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Subjective Response to Alcohol: Interactive Effects of Early Life Stress, Parental Risk for Mood and Substance Use Disorders, and Drinking Context

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Abstract

Early life stress, specifically childhood maltreatment, and parental risk for mood and substance use disorders (SUDs) are associated with increased risk for alcohol use disorder (AUD). There is limited data on how these factors interact to contribute to alcohol-related outcomes. Prior work has suggested early life stress may increase sensitivity to psychostimulants and that subjective response to alcohol is heritable. It is unclear if early life stress alters sensitivity to alcohol and interacts with parental risk for mood/SUDs which in turn may act as a risk factor for AUD. The current study uses within-subjects placebo-controlled alcohol administration methods to investigate the effects of childhood maltreatment on subjective response to alcohol in young adults with and those without parental risk of mood/SUDs. Additionally, we explored interactions with drinking context (i.e., drinking in a bar vs. non-bar context). Within individuals with parental risk for mood/SUDs, there was a positive relation between total Childhood Trauma Questionnaire (CTQ) score and how drunk individuals reported feeling across both alcohol and placebo conditions (parental risk group-by-CTQ interaction p=.01; main effect of CTQ within individuals with parental risk for mood/SUDs p=.005). When exploring interactions with drinking context (bar vs. non-bar context), we observed a significant drinking context-by-parental risk-by-CTQ interaction (p=.03), with CTQ score positively associated with greater positive valence/positive arousal feelings in the parental risk group if they consumed their beverages in the bar context (p=.004) but not if they consumed their beverages in the non-bar context. Results suggest childhood maltreatment may contribute to variation in subjective response to the positive effects of alcohol—possibly mediated by alcohol cues and/or expectancies—in young adults with parental risk for mood/SUDs.

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Keywords

Childhood maltreatment; early life stress; sensitivity; alcohol; familial risk; alcohol expectancies

1.1 Introduction

Early life stress, specifically childhood maltreatment, is associated with increased risk for alcohol use disorder (AUD). Studies support childhood maltreatment is associated with earlier onset of AUD, increased risk of relapse, and poor treatment response (Kirsch et al., 2020; Kirsch and Lippard, 2022). It is unclear how childhood maltreatment translates to risk for AUD over time. Studies suggest childhood maltreatment alters stress and reward processing (Boecker et al., 2014; Hanson et al., 2016; Lippard and Nemeroff, 2022) and these alterations are thought to contribute to risk for, and illness course in, AUD (Koob, 2008; Kirsch et al., 2020). Interactions between stress and reward systems, including neuroadaptations within the stress systems and associations with altered sensitivity to rewarding properties of substances of abuse are suggested (Meaney et al., 2002; Pruessner et al., 2004). For example, higher cortisol response to stress—which has been reported following childhood maltreatment in youth and adults with unipolar depression (Kaufman et al., 1997; Heim et al., 2000; Heim et al., 2008)—is associated with greater drug effects (e.g., self-report of liking, high, desire for drug) following amphetamine administration (Oswald et al., 2005; Wand et al., 2007). Early life stress is also associated with greater striatal dopamine response to amphetamine (Wand et al., 2007; Oswald et al., 2014). Findings converge to suggest early life stress may increase sensitivity to psychostimulants.

While preclinical research suggests early life stress, via maternal separation, is associated with increased response to alcohol (Oreland et al., 2011), the relations between early life stress and subjective response to alcohol are not well understood. A previous exploratory analysis, from data collected as part of an intravenous alcohol self-administration study, found an association between childhood trauma and greater blood alcohol concentration and “wanting” of alcohol following a stress cue exposure (Ramchandani et al., 2018). Childhood trauma is associated with impaired control over drinking which may mediate alcohol use and development of alcohol-related problems (Patock-Peckham et al., 2020). More work on factors that may contribute to impaired control over drinking, (e.g. variability in subjective response to alcohol) could foster novel interventions.

As not everyone exposed to childhood maltreatment will develop AUD, factors that contribute to risk/resiliency following childhood maltreatment also need to be elucidated. Familial risk for substance use disorders (SUDs), including AUD (Dawson et al., 1992; Lieb et al., 2002; Wilens et al., 2014; Yule et al., 2018), and mood disorders (Maier et al., 1995; Maier and Merikangas, 1996; Wilens et al., 2014) are associated with increased risk for AUD. Additionally, prior research indicates common biological underpinnings between mood disorders and addiction (Carmiol et al., 2014; Icick et al., 2022) suggesting overlapping genetic vulnerability associated with familial risk may increase susceptibility for alcohol-related problems. Genetic variation implicated in mood disorders and SUDs are also suggested to contribute to differences in subjective response to alcohol (Fromme et

al., 2004; Ray et al., 2013; Ray et al., 2014; Gatt et al., 2015; Otto et al., 2017; Qi et al., 2020) and subjective response to alcohol is heritable (Viken et al., 2003). It is therefore possible that overlapping genetic variation associated with familial risk for mood/SUDs may contribute to variation in subjective response to alcohol. Indeed, familial risk for AUD is associated with altered subjective response to alcohol (Schuckit et al., 1996; Eng et al., 2005). Additionally, genetic vulnerability and environmental interactions contribute to alcohol-related outcomes (Kaufman et al., 2007; Young-Wolff et al., 2011; Lippard and Nemeroff, 2020; Kirsch et al., 2021; Kendler et al., 2022). To our knowledge no oral alcohol administration study has tested if childhood maltreatment is associated with variation in subjective response to alcohol, and if the relation between childhood maltreatment and subjective response differs between those with and without parental risk for mood/SUDs.

This study investigates the effects of childhood maltreatment on subjective response to alcohol in young adults with and without parental risk of mood/SUDs. The data reported here were obtained from two larger studies using within-subjects placebo-controlled alcohol administration methods to investigate subjective response to alcohol in young adults (NCT04063384 and NCT04716036). For this initial investigation, we focused on young adults without a self-history of mood disorder to test our hypothesis that childhood maltreatment is associated with alterations in subjective response to alcohol with this relation moderated by parental risk for mood/SUDs. Specifically, we hypothesized that childhood maltreatment would be associated with increased positive effects of alcohol during the ascending limb of the breath alcohol concentration (BrAC) curve with effects of childhood maltreatment more robust in individuals with parental risk for mood/SUDs. This hypothesis is based on prior work that childhood maltreatment increases positive subjective response to amphetamine (Oswald et al., 2005), preliminary findings that childhood maltreatment is associated with greater “wanting” of alcohol during an intravenous alcohol self-administration study (Ramchandani et al., 2018), and preclinical research suggesting maternal separation increases response to alcohol (Oreland et al., 2011). Additionally, the two studies data were obtained from differed in drinking context with drinking occurring in a simulated bar in one study (bar context) and in the laboratory in the other (non-bar context). We investigated differences in subjective response to alcohol between the bar context and non-bar context as prior work suggests drinking in a non-bar context is related to greater stimulating effects of alcohol (Corbin et al., 2021) and bar context may tap into alcohol expectancies more than a non-bar context (Corbin et al., 2015).

2.1 Methods

2.1.1 Participants

53 participants (21–26 years of age, 57% women, with no history severe AUD) were recruited from the greater Austin area between July 2019 and September 2022. We used the Structured Clinical Interview for DSM 5, Research Version [SCID-5RV (First et al., 1995)] to confirm participants exhibited no prior psychiatric hospitalizations, lifetime history of a neurodevelopmental disorder, mood disorder, anxiety disorder, psychotic disorder, eating disorder, or >1 month of lifetime psychotropic medication. Exclusion criteria included: neurologic abnormality including significant head trauma (loss of consciousness of ≥5-min);

full Scale IQ <85; contraindication to MRI scanning; positive pregnancy test; history of severe cannabis use disorder; history of severe AUD; ever being in an abstinence-oriented treatment program for alcohol use; reporting wanting to quit drinking but not being able to; a current substance use disorder (other than alcohol, cannabis, or nicotine), any medical, religious, or other reasons for not drinking alcohol; history of heart attack, heart trouble, high blood pressure, diabetes, or liver disease; an adverse reaction to alcoholic beverages; reporting never consuming 4 (men) or 3 (women) or more drinks on a drinking occasion in the past 12 months; or unwillingness to have a friend or family member drive them home after alcohol administration sessions. Phone screens, which included the Alcohol Use Disorders Identification Test [AUDIT; (Babor et al., 2001)], were used to screen out individuals with possible symptoms of alcohol dependence (scores >15). We did not exclude individuals with a history of mild/moderate AUDs to be more generalizable, as it is common for individuals in this age group to binge drink alcohol. All study procedures were approved by the Institutional Review Board at the University of Texas at Austin.

Childhood maltreatment history was obtained using the 28-item self-report Childhood Trauma Questionnaire [CTQ; (Bernstein et al., 2003). The CTQ assesses emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Each statement is scored on a scale ranging from “1-never true” to “5- always true”. Higher scores indicate more severe childhood trauma. Thirty-six (68%) individuals in our sample met established criteria for childhood maltreatment (see table 1). First-degree family history of mental illness—including AUD, SUDs, bipolar disorder, major depressive disorder, and generalized anxiety disorder—was assessed by self-report and using the Family History – Epidemiologic Assessment [FHE; (Lish et al., 1995)]. The FHE asks about symptoms of mental illness and complimented self-report of parental mental illness. For example, the FHE asks if parents ever had a period of at least a month when they were very sad/blue and/or tense or nervous and worried, a period when they were more active/talkative than normal, a period when they drank a lot, etc. For this study, we grouped all individuals with parental risk for mood/SUDs because familial risk for mood/SUDs is suggested to increase risk for offspring AUD. Additionally, studies suggest genetic overlap in mood/SUDs and subjective response to alcohol phenotypes. Intelligence quotient estimates were obtained with the Wechsler Abbreviated Scale of Intelligence matrix reasoning and vocabulary subtests. Frequency and quantity of recent alcohol use (past 30-days) was assessed using the Time Line Follow Back [TLFB; (Sobell, 1992)]. This measure was also used to assess frequency of tobacco and marijuana use over the past 30-days. Using the data collected from the TLFB, we calculated three indices of alcohol consumption: total drinks and days drinking over the past month and average number of drinks per drinking day over the past month.

2.1.2 Alcohol and Placebo Beverage Administration Procedures

Participants completed two counter-balanced beverage administration sessions (alcohol and placebo conditions). Sessions occurred, on average, two days apart. Participants were told they would drink alcohol on both days but could receive different doses of alcohol and that they would not be dosed to exceed a breath alcohol concentration (BrAC) of .08g%. Beverage administration procedures were identical across participants and occurred at the University of Texas at Austin in either a simulated bar lab (51% of participants) or in a

private assessment room in the Biomedical Imaging Center (49% of participants) as part of parent studies.

Mood symptoms were assessed at the beginning of each beverage administration day by self-report surveys, i.e. the Beck Depression Inventory (Beck et al., 1961) and Beck Anxiety Inventory (Beck et al., 1988). Participants were asked to fast from food for 4 hours prior to beverage consumption. Before beginning beverage consumption, participants ate a weight-adjusted, 1 calorie per pound snack of pretzels to delay the rate of alcohol absorption and increase the duration of the ascending limb of the blood alcohol concentration curve (Jones and Jönsson, 1994). Individual alcohol doses were based on the participants' age, sex, height, and weight (Curtin and Fairchild, 2003; Cofresí et al., 2020; Corbin et al., 2021). For both beverage sessions, participants were given 20 minutes to consume two beverages (10 minutes per beverage). The alcohol beverages contained a 1:3 mixture of 80 proof vodka to mixer (cranberry juice, diet cherry 7-up, and lime juice) to achieve a target peak BrAC of .08g%. Dosing was the same for participants drinking in the bar and non-bar settings. Following 20 minutes of drinking and a 10 to 15-minute absorption period, BrAC was collected. The placebo manipulation included using tonic instead of vodka stored in absolute vodka bottles (visual cue), wiping the table with alcohol before the participant arrived (olfactory cue), and using an alcohol floater in drinks (gustatory cues). All other protocols were identical between the placebo and alcohol beverage conditions (Quinn and Fromme, 2016; Cofresí et al., 2020; Corbin et al., 2021). In the simulated bar setting, a research assistant acted as a bartender behind the bar and another research assistant sat and chatted with the participant at the bar. In the non-bar setting (at the Biomedical Imaging Center), a research assistant prepared the beverages on a rolling cart within the participant's view. Another research assistant sat and chatted with the participant during their drinking episodes in the non-bar drinking context.

Self-report of subjective response to alcohol was collected with the Subjective Effects of Alcohol Scale (SEAS) (Morean et al., 2013). Four subscales of subjective response are calculated from the SEAS: positive valence/positive arousal (i.e., lively, talkative, fun, funny); positive valence/negative arousal (i.e., mellow, relaxed, secure, calm); negative valence/positive arousal (i.e., aggressive, rude, demanding); and negative valence/negative arousal (i.e., woozy, dizzy, wobbly). The SEAS was collected before alcohol/placebo consumption began on each respective day and after beverage consumption and absorption period, defined as ascending BrAC. Change in subjective response on the SEAS at the ascending time point (compared to baseline) was calculated for both alcohol and placebo conditions [e.g., SEAS positive valence/positive arousal (ascending BrAC) minus SEAS positive valence/positive arousal before they started beverage consumption on that respective day]. We also assessed the extent to which participants felt drunk using visual analog scales. At the ascending BrAC subjective response assessment, participants also reported how many standard drinks they believed they had consumed on that respective day. This data was used to validate the placebo condition. We only investigated subjective response to alcohol at the ascending BrAC so data between study sites would be comparable, as individuals in the non-bar context completed a fMRI scan following their ascending BrAC measurement while individuals in the bar-context did not. Consistent with NIAAA guidelines for human alcohol studies, BrAC readings continued every 30 minutes until participants were at or

below a 0.04% BrAC at which time they were escorted home. For the placebo condition, participants were told they had reached their exit BrAC approximately one and a half hours after starting to drink in the simulated bar. In the non-bar context, participants were told they had reached their exit BrAC approximately 30 minutes after exiting the scanner during the placebo condition. Participants were informed of their BrAC readings and the nature of the placebo session after completing both beverage sessions.

2.2 Statistical Approach

2.2.1 Between Parental Risk Group and Between Drinking Context Differences in Demographics and Clinical Characteristics

T-tests, Mann-Whitney-Wilcoxon tests, Chi-square, and Fisher's exact as appropriate was used to assess between-group (parental risk for mood/SUDs group vs. no parental risk for mood/SUDs group) and between-context (bar vs. non-bar context) differences in age, sex, race, IQ, BMI, days between beverage sessions, and clinical/environmental factors including history of AUD/SUD, CTQ total score, number of individuals meeting threshold for childhood maltreatment on the CTQ, drinking motives, and recent alcohol and substance use (table 1).

2.2.2 Between/Within Parental Risk Group and Between/Within Drinking Context Differences on Beverage Condition Days

Between-group (parental risk for mood/SUDs group vs. no parental risk for mood/SUDs group) and between-drinking context (bar vs. non-bar context) differences in mood symptoms reported prior to beverage consumption, BrAC, time from when the participant started drinking to BrAC collection, how many drinks participants thought they had consumed (manipulation check), and urine toxicology screens were assessed using Mann-Whitney-Wilcoxon tests, Chi-square, or Fisher Exact as appropriate. Additionally, parental risk group by condition interactions, and drinking context by condition interactions, were modeled with condition a repeated within subject factor to investigate if parental risk group, drinking context, and/or beverage condition days differed in mood symptoms, baseline score on the SEAS dependent variables of interest (prior to beverage consumption), BrAC, time from when the participant started drinking to BrAC collection, how many drinks participants thought they had consumed (placebo manipulation check), and urine toxicology screens (table 2). All findings were considered significant at alpha <.05.

2.2.3 Early Life Stress, Parental Risk, and Drinking Context Effects on Subjective Response to Alcohol

We used mixed models to investigate CTQ-by-parental risk-by-condition interactions with condition as a within subject factor. We hypothesized that childhood maltreatment would be associated with increased sensitivity to positive effects of alcohol; therefore, our a priori dependent variables across all models were baseline-adjusted SEAS positive valence/positive arousal, baseline-adjusted SEAS positive valence/negative arousal, and perception of being drunk (modeled separately). Sex, drinking context (bar vs. non-bar context), order of session (i.e., if alcohol/placebo condition came first or second), coping drinking motives, and total AUDIT score were included as covariates. Data suggest childhood maltreatment

is indirectly related to alcohol-related problems through coping drinking motives (Grayson and Nolen-Hoeksema, 2005; Shin et al., 2020) and coping expectancies (Jester et al., 2015). However, variation in coping drinking motives is also suggested to relate to familial factors that extend beyond childhood maltreatment (Mackie et al., 2011; Müller and Kuntsche, 2011; Stapinski et al., 2016) and drinking motives relate to variability in subjective response to alcohol (Grodin et al., 2019). We therefore included coping drinking motives as a covariate to control for variability in coping drinking motives that might stem from varying levels of genetic risk, socioeconomic status, and parental drinking in our familial risk group. If we did not observe a three-way interaction, the three-way interaction term was dropped and we investigated CTQ-by-condition, parental risk-by-condition, and CTQ-by-parental risk interactions. If there were no significant interactions, the interaction terms were dropped to investigate main effects. As recent data suggests drinking context contributes to subjective response to alcohol we also explored interactions with drinking context in the above models. Findings were considered significant at alpha <.05. All significant findings are reported below.

2.2.4 Sensitivity Analyses

We ran sensitivity analyses for the above models to investigate if main effects of CTQ or CTQ interactions would remain significant after excluding four individuals in the parental risk for mood/SUDs group with CTQ scores >55 (so CTQ scores would not significantly differ between parental risk groups), and when covarying 1) race and ethnicity; 2) BMI; and 3) cannabis use (yes/no) since these factors differed by parental risk group or study site (see table 1). Total CTQ was not normally distributed and we did not transform data in the general linear mixed models above (Lo and Andrews, 2015; Schielzeth et al., 2020). However, to ensure this violation of normality did not affect results, we also re-ran our models after transforming total CTQ scores.

3.1 Results

3.1.1 Demographic Comparisons between Parental Risk Groups and Drinking Contexts

Individuals with parental risk for mood/SUDs had greater total CTQ scores, total AUDIT scores, and number of past-month cannabis users. Individuals who completed their beverage sessions in the bar context had greater total CTQ scores, BMI, and greater number of individuals meeting threshold for childhood maltreatment. The racial/ethnic backgrounds of individuals who completed their beverage sessions in the bar context differed from the racial/ethnic backgrounds of individuals who completed their beverage sessions in the non-bar context (see table 1). No other between parental risk group or drinking context differences were observed.

3.1.2 Between/Within Parental Risk Group and Between/Within Drinking Context Differences on Beverage Condition Days

Individuals with parental risk for mood/SUDs had lower baseline (pre-beverage consumption) SEAS positive valence/positive arousal scores than those without parental risk. No other between parental risk group or drinking context differences on beverage

condition days were observed. Additionally, no parental risk group by condition or drinking context by condition interactions were observed (see table 2).

3.1.3 Early Life Stress, Parental Risk, and Drinking Context Effects on Subjective Response to Alcohol

There was a significant parental risk for mood/SUDs-by-CTQ interaction on feeling drunk ($F=6.6$, $p=.01$, figure 1A). Within individuals with parental risk for mood/SUDs, a positive relation was observed between total CTQ score and how drunk individuals reported feeling (main effect of CTQ: $F=9.1$, $p=.005$). There was no significant relationship between total CTQ score and how drunk individuals reported feeling in young adults with no parental risk for mood/SUDs (main effect of CTQ: $F=3.2$, $p=.08$). There was a main effect of condition such that individuals reported feeling more drunk during the alcohol compared to the placebo condition ($F=86.9$, $p<.0001$). There were no significant interactions with condition.

There were no significant effects of coping drinking motives or total AUDIT score in any of our models. See supplemental tables 1–3 for details of models including other main effects of covariates. Individuals reported feeling more lively/talkative (SEAS positive valence/positive arousal) during the alcohol compared to the placebo condition (main effect of condition: $F=17.9$, $p<.0001$). Furthermore, individuals with parental risk for mood/SUDs reported feeling more lively/talkative during both beverage conditions (main effect of parental risk: $F=4.2$, $p=.04$) compared to individuals without parental risk. Individuals reported feeling more mellow/relaxed during their second beverage session compared to their first beverage session (main effect of beverage order: $F=16.1$, $p=.0001$). Additionally, we observed a significant positive relation between total CTQ score and SEAS positive valence/negative arousal during both beverage conditions ($F=4.0$, $p=.049$).

When exploring interactions with drinking context (bar vs. non-bar context), we observed a significant drinking context-by-parental risk-by-CTQ interaction on SEAS positive valence/positive arousal (e.g. “lively/talkative,” $F=4.9$, $p=.03$, figure 1B). When stratifying by drinking context, we observed a parental risk-by-CTQ interaction if beverages were consumed in the bar context ($F=4.4$, $p=.04$), with CTQ score positively associated with SEAS positive valence/positive arousal scores in the parental risk group ($F=10.8$, $p=.004$) but not in individuals without parental risk ($F=1.1$, $p=.31$). There was no parental risk-by-CTQ interaction if the drinking occurred in the non-bar context ($F=1.2$, $p=.28$).

There was also a significant drinking context-by-condition interaction on SEAS positive valence/positive arousal ($F=6.4$, $p=.01$, figure 2A) and positive valence/negative arousal ($F=5.1$, $p=.03$, figure 2B). Specifically, if individuals completed their beverage sessions in the bar context, there was a significant effect of condition, with greater reported SEAS positive valence/positive arousal scores ($F=22.3$, $p=.0001$) and SEAS positive valence/negative arousal scores ($F=4$, $p=.05$) during the alcohol condition, compared to placebo condition. There was not a main effect of condition on SEAS positive valence/positive arousal or positive valence/negative arousal in individuals who completed their beverage sessions in the non-bar context (SEAS positive valence/positive arousal: $F=2.4$, $p=.13$; SEAS positive valence/negative arousal: $F=1.2$, $p=.3$).

3.1.4 Sensitivity Analyses

When removing four individuals in the parental risk group with CTQ scores >55 (to match CTQ scores in parental risk and non-parental risk groups), the parental risk group-by-total CTQ interaction remained significant (F=6.7, p=.01). Likewise, when removing these four individuals, the drinking context-by-parental risk-by-CTQ interaction on SEAS positive valence/positive arousal remained significant (F=6.6, p=.01). When controlling race/ethnicity, BMI, or cannabis user (yes/no) in the models, the parental risk-by-CTQ interaction on feeling drunk remained significant in all sensitivity analyses. The drinking context-by-parental risk-by-CTQ interaction on SEAS positive valence/positive arousal remained significant when controlling for BMI and cannabis use, but became a trend when controlling for race (p=.078). When transforming CTQ scores all results reported above for CTQ remained significant.

4.1 Discussion

This study, to our knowledge, is the first oral alcohol administration study to test if childhood maltreatment is associated with variation in subjective response to alcohol and if the relation between childhood maltreatment and subjective response differs between those with and without risk for mood/SUDs. In line with our hypothesis, childhood maltreatment was associated with increased positive drug effects (i.e., SEAS positive valence/positive arousal and SEAS positive valence/negative arousal) and how “drunk” individuals reported feeling during beverage sessions. We only observed a positive relation between childhood trauma and SEAS positive valence/positive arousal in young adults with parental risk. Results suggest that genetic vulnerability for mood/SUDs may interact with environmental factors, specifically childhood maltreatment, to contribute to differences in subjective response to alcohol. Interestingly, we did not see an interaction between childhood maltreatment and beverage condition (childhood trauma was associated with increased positive effects reported during both the alcohol and the placebo beverage conditions). Since we also observe a relation between CTQ and positive effects reported following placebo consumption, we hypothesize childhood maltreatment may contribute to alcohol expectancies that in turn contribute to subjective response to alcohol. Recent evidence supports childhood adverse events is associated with alcohol expectancies even in alcohol-naïve youth (Johnson et al., 2023). Alcohol expectancies are well established to contribute to alcohol use and development of AUDs (Gundersen et al., 2008; Sebold et al., 2017) and the placebo manipulation provides an objective measure of alcohol expectancies (Bodnár et al., 2021; Kirsch et al., 2023). This hypothesis is further supported by our finding that the relationship between childhood maltreatment and SEAS positive valence/positive arousal feelings in individuals with parental risk for mood/SUDs was only observed in individuals who drank in the bar context. Prior work suggests a bar context may tap into alcohol expectancies and craving more than a non-bar context because of alcohol cue exposure (Corbin et al., 2015; Kuerbis et al., 2020; Chen et al., 2021), with sensitivity to alcohol moderating craving (Trela et al., 2018). A recent study of college students found that childhood trauma, compared to adult trauma, relates to greater alcohol craving in response to an alcohol cue task (Bing-Canar and Berenz, 2022). Familial factors (i.e., parental alcohol misuse and parent-child conflict) are also supported to contribute to

alcohol expectancies (Patrick et al., 2017) and variability in alcohol cue reactivity even in alcohol naïve adolescents (Nguyen-Louie et al., 2018). Additionally, individuals with family history of AUD have shown a greater memory recall of alcohol cues after consuming alcohol, with heart rate variability during alcohol picture cue viewing predicting greater recall of alcohol cues and related to subjective level of intoxication reported (Leganes-Fonteneau et al., 2021). Findings could suggest familial risk is associated with a cognitive bias towards alcohol cues. Familial risk is undoubtedly complex with both genetic and environmental/social factors contributing to risk and resiliency for psychopathology. Indeed, lower alcohol problems in parents is suggested to contribute to resiliency for alcohol problems of offspring following childhood trauma (Ramchandani et al. 2018). Social factors that may contribute to AUD in individuals with parental risk for mood/SUDs may include alcohol availability, parental support and monitoring, socioeconomic status, as well as peer influences (Tretyak et al. 2022). It is important to note, the lack of an association between childhood maltreatment and SEAS positive valence/positive arousal feelings in the non-bar context could relate to limited power in the non-bar context (i.e. fewer individuals with parental risk for mood/SUDs). However, we did not observe interactions with condition (i.e., childhood maltreatment was related to positive effects reported during both alcohol and placebo conditions) and relations between childhood maltreatment and feeling “drunk” was observed in both drinking contexts. Findings support childhood maltreatment may relate to variability in the subjective experience of intoxication. Future work is needed to determine if variability in alcohol expectancies, alcohol cue reactivity, and/or craving contributes to, or interacts with, variability in subjective response to alcohol, thereby contributing to alcohol use outcomes. Positive alcohol expectancies are a risk factor for alcohol-related problems (Lee et al., 2020; Ramirez et al., 2020; King et al., 2022), with positive alcohol expectancies emerging early during development (Pinquart and Borgolte, 2022), and data suggesting expectancies can be targeted for interventions (e.g., alcohol expectancy challenges) to improve drinking outcomes (Dunn et al., 2020; Dunn et al., 2022; Lau et al., 2022; Schick et al., 2022). Findings support more work on the role(s) of childhood maltreatment, parental risk for mood/SUDs, and subjective response to alcohol, including alcohol expectancies and other factors that affect alcohol consumption and experience of intoxication in a natural drinking environment (Wigmore and Hinson, 1991).

Several limitations should be noted. In comparison to intravenous infusion of alcohol, oral administration results in variability of BrAC, timing of dependent measures, and brain exposure to alcohol. However, oral alcohol administration may provide greater ecological validity compared to infusion paradigms (Cyders et al., 2020). Since we aimed to investigate effects of drinking context we chose oral administration to be more generalizable. Our parental risk for mood/SUDs included young adults with parents with unipolar depression, bipolar disorder, anxiety disorder, AUD, and other SUDs. Parents were not interviewed to confirm their diagnoses and severity of parents’ psychiatric diagnosis was not assessed. Type of parental psychiatric risk varied across individuals and comorbid psychiatric conditions were often reported (see supplemental table 4). We were underpowered to investigate more homogeneous familial risk groups. Future research should investigate similarities and differences based on distinct parental risk groups as documented by the parents or psychiatric records. Previous findings in individuals with a family history of AUD are

consistent with the “low level of response” hypothesis (Quinn and Fromme, 2011). A low response to alcohol (i.e. more alcohol required to feel intoxicated) may identify youth at risk for developing AUD (Ray et al., 2010). Our finding that childhood maltreatment is associated with increased positive stimulating effects of alcohol are more in line with the “differentiator” model, i.e., increased sensitivity to stimulating effects of alcohol during the ascending limb of the BrAC and decreased sensitivity to the sedative effects of alcohol during the descending limb of the BrAC may predispose individuals at increased risk for developing problems overtime. King et al. recently reported increased subjective response to alcohol across the young adult epoch is associated with development/maintenance of AUD (King et al., 2021). We did not investigate sedative effects of alcohol as we only investigated differences in subjective response during the ascending limb of the BrAC to maintain consistency between the studies that data was obtained from. While childhood maltreatment and parental risk for mood/SUDs is associated with offspring risk for AUD, this study cannot discern if differences in subjective response relates to risk/resilience for alcohol misuse. Individuals with parental risk for mood/SUDs reported higher childhood maltreatment, however, when we removed four individuals with the highest CTQ scores (so groups would not significantly differ in CTQ scores) results remained the same. Our findings differed from a prior study that reported drinking in a non-bar context is related to greater stimulating effects of alcohol (Corbin et al., 2021). We observed greater SEAS positive valence effects during the alcohol condition, compared to placebo condition, only in the bar context. While beverage administration was similar up until the point of subjective response assessment at the ascending BrAC time point, individuals who were in the non-bar context subsequently completed a functional neuroimaging scan. Anticipation of this upcoming scan in the non-bar context may have contributed to lower stimulating effects reported in the non-bar context and the overall experience of intoxication. Childhood maltreatment was measured by self-report and we cannot rule out recall bias. In addition, because we included individuals with history of childhood maltreatment and/or family history of mood/SUDs, but without personal psychopathology, our sample may be a resilient cohort and may not be generalizable to the general population. While 68% of individuals in our sample met established criteria for childhood maltreatment, there was variability in severity of childhood maltreatment observed across parental risk groups and study sites (see supplemental table 5). We were also not powered to investigate type of childhood maltreatment reported. Additionally, with a total sample size of 53 participants and 6 covariates, at $p<.05$ the current study was 80% powered to detect an effect size of cohen’s $f \geq .4$ for two-way interactions. Based on prior research, we can infer we would have to increase the number of participants four-fold to detect the same effect size for 3-way interactions involving slope differences in mixed-effects linear models (Heo and Leon, 2010). Our study should be considered preliminary and hypothesis-generating for future studies with larger and more generalizable samples.

In conclusion, data support early life stress, specifically childhood maltreatment, may contribute to variation in subjective response to the positive effects of alcohol. This relationship is most robust in individuals with parental risk for mood/SUDs and may relate to alcohol expectancies. More research, with larger sample sizes, more homogeneous parental risk groups, and objective measures of childhood maltreatment, is needed to

identify mechanisms that contribute to variation in subjective response to alcohol following early life stress and the role(s) of alcohol expectancies to inform novel treatments and intervention strategies that are trauma-informed and more specific to parental risk/genetic vulnerability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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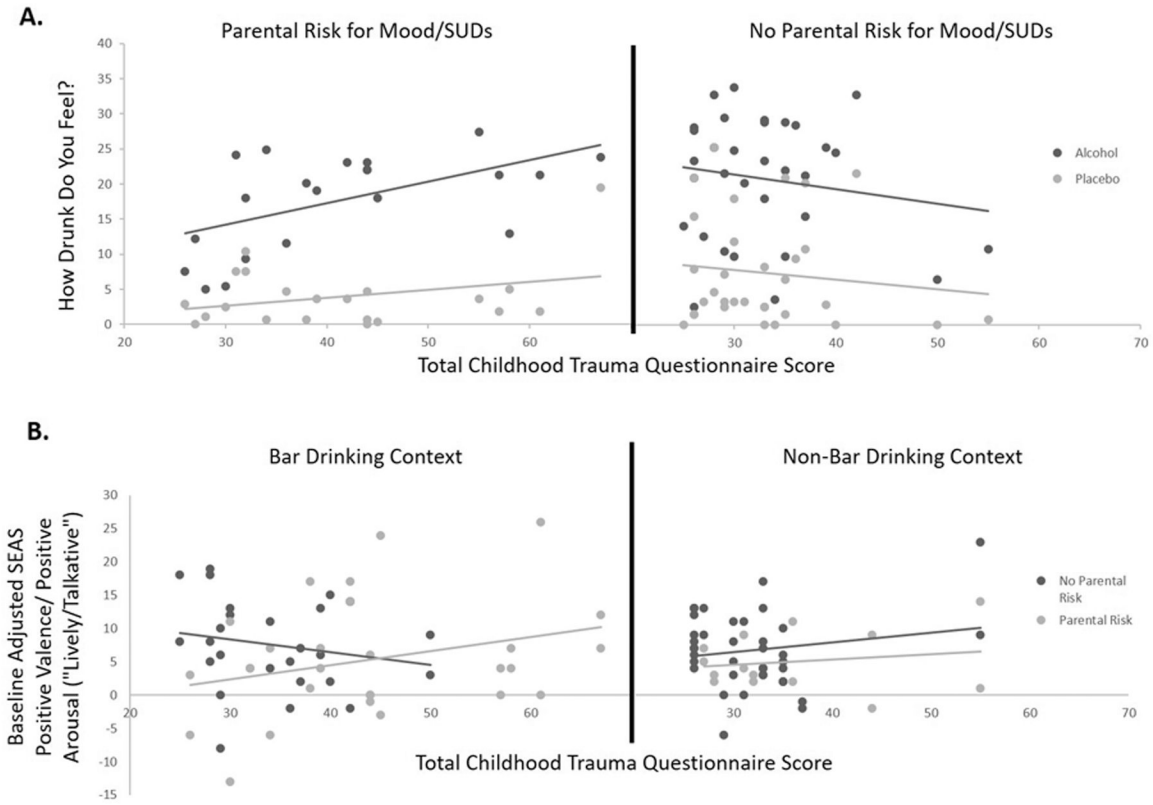

Figure 1.

A) There was a significant parental risk for mood/SUDs-by-CTQ interaction (F=6.6, p=.01) on how "drunk" individuals reported feeling. Within individuals with parental risk for mood/SUDs, a positive relation was observed between total CTQ score and how drunk individuals reported feeling (main effect of CTQ: F=9.1, p=.005). There was no significant relationship between total CTQ score and how drunk individuals reported feeling in youth with no parental risk for mood/SUDs (main effect of CTQ: F=3.2, p=.08). **B)** There was a significant drinking context-by-parental risk-by-CTQ interaction on SEAS positive valence/positive arousal (e.g. lively/talkative, F=4.9, p=.03). Specifically, there was a parental risk-by-CTQ interaction if beverages were consumed in the bar context (F=4.4, p=.04), with CTQ score positively associated with feeling lively/talkative in the parental risk group (F=10.8, p=.004) but not in individuals without parental risk (F=1.1, p=.31). There was no parental risk-by-CTQ interaction if the drinking occurred in the non-bar context (F=1.2, p=.28).

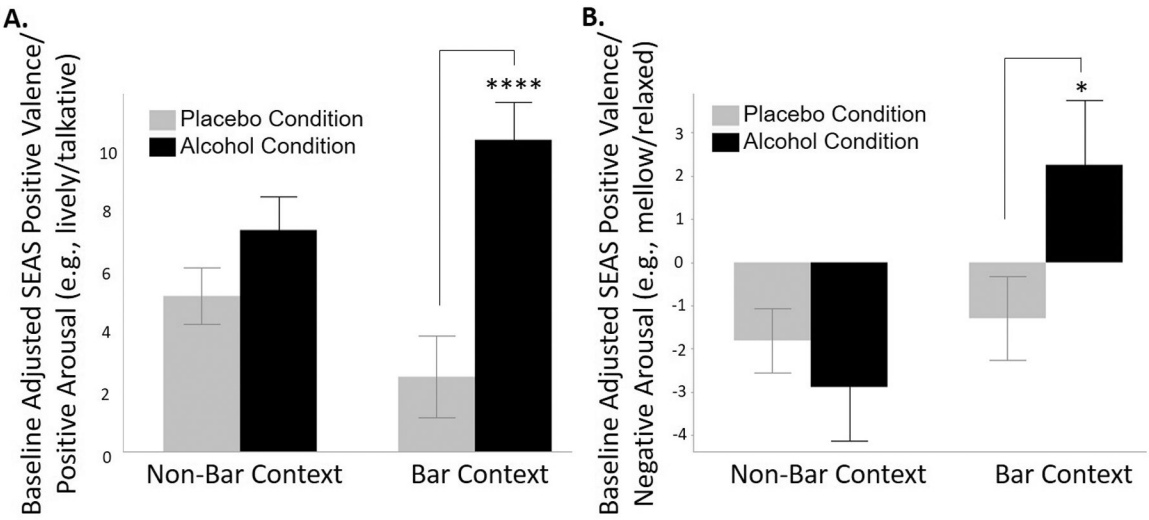

Figure 2.

There was a significant drinking context-by-condition interaction on SEAS positive valence/positive arousal (F=6.4, p=.01) and SEAS positive valence/negative arousal (F=5.1, p=.03). Specifically, if individuals completed their beverage sessions in the BAR context, there was a significant effect of condition, with **A)** greater reported SEAS positive valence/positive arousal (e.g. lively/talkative, F=22.3, p=.0001) and **B)** greater SEAS positive valence/negative arousal (e.g. mellow/relaxed, F=4, p=.05) during the alcohol condition, compared to placebo condition. There was not a main effect of condition on SEAS positive valence/positive arousal (F=2.4, p=.13) or positive valence/negative arousal (F=1.2, p=.3) in individuals who completed their beverage sessions in the non-BAR context. *= p≥.05; ****= p≥.0001

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Table 1.

Between parental risk group (parental risk for mood/substance use disorders vs. no parental risk for mood/substance use disorders), and between study context (BAR vs. non-BAR context), differences in demographics, clinical factors, alcohol and substance use characteristics, and past month alcohol/cannabis/nicotine use were assessed using two-sample t-tests, Mann-Whitney-Wilcoxon tests, Chi-square, or Fisher Exact as appropriate.

	Parental Risk for Mood/ Substance Use Disorders (N=21)	No Parental Risk for Mood/ Substance Use Disorders (N=32)	P-value	BAR Lab (N=27)	Non-BAR Lab (N=26)	P-value
Demographics						
Mean Age (SD)	22.5 (1.2)	22.7 (1.4)	0.9[Z]	22.5 (1.1)	22.8 (1.2)	0.6[Z]
Number of Females (%)	11 (52)	19 (59)	0.6	16 (59)	14 (54)	0.7
Mean WASI-II FSIQ (SD)[A]	113.3 (14.8)	120.1 (12.0)	0.09	114.8 (13.2)	120.1 (13.5)	0.2
Body Mass Index (SD)	26.3 (5.9)	23.5 (3.6)	0.1[Z]	25.8 (5.3)	23.4 (4.0)	***0.04*** [Z]
Asian (%)	3 (14)	10 (31)		3 (11)	10 (38)	
Pacific Islander (%)	0	1 (3)		1 (4)	0	
Caucasian/White (%)	9 (43)	9 (28)	0.2[F]	9 (33)	9 (35)	***0.04***[F]
Hispanic/Latino (%)	9 (43)	9 (28)		13 (48)	5 (19)	
Mixed Race (%)	0	3 (9)		1 (4)	2 (8)	
Parental Risk						
Parental Risk for Mood/Substance Use Disorders (%)	-	-	-	14 (52)	7 (27)	0.06
Parental Risk for Mood Disorders Only (%)	-	-	-	2 (7)	5 (19)	0.3[F]
Parental Risk for Substance Use Disorders Only (%)	-	-	-	6 (22)	1 (4)	0.1[F]
Parental Risk for Both Mood & Substance Use Disorders (%)	-	-	-	6 (22)	1 (4)	0.1[F]
Beverage Sessions						
Beverage Sessions in BAR Lab (%)	14 (67)	13 (41)	0.06	-	-	-
Days Between Beverage Sessions (SD)	1.8 (2.0)	2.2 (1.9)	0.2[Z]	1.8 (2.0)	2.2 (1.9)	0.06[Z]
Clinical Factors						
Total Childhood Trauma Questionnaire Score (SD)	41.4 (12.1)	32.9 (6.9)	***0.006*** [Z]	39.4 (11.2)	33.0 (7.8)	***0.02*** [Z]
Meet Threshold for Childhood Maltreatment (%)[B]	16 (76)	20 (63)	0.3	22 (81)	14 (54)	***0.03***
DMQ Social Motives Score (SD)[C]	4.6 (4.5)	4.4 (4.3)	0.6[Z]	3.2 (1.0)	5.7 (5.9)	0.9[Z]

	Parental Risk for Mood/ Substance Use Disorders (N=21)	No Parental Risk for Mood/ Substance Use Disorders (N=32)	P-value	BAR Lab (N=27)	Non-BAR Lab (N=26)	P-value
DMQ Coping Motives Score (SD)[C]	2.2 (1.8)	2.1 (1.8)	0.9[Z]	1.7 (1.0)	2.6 (2.3)	0.4[Z]
DMQ Enhancement Motives Score (SD)[C]	4.5 (5.5)	4.0 (3.9)	0.9[Z]	3.0 (1.2)	5.5 (6.2)	0.6[Z]
DMQ Conformity Motives Score (SD)[C]	1.9 (1.6)	2.1 (2.8)	0.9[Z]	1.5 (0.9)	2.6 (3.2)	0.3[Z]
Total AUDIT Score (SD)[d]	6.7 (3.5)	3.6 (1.9)	***0.0002*** [Z]	5.3 (2.6)	4.4 (3.4)	0.052[Z]
Past Alcohol Use Disorder, mild (%)	1 (5)	0	0.4[F]	1 (4)	0	1[F]
Current Cannabis Use Disorder, mild (%)	1 (5)	1 (3)	1[F]	1 (4)	1 (4)	1[F]
Past Month Alcohol Use						
Total Drinks (SD)[E]	23.3 (25.9)	13.6 (16.1)	0.4[Z]	17.3 (20.8)	17.7 (21.4)	1[Z]
Total Drinking Days (SD)[E]	4.9 (3.6)	4.6 (4.0)	0.6[Z]	4.4 (2.9)	5.1 (4.5)	0.9[Z]
Drinks/Drinking Days (SD)[E]	3.6 (2.9)	2.8 (1.8)	0.5[Z]	3.2 (2.5)	3.0 (2.1)	0.9[Z]
Past Month Cannabis Use						
Cannabis User [Y/N] (%)[G]	11 (52)	5 (16)	***0.004***	10 (37)	6 (23)	0.3
Cannabis Use Days (SD)[H]	10.1 (11.0)	7.0 (11.8)	0.4[Z]	8.6 (12.1)	10.0 (9.9)	0.7[Z]
Past Month Nicotine/Tobacco Use (%)						
Nicotine/Tobacco User [Y/N] (%)[G]	3 (14)	5 (16)	1[F]	6 (22)	2 (8)	0.3[F]

[F] represents p-value calculated with Fisher exact test.

[Z] represents p-value calculated with a Mann-Whitney-Wilcoxon test.

[A] FSIQ-2 represents the composite score for the full-scale intelligence quotient comprising verbal comprehension and matrix reasoning subsets on the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II).

[B] Threshold for Childhood Maltreatment was defined per the Childhood Trauma Questionnaire (CTQ) manual. The CTQ includes Emotional Abuse, Physical Abuse, Sexual Abuse, Emotional Neglect, and Physical Neglect subscales. Low, medium, and high severity thresholds are defined for each subscale. For Emotional Abuse, the threshold score for low is 12, medium is 15, and high is 16+. For Physical Abuse, the threshold score for low is 9, medium is 12, and high is 13+. For Sexual Abuse, the threshold score for low is 7, medium is 12, and high is 13+. For Emotional Neglect, the threshold score for low is 14, medium is 17, and high is 18+. For Physical Neglect, the threshold score for low is 9, medium is 12, and high is 13+. If a participant met at least low threshold on at least 1 subscale, the individual was categorized as meeting threshold for Childhood Maltreatment.

[C] Drinking Motives Questionnaire.

[D] Alcohol Use Disorders Identification Test.

[E] Recent alcohol use was measured with the Timeline Follow Back Assessment (TLFB).

[G] Recent cannabis and tobacco use was measured with the Timeline Follow Back Assessment (TLFB).

[H] Mean number of cannabis use days in individuals reporting past month cannabis use.

Table 2.

Between-group (parental risk for mood/substance use disorders group vs. no parental risk for mood/substance use disorders group) and between-context (bar vs. non-bar context) differences in mood symptoms reported prior to beverage consumption (measured with the beck anxiety and beck depression inventories), SEAS scores prior to beverage consumption (baseline), BrAC, time from when the participant started drinking to BrAC collection, how many drinks participants thought they had consumed (manipulation check), and urine toxicology screens were assessed using Mann-Whitney-Wilcoxon tests, Chi-square, or Fisher Exact as appropriate. Additionally, parental risk group by condition interactions, and study context by condition interactions, were modeled with condition a repeated within subject factor to investigate if parental risk group, study context, and/or beverage condition days differed in anxiety or depression symptoms, BrAC, time from when the participant started drinking to BrAC collection, how many drinks participants thought they had consumed (placebo manipulation check), and urine toxicology screens.

	Condition	Parental Risk for Mood/ Substance Use Disorders (N=21)	No Parental Risk for Mood/ Substance Use Disorders (N=32)	P-value for Effect of Parental Risk	P-value for Effect of Condition	P-value for Parental Risk-By-Condition Interaction	Bar Lab (N=27)	Non-Bar (N=26)	P-value for Effect of Drinking Context	P-value for Effect of Condition	P-value for Drinking Context-By-Condition Interaction
Mood Symptoms											
Beck Anxiety Inventory	Placebo	1.0 (1.8)	1.2 (1.2)	0.1[Z]	0.5	0.8	1.3 (1.7)	1.0 (1.1)	0.7[Z]	0.5	0.6
	Alcohol	0.7 (1.0)	1.1 (1.8)	0.7[Z]			0.9 (1.2)	0.9 (1.9)	0.5[Z]		
Beck Depression Inventory	Placebo	1.3 (2.1)	2.7 (4.7)	0.5[Z]	0.5	0.7	2.4 (4.3)	1.3 (2.1)	0.8[Z]	0.5	0.8
	Alcohol	3.4 (4.7)	1.6 (2.3)	0.2[Z]			3.0 (4.4)	1.6 (2.2)	0.4[Z]		
Baseline Subjective Effects of Alcohol Scale (SEAS)											
Positive Valence/Positive Arousal	Placebo	11.1 (7.5)	11.5 (7.1)	0.9[Z]	0.9	0.1	11.0 (7.6)	11.6 (7.0)	0.8[Z]	0.9	0.7
	Alcohol	8.9 (6.9)	13.4 (7.0)	***0.03*** [Z]			10.7 (8.0)	12.5 (6.4)	0.4[Z]		
Positive Valence/ Negative Arousal	Placebo	22.2 (9.0)	22.1 (6.4)	0.96[Z]	0.9	0.7	20.9 (8.3)	23.4 (6.3)	0.2[Z]	0.9	0.6
	Alcohol	21.1 (10.1)	22.4 (8.3)	0.6[Z]			19.9 (8.9)	24.0 (8.8)	0.1[Z]		
Breath Alcohol Concentration (BrAC) Collection											
BrAC	Placebo	0 (0)	0.0003 (0.002)	0.4[Z]	<***.0001***[Z]	0.8	0	0.0003 (0.002)	0.3[Z]	<***.0001***[Z]	0.4
	Alcohol	0.07 (0.01)	0.07 (0.01)	0.7[Z]			0.07 (0.01)	0.07 (0.01)	0.4[Z]		
Time from when the participant started drinking to BrAC collection (mins)	Placebo	34.9 (4.0)	35.8 (7.5)	0.5[Z]	0.9	0.4	38.9 (6.1)	31.8 (4.3)	<***0.0001***[Z]	0.9	0.9
	Alcohol	36.2 (5.0)	35.1 (5.4)	0.3[Z]			39.1 (5.1)	31.9 (1.3)	<***0.0001***[Z]		

	Condition	Parental Risk for Mood/ Substance Use Disorders (N=21)	No Parental Risk for Mood/ Substance Use Disorders (N=32)	P-value for Effect of Parental Risk	P-value for Effect of Condition	P-value for Parental Risk-By-Condition Interaction	Bar Lab (N=27)	Non-Bar (N=26)	P-value for Effect of Drinking Context	P-value for Effect of Condition	P-value for Drinking Context-By-Condition Interaction
Manipulation Check											
How many standard drinks did you consume?	Placebo	1.8 (1.4)	1.9 (0.9)	0.6[Z]	***<.0001***[Z]	0.8	2.0 (1.3)	1.7 (0.8)	0.4[Z]	***<.0001***[Z]	0.7
	Alcohol	3.2 (1.2)	3.5 (1.1)	0.4[Z]			3.4 (1.1)	3.3 (1.2)	0.6[Z]		
Urine Toxicology											
Tetrahydrocannabinol (%)	Placebo	6 (29)	3 (9)	0.1[F]	1	1	4 (15)	5 (19)	0.7[F]	1	0.6
	Alcohol	6 (29)	3 (9)	0.1[F]			5 (19)	4 (15)	1[F]		

[F] represents p-value calculated with Fisher exact test.

[Z] represents p-value calculated with a Mann-Whitney-Wilcoxon test.