive interactions between these positively valenced effects and alcohol sensitivity as one may have expected. As previously discussed, the finding of a negative interactions between record type and alcohol sensitivity for composite negative affect and feeling distressed could be interpreted as evidence for the LLRM; it could just as reasonably be interpreted as support for the DM. In this case, the differentially greater decrease in negatively valenced states (i.e. negative reinforcement) for those low in sensitivity could be considered analogous to acute sensitization of positively valenced effects predicted by the DM.

Craving is not directly discussed in either the LLRM or DM. The results of this study provide evidence from a naturalistic environment that the DPM’s prediction of increased approach motivation in the presence of alcohol cues has some truth. As seen in Table 1, craving for a drink increased in the moments following a first drink report. Craving was not affected significantly over the course of the ascending limb. This non-effect is somewhat confusing: Increases might be expected as the participant continues to be exposed to alcohol cues, but decreases might also be expected as more drinks are consumed. One potential explanation is that a self-medicating effect may be occurring. There may, in fact, be increases in craving related to continued exposure, but these increases were met with the consumption of additional drinks that in turn reduced the level of craving. The timeline for drinking follow-up reports, however, was not finely grained enough to say this definitively. As craving relates to the LLRM and DM, there is some evidence of limb specific effects in line with the DM. Craving increased in the first drink relative to the pseudo baseline state, but then decreased sharply as eBAC began to
decrease. There was not any strong evidence that craving was related to alcohol sensitivity level. There was no evidence in the present study that suggests alcohol sensitivity is significantly related to alcohol craving. A future direction for research that might elucidate potential relationships between alcohol sensitivity and craving would be to examine changes in craving over the course of a day leading up to a drinking episode. It might be the case that low sensitivity drinkers show greater craving responses to alcohol related cues (e.g. certain physical locations or time of day) than higher sensitivity drinkers, but that the initiation of drinking has a similar effect regardless of sensitivity.

In addition to the stated goals of the project, this study coincidentally provided support for the utility of the SRE. The SRE had previously been shown to be an effective index of alcohol sensitivity for laboratory based studies and analyses (Schuckit et al., 1997a; 1997b). Here the SRE effectively indexed sensitivity and showed predictive validity in the form of several interactions and main effects in a naturalistic environment. This is in addition to previous work from our lab (Piasecki et al., 2012a) that showed SRE scored were predictive of total drinks consumed and peak eBAC within drinking episodes in naturalistic environments.

This study had both strengths and weaknesses. Several of those weaknesses related to attempts to make the electronic diary recording as least burdensome as possible. For instance, the ability for participants to enter a report that they were retiring to bed, thus canceling all remaining drinking follow-ups led to the vast majority of recorded moments falling on the ascending limb of each episode (8,817 ascending moments vs. 2,735 descending moments). Similarly, there was no true baseline prior to
the first drink of an each drinking episode. Several options were considered for calculating a pseudo-baseline that the first drink could be compared to. Each option represented a trade-off between bandwidth and fidelity of the data – that is, several hundred more records could have been analyzed if a different cut-off was used to consider a random prompt temporally relevant, but the longer the window considered, the less confidence one could have in the conclusion that observed effects were caused by the drink. Ultimately the use of random prompts falling within an hour prior to a first drink record as a pseudo-baseline seemed an adequate balance. Future investigations would be much improved with the inclusion of a pre-drink report to eliminate the above problem. A pre-drink report could also serve to improve eBAC estimations by more accurately capturing the time to consume a drink, rather than using an arbitrary time period applied to all participants and episodes. A final weakness that bears discussion is the lack of a validated measure for subjective responses. The items that were used in the study represented a short, face-valid collection of items to assess the positive and negative effects of alcohol. In the future, short, empirically-validated instruments like the Brief Biphasic Alcohol Effects Scale (Rueger & King, 2013) could be used to accomplish the same task without a significant change in participant burden.

Strengths of the study included the volume of data collected for naturalistic drinking episodes. All things considered, over 11,500 data points were collected for close to 400 participants in an ecologically valid study of drinking. These rich data allowed for partialing out of potentially important contextual effects in each episode (e.g. physical location and social environment) that would ordinarily be lost in an in-lab assessment of
alcohol’s effects. Similarly, the extramural ad lib nature of each drinking episode allowed for examination of drinkers as they normally drink, rather than constraining those drinkers to a potentially alien scenario where they consume a specific beverage in a given amount of time that is not representative of their regular behavior.

Future studies could build on the present investigation. As noted above, the lack of a true baseline state prior to each drinking episode was a definite limitation of the analyses presented here. This seemed especially true for craving, since the pattern of results was unexpected and potentially an artifact of the sampling method. There is also the potential for measuring the drinks consumed even more accurately – recent advances with smartphones and other handheld electronics could allow for participants to photograph the bottle of the beer they were drinking, or videotaping a mixed drink being made such that laboratory staff could determine with a high degree of confidence the number of standard drinks consumed. Such a sampling method could also allow for examination of whether there are certain sub-types of drinkers that prefer a given type of beverage (e.g. 80% of participant A’s alcohol comes from liquor), or whether certain types of beverages elicit differential effects in different drinking contexts.

The pattern of results in the present study are more supportive of the LLRM than the DM in terms of characterizing alcohol response. Furthermore, the results were obtained in a naturalistic environment, effectively providing evidence that the LLRM generalizes outside of the laboratory. Participants in the study provided several thousand momentary reports of their subjective state over hundreds of naturalistic drinking
episodes. The relationship of alcohol craving in the natural environment with these two theories remains unclear, however, and should be the focus of future investigation.
References


Table 1
*Effects of Alcohol Sensitivity, Drinking Moments, and their Interaction Relative to Proximal Random Prompts*

<table>
<thead>
<tr>
<th>Subjective State</th>
<th>ZSRE</th>
<th>Drink Record</th>
<th>ZSRE x Drink Record</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b</td>
<td>SE</td>
<td>p</td>
</tr>
<tr>
<td>Positive Affect</td>
<td>-0.027</td>
<td>0.058</td>
<td>0.637</td>
</tr>
<tr>
<td>Happy</td>
<td>-0.013</td>
<td>0.056</td>
<td>0.818</td>
</tr>
<tr>
<td>Excited</td>
<td>-0.035</td>
<td>0.068</td>
<td>0.609</td>
</tr>
<tr>
<td>Enthusiastic</td>
<td>-0.041</td>
<td>0.067</td>
<td>0.539</td>
</tr>
<tr>
<td>Negative Affect</td>
<td>-0.032</td>
<td>0.047</td>
<td>0.493</td>
</tr>
<tr>
<td>Sad</td>
<td>-0.028</td>
<td>0.047</td>
<td>0.549</td>
</tr>
<tr>
<td>Distressed</td>
<td>-0.033</td>
<td>0.057</td>
<td>0.558</td>
</tr>
<tr>
<td>Buzzed</td>
<td>-0.090</td>
<td>0.041</td>
<td>0.028</td>
</tr>
<tr>
<td>Dizzy</td>
<td>-0.010</td>
<td>0.020</td>
<td>0.623</td>
</tr>
<tr>
<td>Sluggish</td>
<td>-0.079</td>
<td>0.045</td>
<td>0.082</td>
</tr>
<tr>
<td>Headache</td>
<td>-0.024</td>
<td>0.035</td>
<td>0.503</td>
</tr>
<tr>
<td>Nauseous</td>
<td>0.012</td>
<td>0.023</td>
<td>0.590</td>
</tr>
<tr>
<td>Craving</td>
<td>0.037</td>
<td>0.082</td>
<td>0.649</td>
</tr>
</tbody>
</table>

Drink Appraisals

<table>
<thead>
<tr>
<th></th>
<th>b</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleasurable</td>
<td>0.069</td>
<td>0.038</td>
<td>0.068</td>
</tr>
<tr>
<td>Relieved Displeasure</td>
<td>0.091</td>
<td>0.057</td>
<td>0.109</td>
</tr>
<tr>
<td>Punishing</td>
<td>0.005</td>
<td>0.017</td>
<td>0.766</td>
</tr>
</tbody>
</table>

*Note:* Models covaried for both episode-level and participant-level variables.
Table 2
Ascending Limb: Effects of Alcohol Sensitivity, eBAC, and Interaction

<table>
<thead>
<tr>
<th>Subjective State</th>
<th>eBAC</th>
<th></th>
<th>ZSRE</th>
<th></th>
<th>ZSRE x eBAC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b</td>
<td>SE</td>
<td>p</td>
<td>b</td>
<td>SE</td>
<td>p</td>
</tr>
<tr>
<td>Positive Affect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Happy</td>
<td>0.737</td>
<td>0.207</td>
<td>&lt; 0.001</td>
<td>-0.016</td>
<td>0.033</td>
<td>0.624</td>
</tr>
<tr>
<td>Excited</td>
<td>1.266</td>
<td>0.222</td>
<td>&lt; 0.001</td>
<td>-0.002</td>
<td>0.039</td>
<td>0.964</td>
</tr>
<tr>
<td>Enthusiastic</td>
<td>1.062</td>
<td>0.220</td>
<td>&lt; 0.001</td>
<td>-0.023</td>
<td>0.041</td>
<td>0.571</td>
</tr>
<tr>
<td>Negative Affect</td>
<td>0.102</td>
<td>0.160</td>
<td>0.553</td>
<td>-0.012</td>
<td>0.027</td>
<td>0.657</td>
</tr>
<tr>
<td>Sad</td>
<td>0.265</td>
<td>0.173</td>
<td>0.127</td>
<td>-0.030</td>
<td>0.028</td>
<td>0.284</td>
</tr>
<tr>
<td>Distressed</td>
<td>-0.097</td>
<td>0.193</td>
<td>0.617</td>
<td>0.006</td>
<td>0.032</td>
<td>0.847</td>
</tr>
<tr>
<td>Buzzed</td>
<td>7.319</td>
<td>0.392</td>
<td>&lt; 0.001</td>
<td>-0.039</td>
<td>0.037</td>
<td>0.290</td>
</tr>
<tr>
<td>Dizzy</td>
<td>2.644</td>
<td>0.247</td>
<td>&lt; 0.001</td>
<td>-0.028</td>
<td>0.020</td>
<td>0.166</td>
</tr>
<tr>
<td>Sluggish</td>
<td>0.847</td>
<td>0.237</td>
<td>&lt; 0.001</td>
<td>-0.058</td>
<td>0.031</td>
<td>0.059</td>
</tr>
<tr>
<td>Headache</td>
<td>0.421</td>
<td>0.134</td>
<td>0.002</td>
<td>-0.016</td>
<td>0.022</td>
<td>0.464</td>
</tr>
<tr>
<td>Nauseous</td>
<td>0.610</td>
<td>0.153</td>
<td>&lt; 0.001</td>
<td>-0.015</td>
<td>0.017</td>
<td>0.371</td>
</tr>
<tr>
<td>Craving</td>
<td>-0.085</td>
<td>0.295</td>
<td>0.773</td>
<td>0.090</td>
<td>0.052</td>
<td>0.083</td>
</tr>
<tr>
<td>Drink Appraisals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasurable</td>
<td>0.073</td>
<td>0.254</td>
<td>0.774</td>
<td>0.060</td>
<td>0.035</td>
<td>0.087</td>
</tr>
<tr>
<td>Relieved Displeasure</td>
<td>-0.030</td>
<td>0.282</td>
<td>0.914</td>
<td>0.025</td>
<td>0.052</td>
<td>0.632</td>
</tr>
<tr>
<td>Punishing</td>
<td>1.227</td>
<td>0.180</td>
<td>&lt; 0.001</td>
<td>0.006</td>
<td>0.016</td>
<td>0.715</td>
</tr>
</tbody>
</table>

Note: Models covaried for both episode-level and participant-level variable
Table 3

Descending Limb: Effects of Alcohol Sensitivity, eBAC, Interaction, and Peak eBAC

<table>
<thead>
<tr>
<th>Subjective State</th>
<th>eBAC</th>
<th>SE</th>
<th>p</th>
<th>ZSRE</th>
<th>SE</th>
<th>p</th>
<th>ZSRE x eBAC</th>
<th>SE</th>
<th>p</th>
<th>Peak eBAC</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Affect</td>
<td>-1.539</td>
<td>0.597</td>
<td>0.010</td>
<td>-0.056</td>
<td>0.043</td>
<td>0.199</td>
<td>-0.390</td>
<td>0.370</td>
<td>0.293</td>
<td>1.487</td>
<td>0.554</td>
<td>0.007</td>
</tr>
<tr>
<td>Happy</td>
<td>-1.387</td>
<td>0.678</td>
<td>0.041</td>
<td>-0.085</td>
<td>0.043</td>
<td>0.048</td>
<td>-0.470</td>
<td>0.412</td>
<td>0.254</td>
<td>1.227</td>
<td>0.619</td>
<td>0.048</td>
</tr>
<tr>
<td>Excited</td>
<td>-1.829</td>
<td>0.726</td>
<td>0.012</td>
<td>-0.037</td>
<td>0.049</td>
<td>0.453</td>
<td>-0.523</td>
<td>0.446</td>
<td>0.242</td>
<td>1.962</td>
<td>0.669</td>
<td>0.003</td>
</tr>
<tr>
<td>Enthusiastic</td>
<td>-1.731</td>
<td>0.688</td>
<td>0.012</td>
<td>-0.048</td>
<td>0.050</td>
<td>0.334</td>
<td>-0.095</td>
<td>0.419</td>
<td>0.820</td>
<td>1.433</td>
<td>0.632</td>
<td>0.024</td>
</tr>
<tr>
<td>Negative Affect</td>
<td>-0.443</td>
<td>0.527</td>
<td>0.401</td>
<td>0.011</td>
<td>0.036</td>
<td>0.756</td>
<td>0.240</td>
<td>0.325</td>
<td>0.459</td>
<td>0.548</td>
<td>0.486</td>
<td>0.260</td>
</tr>
<tr>
<td>Sad</td>
<td>-0.011</td>
<td>0.564</td>
<td>0.985</td>
<td>-0.015</td>
<td>0.037</td>
<td>0.677</td>
<td>0.710</td>
<td>0.342</td>
<td>0.038</td>
<td>-0.011</td>
<td>0.515</td>
<td>0.983</td>
</tr>
<tr>
<td>Distressed</td>
<td>-0.748</td>
<td>0.660</td>
<td>0.257</td>
<td>0.039</td>
<td>0.042</td>
<td>0.354</td>
<td>-0.209</td>
<td>0.404</td>
<td>0.606</td>
<td>1.043</td>
<td>0.605</td>
<td>0.085</td>
</tr>
<tr>
<td>Buzzed</td>
<td>5.055</td>
<td>0.627</td>
<td>&lt;0.001</td>
<td>-0.041</td>
<td>0.039</td>
<td>0.294</td>
<td>0.000</td>
<td>0.385</td>
<td>0.999</td>
<td>-1.230</td>
<td>0.576</td>
<td>0.033</td>
</tr>
<tr>
<td>Dizzy</td>
<td>1.304</td>
<td>0.410</td>
<td>0.002</td>
<td>-0.016</td>
<td>0.028</td>
<td>0.570</td>
<td>0.029</td>
<td>0.247</td>
<td>0.905</td>
<td>0.056</td>
<td>0.373</td>
<td>0.880</td>
</tr>
<tr>
<td>Sluggish</td>
<td>1.692</td>
<td>0.715</td>
<td>0.018</td>
<td>-0.075</td>
<td>0.044</td>
<td>0.092</td>
<td>0.028</td>
<td>0.431</td>
<td>0.948</td>
<td>-1.092</td>
<td>0.650</td>
<td>0.093</td>
</tr>
<tr>
<td>Headache</td>
<td>0.489</td>
<td>0.507</td>
<td>0.335</td>
<td>-0.020</td>
<td>0.032</td>
<td>0.544</td>
<td>0.029</td>
<td>0.305</td>
<td>0.925</td>
<td>-0.296</td>
<td>0.461</td>
<td>0.521</td>
</tr>
<tr>
<td>Nauseous</td>
<td>0.864</td>
<td>0.381</td>
<td>0.023</td>
<td>-0.026</td>
<td>0.025</td>
<td>0.288</td>
<td>0.365</td>
<td>0.231</td>
<td>0.115</td>
<td>-0.286</td>
<td>0.348</td>
<td>0.412</td>
</tr>
<tr>
<td>Craving</td>
<td>-4.966</td>
<td>0.765</td>
<td>&lt;0.001</td>
<td>0.057</td>
<td>0.048</td>
<td>0.231</td>
<td>0.007</td>
<td>0.473</td>
<td>0.988</td>
<td>4.781</td>
<td>0.705</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Note:* Models covaried for both episode-level and participant-level variables