Published in final edited form as:

Alcohol Clin Exp Res. 2017 December ; 41(12): 2041–2050. doi:10.1111/acer.13523.

Interaction between the μ -opioid receptor gene and the number of heavy drinking peers on alcohol use

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Abstract

Background—The presence of heavy drinking peers may trigger genetic vulnerabilities to alcohol use. Limited correlational findings, albeit mixed as a function of age, suggest that carriers of a μ -opioid receptor (*OPRM1*) G allele may be more vulnerable than noncarriers to alcohol-promoting perceived peer environments. However, research has not yet examined such genetic susceptibility to actual (rather than perceived) peer environments through an experimental, ad libitum alcohol administration design. The current study examined whether *OPRM1* modulates the effects of heavy drinking group size on alcohol consumption and explored potential mediators of such *OPRM1*-based differences.

Methods—Caucasian young adult moderate to heavy drinkers ($N = 116$; mean age = 22 years [$SD = 2.21$], 49% female) were randomly assigned to consume alcohol in the presence of none, one, or three heavy drinking peer confederates.

Results—Results showed no significant moderating effects of *OPRM1* in the relationship between the number (or presence) of heavy drinking peers and voluntary alcohol consumption (partial $\eta^2 = .01$). This result remained the same after controlling for sex, age, and typical drinking quantity as well as their two-way interactions with *OPRM1* and social drinking condition. In addition, *OPRM1* did not moderate the peer influence on any proposed mediating variables, including craving for alcohol and subjective responses to alcohol.

Conclusions—Findings suggest no *OPRM1*-based susceptibility to the number of heavy drinking peers, adding to the existing mixed findings from correlational studies. Future research on *OPRM1*-related susceptibility to alcohol-promoting peer environments through meta-analytic synthesis and both experimental and prospective, multi-wave designs is needed to resolve these mixed findings.

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Financial Disclosure:

Conflict of Interest: The authors have no conflicts of interest to disclose.

Keywords

gene-environment interaction; peer drinkers; *OPRM1*; alcohol

Introduction

Young adults drink more heavily than any other age group (Substance Abuse and Mental Health Services Administration, 2005). Over 80% report consuming alcohol, and 63% report drinking to intoxication in the past year (Johnston et al., 2015). Most young adult drinking occurs in the presence of others (Cullum et al., 2012; Geller et al., 1986), and research has demonstrated strong support for peer influences on drinking through observational and experimental designs (see Borsari and Carey, 2001; Quigley and Collins, 1999). Experimental research into peer influences has often employed human laboratory taste-test paradigms to test whether individuals voluntarily consume more alcohol when in the presence of a same-sex, heavy drinking peer model (i.e., a confederate) as compared to either a light-drinking or non-drinking model (e.g., Caudill and Kong, 2001; Caudill and Marlatt, 1975; Lied and Marlatt, 1979). These investigations have demonstrated relatively consistent support for increased alcohol consumption in the presence of a heavy relative to light or non-drinking confederate, with a meta-analysis suggesting a strong effect size across 27 investigations (weighted Cohen's $d = 0.97$; Quigley and Collins, 1999). Subsequent research has expanded the taste-test paradigm to examine factors associated with these peer effects (e.g., drinking motives, personality traits, need for social approval; Caudill and Kong, 2001; Kuendig and Kuntsche, 2013; Kuntsche and Kuendig, 2012) and influences of larger groups on drinking behavior (Kuendig and Kuntsche, 2012). Since drinking group size has been positively associated with alcohol consumption among college students (Cullum et al., 2012) and young adults have consumed more alcohol in the presence of multiple peers than a single peer (Rosenbluth et al., 1978), not only the presence of a drinking peer but also a greater number of peers may increase young adult drinking.

Genetic susceptibilities may exacerbate the influence of peer environments through gene-environment (G×E) interactions (Plomin et al., 1977; Rutter et al., 2006; Shanahan and Hofer, 2005). Alcohol use and alcohol use disorders are multifaceted conditions arising from socioenvironmental, psychosocial, and biological contributors, with the estimated heritability of alcohol use disorders approximately 50% (Verhulst et al., 2015). G×E interaction research allows for better understanding of the etiology of alcohol use by characterizing these multifaceted contributors to drinking and their interplay on alcohol use behaviors. In a twin study, the overall genetic contribution to drinking was greater among adolescents whose friends reported higher levels of drinking than adolescents whose friends reported lower drinking (Guo et al., 2009). Genes of the opioid system, specifically the μ -opioid receptor (*OPRM1*) gene, may contribute to increased alcohol consumption in an environment with heavy drinking peers. One of the most frequently studied single nucleotide polymorphisms of *OPRM1* is conferred by an Asn40Asp substitution in the +118 position of exon 1 (A118G). The G allele has been associated with greater neural responses to alcohol cues, alcohol-related stimulation/sedation, subjective intoxication, and approach bias for alcohol (Filbey et al., 2008; Ray and Hutchison, 2004; Wiers et al., 2009). Further, a recent

meta-analysis demonstrated a significant association of the G allele with general substance dependence (i.e., lifetime alcohol, nicotine, cannabis, cocaine, and/or opioid dependence) among European-ancestry subjects; the G allele showed a comparable pattern of association with alcohol dependence specifically, although findings were nonsignificant potentially due to low power (Schwantes-An et al., 2016).

Existing, albeit limited, G×E interaction research suggests alcohol-promoting perceived peer environments may exacerbate *OPRM1*-based susceptibility to alcohol use. In a cross-sectional study of European-American adolescents ($N = 104$), G allele carriers were more likely to meet criteria for an alcohol use disorder when endorsing high relative to low deviant peer affiliation (Miranda et al., 2013). In a longitudinal observational study ($N = 238$), *OPRM1*'s G allele magnified the influence of heavy drinking peer affiliation (i.e., perceived peer drinking norms) among Caucasian women, but not men, on alcohol use disorder symptoms at 17–23 (but not 23–40) years of age (Chassin et al., 2012). Existing research on *OPRM1*-based susceptibility to peer environments has been inconclusive and exclusively correlational. Experimental designs are needed to expand upon such inconclusive, correlational research by isolating G×E interaction (i.e., *OPRM1*-based susceptibility to peer environments) from gene-environment correlation (rGE; i.e., *OPRM1*-based differences in exposure to peer environments) through random assignment of individuals into levels of environmental risk.

Finally, the mechanisms underlying *OPRM1*-based susceptibility to peer environments remain unknown. Carriers may drink heavily due to increased craving for alcohol when exposed to heavy drinking peers, who may serve as powerful alcohol-related cues. Craving following alcohol-related cues has been higher among G allele carriers than noncarriers (van den Wildenberg et al., 2007). Additionally, carriers may experience heightened subjective responses to alcohol in a heavy drinking peer environment. Carriers have reported greater subjective responses to alcohol than noncarriers (Ray and Hutchison, 2004), and these differences may be magnified among heavy drinking peers.

The current experimental G×E interaction study had two aims: (a) to examine whether *OPRM1*'s G allele exacerbates the influence of the number of heavy drinking peers on alcohol consumption and (b) to characterize potential mechanisms of this G×E interaction. Participants were randomly assigned to voluntarily consume alcohol in the presence of none, one, or three heavy drinking peer confederates. Manipulating the number of heavy drinking peers allowed the current study to expand upon prior inconclusive correlational findings (Chassin et al., 2012; Miranda et al., 2013) as well as examine the influence of drinking group size (one versus three peers) and peer presence (versus absence) on alcohol consumption. We hypothesized a significant interaction between *OPRM1* and the number of heavy drinking peers on alcohol consumption; specifically, carriers of a G allele were hypothesized to drink more than noncarriers as the number of drinking peers increased. We further hypothesized that this G×E interaction would be mediated by craving for alcohol and subjective responses to alcohol. In sum, the current study examined whether certain young adults may be more susceptible to the alcohol-promoting influences of heavy drinking peers based on genetic factors in an attempt to better understand individual differences in peer environmental effects on drinking behavior. Such research has important clinical

implications, such as permitting the development of more targeted, genetically informed prevention/intervention efforts (e.g., social interventions aimed at young adults with high genetic risks for problematic alcohol use) and identifying potentially malleable mediators of these G×E interaction effects that may serve as important targets for prevention/intervention efforts.

Materials and Methods

Participants

Young adults ($N = 116$) were recruited from a mid-sized northeastern community with several universities through flyers, online advertisements, newspaper postings, email solicitations to electronic mailing lists, phone calls to participants in a related study, class announcements, and a university's undergraduate research participation pool. Eligible participants were Caucasian young adults (21 – 30 years old) classified as moderate to heavy drinkers (i.e., over the past year, consuming an average of two drinks on at least one occasion every two weeks and/or at least four drinks on at least one occasion every month; Creswell et al., 2012). Exclusion criteria included pregnancy in females, a blood alcohol content (BAC) above 0.00% at session initiation, history of adverse reactions to the alcoholic beverages offered, current medical problems or use of a medication contraindicated with alcohol, weight outside 15% of ideal body weight based on height (to account for weight-based differences in alcohol metabolism rates), smoking more than 15 cigarettes per day (to avoid nicotine withdrawal; Creswell et al., 2012), past/current psychiatric problems (to reduce possible exacerbation of mental health symptoms following alcohol consumption, as assessed with the Center for Epidemiologic Studies – Depression Scale (Radloff, 1977) and the Brief Symptom Inventory (Derogatis and Melisaratos, 1983)), and past/current alcohol use disorder (i.e., conditions for which reductions in alcohol consumption would be recommended, see American Psychiatric Association, 2013; National Institute on Alcohol Abuse and Alcoholism).

Procedures

The study was advertised as an alcohol taste test, a cover story to disguise the true aim to measure voluntary alcohol consumption. Interested participants were screened for eligibility and scheduled for an experimental session beginning after 1:00p.m., consistent with previous alcohol administration studies beginning after noon (e.g., Christiansen et al., 2013; Creswell et al., 2012). There were no significant differences in session start time, $F(2,113) = 1.72$, $p = .18$, or day of the week (i.e., weekday [Monday-Thursday] versus weekend [Friday-Sunday]), $\chi^2(2) = 0.88$, $p = .64$, across conditions. Most sessions began at or after 5:00p.m. (58%), with additional sessions beginning at 1:00p.m. (20%) or between 2:00p.m. to 4:30p.m. (22%). Most sessions occurred on weekdays (Monday: 21%; Tuesday: 18%; Wednesday: 19%; Thursday: 16%), with additional sessions on the weekend (Friday: 14%; Saturday: 4%; Sunday: 8%). Upon arriving to the test site, participants were briefed on study procedures, provided written informed consent, completed additional eligibility verification (e.g., initial BAC, pregnancy testing for females), donated a saliva sample for genotyping, and completed a baseline questionnaire. Participants then completed three, 10 min alcohol taste test sessions in a bar laboratory where they were presented with two vodka:tonic

drinks, each one-half of a standard drink (i.e., 0.75 fl oz 40-proof vodka, 3 fl oz tonic water, lime); participants could consume up to three standard drinks across the three taste test sessions (which lasted approximately one hour in total, including questionnaires). Participants completed a questionnaire on their opinions of the drinks and the proposed mediators after each session.

Participants were randomly assigned to one of three groups: (a) drinking in isolation, (b) drinking in the presence of one confederate, or (c) drinking in the presence of three confederates. Confederates were heavy drinking peer models, consuming all available drinks at a natural pace across sessions; however, confederates consumed placebo samples to retain sobriety. Confederate interactions were sociable and warm, as conveyed through verbal (e.g., reinforcing participant comments) and nonverbal (e.g., maintaining eye contact, open body language) manners. Confederates behaved in an increasingly intoxicated, albeit believable, manner across the drinking sessions, consistent with their apparent heavy drinking. Confederate and participant sex was matched (Caudill and Kong, 2001; Kuendig and Kuntsche, 2012; Kuendig and Kuntsche, 2013) to account for potential sex differences in peer effects on drinking (Lied and Marlatt, 1979; but see Larsen et al., 2010), and confederates did not know participants to reduce familiarity effects on drinking. Confederates were trained through individual and group instruction, and all drinking sessions were observed by the first author to ensure adherence to the confederate protocol. A research assistant was present only to explain the taste test procedure, leaving during drinking sessions to prevent supplementary social interaction.

Following the taste test sessions, participants evaluated a film related to alcohol (a cover story to allow time for participant BAC to decrease) and completed a questionnaire assessing manipulation success. Participants were compensated with research credit (if recruited through the research pool; $n = 15$) or \$5 per half hour of participation (if recruited through other means; $n = 101$). There were no significant differences in any study variables as a function of recruitment source at $p < .05$, with the exception that participants recruited through the research pool were younger than participants recruited through other means, $t(111.94) = 6.66, p < .001$. All study procedures were approved by the university's institutional review board.

Measures

***OPRM1* genotype**—Genomic DNA for polymerase chain reaction (PCR) was extracted from saliva samples using the Qiagen DNeasy Blood and Tissue Kit (Valencia, California). *OPRM1* A118G (rs1799971) was genotyped using the ThermoFisher TaqMan® genotyping assay by Salimetrics, LLC (Carlsbad, California). Four samples could not be genotyped after multiple attempts and were excluded from analyses. Genotype frequencies did not deviate significantly from Hardy-Weinberg equilibrium, $\chi^2(1, n = 116) = 2.92, p = .09$. Participants were dichotomized as either G allele carriers (A/G, G/G; $n = 37, 32\%$) or noncarriers (A/A; $n = 79, 68\%$) consistent with previous research (Chassin et al., 2012; Miranda et al., 2013) and suggestions that a cross-product G×E interaction term using a three-category polymorphic genotype may increase false positive and negative findings (Aliev et al., 2014). Although social drinking conditions were not stratified by genotype due to random

assignment, participants were generally evenly distributed across the 0 ($n = 13$ for carriers, $n = 25$ for noncarriers), 1 ($n = 12$ for carriers, $n = 27$ for noncarriers), and 3 ($n = 12$ for carriers, $n = 27$ for noncarriers) confederate conditions. Ancillary analyses with a continuous genotype classification (i.e., number of G alleles) yielded the same pattern of significance for models predicting both voluntary alcohol consumption and BAC as results presented below.

Alcohol outcomes—The number of standard drinks consumed across all taste test sessions was calculated by subtracting the volume of alcohol remaining in the participant's glass from the original 3.75 fl oz available in each sample. This volume was converted into units of standard drinks to aid in interpretation of results by dividing the total amount of alcohol consumed (0 – 22.5 fl oz) by the volume of a single standard drink (7.5 fl oz). As a secondary outcome, BAC was assessed using a breathalyzer approximately ten minutes after the final taste test session.

Potential mediators—Potential mediators were assessed after each taste test session. Craving was assessed with the Alcohol Urge Questionnaire (Bohn et al., 1995). Participants reported the extent to which they agreed or disagreed with 8 items (e.g., “All I want to do now is have a drink”) reflecting their desire to consume alcohol using a 7-point Likert scale. A sum score was used for analyses (Cronbach's $\alpha = .85$). Subjective responses to alcohol were assessed with the 14-item Subjective Effects of Alcohol Scale (Morean et al., 2013), which has demonstrated convergent validity with the Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993). Participants rated their drinking experiences using a 10-point Likert scale along four subscales: high arousal negative (e.g., “Aggressive;” Cronbach's $\alpha = .79$), low arousal negative (e.g., “Dizzy;” Cronbach's $\alpha = .90$), high arousal positive (e.g., “Lively;” Cronbach's $\alpha = .92$), and low arousal positive (e.g., “Relaxed;” Cronbach's $\alpha = .89$). Subscale sum scores were used for analyses. Exploratory and confirmatory factor analyses have supported a four-factor model (Morean et al., 2013).

Potential confounding variables—Participant sex, age, and past-90-day typical drinking quantity assessed through the Timeline Follow Back calendars were included as covariates in all analyses. Social alcohol expectancies (as assessed with the sociability subscale [$\alpha = .79$] of the Comprehensive Effects of Alcohol questionnaire; Fromme et al., 1993), social drinking motives (as assessed with the social motives subscale [$\alpha = .83$] of the Drinking Motives Questionnaire-Revised; Cooper, 1994), and sensation seeking (as assessed with the UPPS-P Impulsive Behavior Scale [$\alpha = .83$]; Lynam et al., 2006) were included as potential covariates in initial models but dropped from final analysis of covariance models due to their nonsignificant main effects and nonsignificant interactions with either *OPRM1* or social drinking condition on both voluntary alcohol consumption and BAC.

Manipulation check—Participants completed open-ended items on the study's perceived aim (i.e., “To the best of your ability, please comment on the study's goals. In other words, what do you think we were interested in studying today?”), whether deception was present (i.e., “Was there anything unusual about the study, in your opinion?”), and their overall opinion of participation (i.e., “Describe your overall opinion of participation,” “Is there

anything else you would like us to know about your participation in the study?”). Participants also completed multiple-choice items assessing external validity, including similarity of the confederate(s) to their current drinking friends (e.g., “How similar were the other participants to the friends you usually drink alcohol with?”), the effect of the confederate(s) on their drinking (e.g., “What effect did the presence of other participants have on your alcohol use?” “How much of an effect did the presence of other participants have on your alcohol use?”), and their perceptions of confederate drinking quantity (e.g., “About how many standard drinks did the other participants consume throughout the entire study?”).

Data Analytic Strategies

Analyses were conducted in *SPSS*, Version 23 (Armonk, NY). Independent-sample *t*-tests (for continuous variables) and Pearson χ^2 difference tests (for categorical variables) compared variables as a function of *OPRMI*. One-way analysis of variance and Pearson χ^2 difference tests compared variables as a function of three social drinking conditions; in cases of a significant omnibus test, Tukey honest significant difference post-hoc tests were used to determine patterns of significance across multiple comparisons. Two-way, 2×3 analysis of covariance (ANCOVA) was conducted to examine the interaction between *OPRMI* and social drinking condition on alcohol outcomes. Separate main effect only models (with main effects of G, E, and covariates) and interaction effect models (with main effects of G, E, and covariates as well as $G \times E$, $G \times \text{covariate}$, and $E \times \text{covariate}$ terms) were conducted. Bayesian ANCOVA was conducted in *JASP*, Version 0.7.5 to compare support for the $G \times E$ interaction term in the above interaction effect model. Bayesian analyses estimate the amount of support for an alternative hypothesis, expanding upon limitations inherent in *p*-value null hypothesis significance testing (Jarosz and Wiley, 2014; Wagenmakers, 2007). Exploratory multiple linear regression analyses were conducted to examine the $G \times E$ interaction hypotheses outside the laboratory paradigm by testing interaction effects of *OPRMI* with baseline descriptive peer norms (as assessed through five self-report items on close friends’ drinking [$\alpha = .65$; adapted from (Johnston et al., 2015) on typical drinking quantity (as assessed through the Timeline Follow Back calendars); nevertheless, because these exploratory analyses were based on self-report (rather than experimental) data, findings should be interpreted with caution due to potential concerns with statistical power given the limited ability of observational research to control for extraneous confounding variables.

Because the hypothesized interactions between *OPRMI* and social drinking condition on alcohol outcomes were not observed, mediated moderation analyses were not conducted. Instead, ancillary analyses tested interaction effects between *OPRMI* and the peer environment on the proposed mediators (i.e., craving for alcohol, subjective responses to alcohol) assessed after the final taste test session. All possible two-way interactions of study covariates with both *OPRMI* and social drinking condition were included to account for their potential confounding effects on the $G \times E$ interaction (Keller, 2014); ancillary analyses dropping all covariate interaction terms yielded the same pattern of significance for the $G \times E$ interaction as results presented below.

Power analyses—*A priori* power analyses were conducted in Quanto, Version 1.2.4 (Gauderman, 2002) with a threshold power of .80 and two-tailed α level of .05, using a 27% prevalence of the AG/GG genotype in Caucasian/European American samples (Chassin et al., 2012; Miranda et al., 2013), minimal to small main effect of *OPRM1* ($R^2 = 0.02$; Bart et al., 2005; Bergen et al., 1997; Town et al., 1999), and small/medium main effect of heavy drinking peers ($R^2 = 0.07$; Kuendig and Kuntsche, 2012); when necessary, effect size estimates were derived from available data (Lipsey and Wilson, 2001; Lyons, 2003). There were only two prior G×E interaction studies on *OPRM1* and peer environments, one of which did not provide standardized coefficients for effect sizes (Chassin et al., 2012) and another which demonstrated a large effect of the interaction ($\beta = 2.03$; Miranda et al., 2013), which may not be typical of G×E interactions. Thus, we specified a small/medium G×E interaction effect ($R^2 = 0.06$), which is more in line with the smaller effects reported in a nationally-representative sample examining peer moderating effects on alcohol use (Harden et al., 2008) and meta-analyses of G×E interactions predicting problematic behavior (Byrd and Manuck, 2014; Taylor and Kim-Cohen, 2007). Power analyses yielded a required 115 participants to detect an existing interaction. Further, experimental investigations into G×E interaction effects often afford increased power and require smaller samples than observational designs due to greater control over the distribution of environmental exposure (see Caspi and Moffitt, 2006; Thomas, 2010).

Results

Descriptive Statistics

Means and standard deviations (or percentages) of study variables are shown in Table 1, and bivariate correlation coefficients between study variables are shown in Table 2. Most participants were undergraduate or graduate students (85%), with 1% sophomores, 16% juniors, 58% seniors, and 25% graduate students. Participants consumed an average of over 2 standard drinks in total, reaching an average BAC of almost 0.04% after the final session. Notably, over 54% of participants consumed at least 2.5 of the 3 standard drinks available, and 50% reported that their drinking during the study was lower than usual. In descriptive group comparison analyses (using analysis of variance with no additional predictors or covariates), there were significant differences in alcohol consumption as a function of social drinking condition (last column of Table 1); post hoc tests revealed that participants drinking with three heavy drinking peers consumed significantly more alcohol than participants drinking alone. There were no significant differences in baseline or alcohol use variables based on *OPRM1*; results available upon request.

Regarding experimental manipulation, no participants reported suspicion that confederates were research assistants or the study's main focus was on alcohol consumption. On average, participants correctly estimated that confederates drank three to four standard drinks in total. Regarding external validity, participants reported that their drinking during the study was lower (50%), typical (35%), or higher (15%) than their usual drinking level. Participants reported that confederates drank a lower (28%), similar (66%), or higher (7%) amount of alcohol than their peers, and they reported that confederates were very (9%), mostly (21%), somewhat (57%) or not at all (13%) similar to their current drinking friends.

***OPRM1* × Social Drinking Condition on Alcohol Outcomes**

Alcohol consumption—In the main effect only model, social drinking condition, $F(2,107) = 3.77$, $p = .03$, but not *OPRM1*, $F(1,107) = 1.61$, $p = .21$, was significantly associated with alcohol consumption, after controlling for sex, age, and typical drinking quantity (data not shown in tables), indicating successful manipulation of heavy drinking peer influence on alcohol consumption.

In the interaction effect model, there were no significant interaction effects between *OPRM1* and social drinking condition on alcohol consumption, $F(2,96) = 0.66$, $p = .52$, partial $\eta^2 = .01$ (Table 3, first column of data). That is, contrary to our hypotheses that *OPRM1* would moderate peer effects on alcohol outcomes, the relationship between *OPRM1* and alcohol consumption did not change based upon the number of heavy drinking peers. As shown in Figure 1, carriers did not consume significantly more alcohol than noncarriers as the number of heavy drinking peers increased. Ancillary analyses examining the presence (rather than number) of heavy drinking peers yielded the same nonsignificant $G \times E$ interaction effects on alcohol consumption, $F(1,101) = 1.23$, $p = .27$. Ancillary Bayesian ANCOVA yielded an estimated Bayes factor that suggested the model without the $G \times E$ interaction effect may be preferred over the model with the $G \times E$ term ($BF_{01} = 2.74$), with weak (anecdotal) evidence against the $G \times E$ interaction hypothesis (Jarosz and Wiley, 2014). Exploratory analyses using cross-sectional, observational data testing the moderating role of *OPRM1* in the association of descriptive peer norms with typical drinking quantity (after controlling for sex, age, and their interactions with both *OPRM1* and peer norms) yielded the same nonsignificant $G \times E$ interaction effects, $F(1,103) = 0.23$, $p = .63$; results available upon request.

BAC—In the main effect only model, social drinking condition, $F(2,107) = 3.24$, $p = .04$, but not *OPRM1*, $F(1,107) = 1.29$, $p = .26$, was significantly associated with BAC, after controlling for sex, age, and typical drinking quantity (data not shown in tables), indicating successful manipulation of heavy drinking peer influence on BAC.

In the interaction effect model, there were no significant interaction effects between *OPRM1* and social drinking condition on BAC, $F(2,96) = 0.04$, $p = .96$, partial $\eta^2 = .00$ (Table 3, second column of data). That is, similar to models predicting alcohol consumption, the relationship between *OPRM1* and BAC did not differ significantly based upon the number of heavy drinking peers. Ancillary analyses examining the presence of heavy drinking peers yielded the same nonsignificant $G \times E$ interaction effect on BAC, $F(1,101) = 0.00$, $p = .99$. Similar to analyses for alcohol consumption, Bayesian ANCOVA suggested the model without the $G \times E$ interaction effect was preferred over the model with the $G \times E$ term ($BF_{01} = 6.22$), with positive evidence against the $G \times E$ interaction hypothesis (Jarosz and Wiley, 2014).

***OPRM1* × Social Drinking Condition on Potential Mediators**

There were no significant interaction effects between *OPRM1* and social drinking condition on the originally proposed mediators (i.e., craving for alcohol, the four subscales of subjective responses; Table 3, third through seventh columns of data). In the interaction effect model, there were significant main effects of *OPRM1* on high negative arousal,

$F(1,95) = 6.83, p = .01$, such that carriers reported greater high negative arousal than noncarriers. There were significant main effects of social drinking condition on high positive arousal, $F(2,95) = 4.30, p = .02$, and low positive arousal, $F(2,95) = 5.60, p = .01$, such that there were increases in high positive and decreases in low positive arousal with an increasing number of heavy drinking peers. Ancillary analyses examining presence (rather than number) of heavy drinking peers yielded the same significance of main and interaction effects of *OPRM1* and social drinking condition on any of the potential mediators, with the exception that the main effect of social drinking condition on high positive arousal became marginally significant, $F(1,100) = 3.30, p = .07$.

Discussion

The current study examined whether carrying *OPRM1*'s G allele exacerbates the influence of heavy drinking peers on alcohol consumption and explored potential mediators of *OPRM1*-based susceptibility to an alcohol-promoting peer environment. By randomly assigning and manipulating the number of heavy drinking peers, the experimental design was better equipped than previous correlational research to control for potential third variables that may be associated with alcohol consumption as a function of *OPRM1*. Alcohol consumption varied significantly based upon social drinking condition after controlling for *OPRM1*, sex, age, and typical drinking quantity. There were no significant main effects of *OPRM1* on alcohol outcomes, consistent with a previous candidate gene study of *OPRM1* among Caucasian/European American samples (Bergen et al., 1997). Contrary to hypotheses, *OPRM1* did not exacerbate the influence of the number (or presence) of heavy drinking peers on alcohol consumption. That is, carriers did not consume significantly more alcohol than noncarriers as the number of drinking peers increased. *OPRM1* also did not exacerbate the influence of the number (or presence) of drinking peers on craving for alcohol or subjective responses to alcohol.

The current experimental alcohol administration investigation indicates that *OPRM1* did not exacerbate the influence of an alcohol-promoting peer environment in an experimental alcohol administration paradigm. This nonsignificant G×E interaction finding was replicated in exploratory analyses using cross-sectional, self-report data on perceived peer drinking norms and typical drinking quantity over the past 90 days. Existing research suggests *OPRM1* G allele carriers are more vulnerable than noncarriers to affiliation with deviant (Miranda et al., 2013) or heavy drinking (Chassin et al., 2012) peers. *OPRM1*-based susceptibility to alcohol-promoting peer environments has been observed among adolescents ages 12–19 (Miranda et al., 2013) and women at 17–23 years (Chassin et al., 2012), but not among early and middle adults ages 23–40 (Chassin et al., 2012). Carriers may be more susceptible to peer drinking during adolescence, when peer influences on alcohol/substance use may be most salient (Jacob and Loanord, 1994). Relatedly, these G×E interaction effects may vary based on legal drinking status, with underage drinkers carrying an *OPRM1* G allele more susceptible to alcohol-promoting peer environments than carriers of legal drinking age. Finally, support for *OPRM1*-based susceptibility to self-reported perceived peer environments contradicts the current study's lack of support for *OPRM1*-based susceptibility to manipulated peer environments (with the exception of exploratory analyses using cross-sectional, observational data that may have been underpowered). Carriers may

be more likely to be exposed to alcohol-promoting peer environments (i.e., rGE) rather than more susceptible to such environments (i.e., G×E) as was examined in the current experimental paradigm.

Cross-sectional demonstrations of *OPRM1*-related differences in alcohol-promoting peer affiliation may reflect both *OPRM1*'s effects on vulnerability to alcohol-promoting peer environments (i.e., peer socialization) and on selection into peer networks compatible with personal alcohol use (i.e., peer selection). The current study focused upon *OPRM1*-based peer socialization, eliminating peer selection effects through random assignment of young adults into peer environments regardless of genotype. Research suggests peer selection differences as a function of *OPRM1* (Chassin et al., 2012) and other risk genotypes (e.g., Park et al., 2016). *OPRM1*-based differences in young adults' tendency to associate with alcohol-promoting peers, and whether these differences may in part underlie existing G×E interaction findings, remain unknown. Future research examining both peer selection and socialization as a function of *OPRM1* is needed to resolve these current mixed findings.

Findings indicate no significant *OPRM1*-based differences in craving for alcohol or subjective responses to alcohol based upon the peer environment. Previous research suggests an impact of *OPRM1* on self-reported craving (van den Wildenberg et al., 2007) and subjective responses to alcohol (Ray and Hutchison, 2004). Genetic differences in craving and subjective responses may be stronger among heavier drinkers, as in previous samples (Ray and Hutchison, 2004; van den Wildenberg et al., 2007), than the current sample of moderate to heavy drinkers. The effect sizes of genetic differences in craving and subjective responses were stronger among a subset of heavy drinkers in the current study than the entire sample, and heavy drinkers have shown greater reactivity to alcohol-related cues than light drinkers (Herrmann et al., 2001). Future research could explore possible *OPRM1*-related differences in craving and subjective responses as a function of heavy drinking status.

Several limitations should be noted. First, findings are based upon a restricted sample of Caucasian moderate to heavy drinking young adults, mainly undergraduate or graduate students, who met various inclusion/exclusion criteria (e.g., no psychiatric concerns, did not meet criteria for alcohol use disorder). Such criteria were necessary to protect participant safety during alcohol administration or rule out potential confounding variables (e.g., allele frequency differences across racial groups) and, thus, enhance the internal validity of current findings. However, generalizability of results to adolescents, light drinkers, and other samples needs to be demonstrated empirically. Relatedly, it remains unknown to what extent the current findings generalize to real-world young adult drinking. Participants were able to consume only a total of three standard drinks across all taste test sessions (to ensure participant safety), and peer confederates were all matched in sex to participants (to address potential confounding effects of sex in peer environmental associations with drinking). Although the majority of participants (70%) described the confederates as only somewhat similar or dissimilar to their current drinking friends, the majority (66%) also reported that confederates drank a similar amount of alcohol as their peers. Thus, participants may have perceived the confederates as relatively dissimilar to their peers on some dimensions (e.g., shared interests, personality, etc.) yet relatively similar in relation to alcohol consumption,

which may be a stronger approximate of the current study's applicability to real-world drinking behavior. Nevertheless, it remains unknown to what extent the current findings generalize to real-world young adult drinking environments, such as those characterized by larger, mixed-sex drinking groups composed of close friends and/or acquaintances. Second, the G×E interaction effects may have been influenced by low variability and ceiling effects in the alcohol outcomes (see Results), which may have contributed to the nonsignificant G×E interaction findings. Carriers drinking with three heavy drinking peers may have consumed more alcohol if it had been provided. Future research could explore genetic differences in susceptibility to alcohol-promoting peers when young adults drink at their typical levels, while being careful to prevent harmful drinking.

Finally, initial G×E interaction findings often report larger effect sizes than replication efforts (see Duncan and Keller, 2011). While our *a priori* power analyses assumed a small/medium effect size that was more conservative than initial reports (Miranda et al., 2013) as well as G×peer environment effects reported in a large, nationally-representative sample (Harden et al., 2008), and we used an experimental design unlike prior correlational studies, the current investigation may have been underpowered to detect existing G×E interaction effects. Ancillary *post hoc* power analyses demonstrated that the current study ($N = 116$, 32% AG/GG genotype) had more than 99% power to detect a true large G×E interaction effect ($R^2 = 0.25$), 92% power for a medium effect ($R^2 = 0.09$), and 79% power for a small/medium effect ($R^2 = 0.06$), assuming the observed small main effect of *OPRM1* ($R^2 = 0.01$) and small/medium main effect of heavy drinking peers ($R^2 = 0.05$) mirror population parameters. Power to detect the observed small G×E interaction effect ($R^2 = 0.02$), however, was only 38% such that the finding of a nonsignificant G×E interaction could indicate absence of a G×E interaction effect or insufficient power to detect a true small effect. The current study appeared adequately powered to replicate the previously reported *OPRM1*×peer environment findings (Miranda et al., 2013) and more conservative small/medium G×peer environment effects obtained in larger samples (Harden et al., 2008). However, these ancillary power analyses should be interpreted with caution due to the direct relationship of observed power with obtained *p* values, assumption that obtained effect sizes equal population parameters, and low precision of power estimates in studies with large sampling error and small effect sizes (see Hoenig and Heisey, 2001; Yuan and Maxwell, 2005). Within the context of the high false positive rates and low reproducibility of initial candidate G×E interaction findings (see Dick et al., 2015), the current findings await adequately powered replication efforts.

The current study examined *OPRM1*-based differences in young adults' susceptibility to an alcohol-promoting peer environment using an experimental alcohol administration design that could control for a variety of potential confounding factors. Findings of a nonsignificant G×E interaction join inconclusive observational research on *OPRM1*-related susceptibility to peer environments and suggest such differences may be less robust than previously demonstrated. Future meta-analytic synthesis is warranted as well as prospective, multi-wave research to examine any developmentally-specific peer socialization and selection influences.

Acknowledgments

This research was supported in part by a Graduate Student Research Award from the American Psychological Association (APA) Division 38: Health Psychology to Michelle J. Zaso and an NIH grant R15 AA022496 to Aesoon Park.

We thank all the young adults who participated, and we thank all project research assistants/confederates for their assistance with data collection. We gratefully acknowledge Michael Kalish, Ph.D. for his assistance with ancillary Bayesian analyses.

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Figure 1.

Interaction between *OPRM1* and social drinking condition on alcohol consumption.

Estimated mean number of standard drinks (and standard error bars) consumed across all three taste test sessions, as a function of the *OPRM1* genotype and social drinking condition, after controlling for participant age, sex, past-90-day typical quantity of alcohol consumed, and all possible two-way interactions between covariates (i.e., sex, age, past-90-day drinking quantity) and either the genetic or environmental risk. *OPRM1* = μ -opioid receptor gene.

Table 1
Percentages or Means (and SDs) of Select Study Variables in All Participants and as a Function of Social Drinking Condition

Variable	All participants (<i>N</i> = 116)	0 confederates (<i>n</i> = 38)	1 confederate (<i>n</i> = 39)	3 confederates (<i>n</i> = 39)	Group comparison test statistic
Demographics					
<i>OPRM1</i> G allele (0 = no; 1 = yes)	32%	34%	31%	31%	$\chi^2(2) = 0.14$
Sex (0 = female; 1 = male)	51%	50%	51%	51%	$\chi^2(2) = 0.02$
Age (21 – 30)	22.45 (2.21)	22.74 (2.46)	22.33 (1.94)	22.28 (2.25)	$F(2,113) = 0.48$
Baseline alcohol use					
Past 90-day typical alcohol quantity	4.03 (2.23)	4.46 (2.79)	3.92 (1.78)	3.71 (2.01)	$F(2,111) = 1.13$
Potential mediators following the last taste session					
Craving for alcohol	13.17 (9.84)	13.57 (10.17)	12.33 (9.73)	13.62 (9.85)	$F(2,112) = 0.21$
Subjective responses, high arousal negative	3.69 (1.78)	3.38 (1.06)	3.54 (1.64)	4.13 (2.33)	$F(2,112) = 1.92$
Subjective responses, low arousal negative	6.60 (4.53)	5.22 (3.99)	7.08 (4.22)	7.44 (5.08)	$F(2,112) = 2.69$
Subjective responses, high arousal positive	22.66 (8.20)	19.54 (7.87) ^{a,b}	24.23 (7.55) ^a	24.05 (8.49) ^b	$F(2,112) = 4.17^*$
Subjective responses, low arousal positive	25.19 (7.88)	24.95 (9.20)	25.74 (6.52)	24.87 (7.93)	$F(2,112) = 0.14$
Alcohol outcomes following the last taste session					
Voluntary alcohol consumption	2.28 (0.85)	1.99 (0.94) ^a	2.39 (0.78)	2.45 (0.76) ^a	$F(2,113) = 3.55^*$
BAC	0.04 (0.02)	0.03 (0.02) ^a	0.04 (0.02) ^a	0.04 (0.02)	$F(2,113) = 3.34^*$

For group comparisons, one-way analysis of variance was used for continuous variables and χ^2 difference tests were used for categorical variables. Tukey honest significant difference post hoc tests were used for multiple comparisons; subscripts designate multiple comparisons significant at $p < .05$ in post hoc tests. *OPRM1* = μ -opioid receptor gene. BAC = blood alcohol content.

* $p < .05$.

Table 2

Bivariate Correlation Coefficients of Select Study Variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. Drinking condition	–										
2. <i>OPRM1</i> genotype	-.30	–									
3. Male sex	.01	.01	–								
4. Age	-.11	.05	.22*	–							
5. Baseline typical alcohol quantity	-.10	-.09	.38***	-.12	–						
6. Craving for alcohol	.03	.05	.06	-.10	.07	–					
7. Subjective responses, high arousal negative	.10	.06	.24*	-.02	.17	.13	–				
8. Subjective responses, low arousal negative	.24*	.06	-.00	-.11	-.09	.18	.38***	–			
9. Subjective responses, high arousal positive	.24**	-.01	.06	-.15	.04	.38***	.26**	.25**	–		
10. Subjective responses, low arousal positive	-.02	.05	.06	-.36***	.16	.25**	.14	.17	.55***	–	
11. Voluntary alcohol consumption	.24**	.11	.27**	-.09	.14	.29**	.20*	.27**	.40***	.29**	–
12. BAC	.18*	.11	-.06	-.10	-.02	.20*	-.02	.19*	.30**	.24*	.75***

N = 113 – 116, due to missing data. Spearman's ρ reported for ordinal variables (i.e., social drinking condition), and Pearson product-moment or point-biserial correlations reported for continuous and dichotomous variables. Drinking condition was coded as 0 = no heavy-drinking peer confederates, 1 = 1 heavy-drinking peer confederate, and 2 = 3 heavy-drinking peer confederates. *OPRM1* = μ -opioid receptor gene. BAC = blood alcohol content.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 3

Two-way, 2×3 Analysis of Covariance Examining the Effects of OPRM1 Genotype, Social Drinking Condition, and Their Interaction on Potential Mediators and Alcohol Outcomes, After Controlling for Sex, Age, and Prior Alcohol Consumption

	Main Outcomes		Potential Mediators				High arousal positive	Low arousal positive
	Alcohol consumption	BAC	Craving for alcohol	High arousal negative	Low arousal negative			
<i>OPRM1</i> genotype	$F(1,96) = 0.10$	$F(1,96) = 0.07$	$F(1,95) = 0.39$	$F(1,95) = 6.83^*$	$F(1,95) = 3.34$		$F(1,95) = 0.63$	$F(1,95) = 0.01$
Drinking condition	$F(2,96) = 0.40$	$F(2,96) = 0.04$	$F(2,95) = 0.62$	$F(2,95) = 2.74$	$F(2,95) = 0.78$		$F(2,95) = 4.30^*$	$F(2,95) = 5.60^{**}$
<i>OPRM1</i> × Drinking condition	$F(2,96) = 0.66$	$F(2,96) = 0.04$	$F(2,95) = 0.89$	$F(2,95) = 0.50$	$F(2,95) = 0.03$		$F(2,95) = 0.20$	$F(2,95) = 1.74$
Sex	$F(1,96) = 3.52$	$F(1,96) = 1.05$	$F(1,95) = 0.13$	$F(1,95) = 5.86^*$	$F(1,95) = 0.67$		$F(1,95) = 0.36$	$F(1,95) = 1.38$
Sex × <i>OPRM1</i>	$F(1,96) = 0.02$	$F(1,96) = 0.06$	$F(1,95) = 0.22$	$F(1,95) = 1.33$	$F(1,95) = 2.93$		$F(1,95) = 0.02$	$F(1,95) = 0.64$
Sex × Drinking condition	$F(2,96) = 0.77$	$F(2,96) = 0.56$	$F(2,95) = 0.03$	$F(2,95) = 0.80$	$F(2,95) = 0.31$		$F(2,95) = 0.27$	$F(2,95) = 0.37$
Age	$F(1,96) = 0.03$	$F(1,96) = 0.06$	$F(1,95) = 0.91$	$F(1,95) = 1.49$	$F(1,95) = 1.76$		$F(1,95) = 1.10$	$F(1,95) = 9.76^{**}$
Age × <i>OPRM1</i>	$F(1,96) = 0.04$	$F(1,96) = 0.01$	$F(1,95) = 0.45$	$F(1,95) = 5.67^*$	$F(1,95) = 2.13$		$F(1,95) = 0.36$	$F(1,95) = 0.00$
Age × Drinking condition	$F(2,96) = 0.51$	$F(2,96) = 0.14$	$F(2,95) = 0.45$	$F(2,95) = 2.80$	$F(2,95) = 0.69$		$F(2,95) = 4.39^*$	$F(2,95) = 5.83^{**}$
Typical alcohol quantity	$F(1,96) = 0.21$	$F(1,96) = 0.09$	$F(1,95) = 0.25$	$F(1,95) = 0.54$	$F(1,95) = 1.87$		$F(1,95) = 0.76$	$F(1,95) = 0.01$
Quantity × <i>OPRM1</i>	$F(1,96) = 0.00$	$F(1,96) = 0.18$	$F(1,95) = 0.01$	$F(1,95) = 2.66$	$F(1,95) = 5.13^*$		$F(1,95) = 1.56$	$F(1,95) = 0.00$
Quantity × Drinking condition	$F(2,96) = 1.92$	$F(2,96) = 1.59$	$F(2,95) = 0.32$	$F(2,95) = 3.29^*$	$F(2,95) = 0.10$		$F(2,95) = 0.40$	$F(2,95) = 0.43$

$N = 112 - 114$, due to missing data. *OPRM1* = μ -opioid receptor gene. BAC = blood alcohol content.

* $p < .05$.

** $p < .01$.