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Effects of the serotonin transporter gene, sensitivity of response to alcohol, and parental monitoring on risk for problem alcohol use

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Abstract

The serotonin transporter-linked polymorphic region (5-HTTLPR) of the serotonin transporter gene (*SLC6A4*) has been previously associated with alcohol-related risk. Most findings point to short (S) allele carriers being at increased risk for negative alcohol outcomes relative to long allele homozygotes, although some work indicates a more complex relationship. The current prospective study aimed to clarify *how* and *under what circumstances* variations in 5-HTTLPR transmit risk for various alcohol-related outcomes. Participants were 218 adolescents and young adults (29% female) enrolled in the Michigan Longitudinal Study. We tested a moderated mediation model with 5-HTTLPR as the predictor, Self-Rating of the Effects of Alcohol (SRE) score as the mediator, alcohol-related outcomes as the dependent variables, parental monitoring as the moderator of the SRE to alcohol outcomes path, and prior drinks, sex, age, and body mass index as covariates. Four alcohol-related outcomes were tested. The S allele was associated with higher SRE scores (i.e., lower response to alcohol). Parental monitoring was a significant moderator: At low levels of parental monitoring, higher SRE scores predicted more drinks consumed and binge drinking episodes. At high levels of monitoring, higher SRE scores were significantly related to fewer alcohol-related problems. Findings suggest that one mechanism by which 5-HTTLPR

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variation transmits alcohol-related risk is through level of response to alcohol. Furthermore, the strength and direction of this effect varied by level of parental monitoring, indicating that even in the presence of genetic and physiological vulnerability, parents can influence the likelihood of offspring developing problematic alcohol-related behaviors.

Keywords

5-HTTLPR; Adolescence; Self-Rating of the Effects of Alcohol (SRE); Conditional process modeling; Moderated mediation

1. Introduction

Research focused on identifying specific genetic variants associated with problematic alcohol use has proliferated over the last two decades. One likely candidate emerging from this line of work is the serotonin transporter-linked polymorphic region (5-HTTLPR) of *SLC6A4*, the gene that codes for the serotonin transporter protein (5-HTT; Lichtermann et al., 2000; Schuckit et al., 1999). 5-HTT is an integral membrane protein that removes and recycles serotonin from synaptic spaces, and a repeat length polymorphism in the promoter region of this gene can affect the rate of serotonin uptake (Lesch et al., 1996). Two commonly studied human variants of this region are the short (S) and long (L) alleles; individuals can be homozygous short (SS), homozygous long (LL), or heterozygous (LS). Research has shown that homozygous long individuals have greater 5-HTT availability and function (Heinz et al., 2000; Lesch et al., 1996; Stoltenberg, 2003). It is important to note that Hu et al. (2006) have suggested that a triallelic coding of 5-HTTLPR, which involves a nearby single nucleotide polymorphism (SNP; rs25531), may be more accurate. In Caucasians, approximately 10% of L alleles contain the SNP (Haberstick et al., 2015), but brain imaging and molecular studies are not entirely consistent as to the functional significance of this SNP (Martin, Cleak, Willis-Owen, Flint, & Shifman, 2007; Murthy et al., 2010; Philibert, Sandhu, Hollenbeck, Gunter, Adams, Madan, 2007).

Much of the prior work involving alcohol and 5-HTTLPR points to S carriers being at increased risk for negative alcohol outcomes, including more binge drinking occasions (Chen et al., 2014; Herman, Philbeck, Vasilopoulos, & Depetrillo, 2003), more drinks per drinking occasion (Covault et al., 2007), earlier age of drinking initiation (Kaufman et al., 2007), and more frequent occasions of drinking with intentions to become intoxicated (Covault et al., 2007). Two meta-analyses support this pattern of findings (Feinn, Nellissery, & Kranzler, 2005; McHugh, Hofmann, Asnaani, Sawyer, & Otto, 2010); however, at least four studies have found the LL genotype to be the variant that confers alcohol-related risk (Hinckers et al., 2006; Hu et al., 2005; Schuckit et al., 1999; Sen et al., 2004b), and three studies found no association between 5-HTTLPR and alcohol risk (Hill et al., 2002; Kranzler, Lappalainen, Nellissery, & Gelernter, 2002; Stoltenberg et al., 2002). These contradictory findings suggest a more complex relationship than previously thought as well as the presence of intervening and/or moderating variables. Furthermore, the alcohol-related outcomes varied across the aforementioned studies, which may serve as an additional

explanation for discrepant findings. The current study aims to clarify *how* and *under what circumstances* variations in 5-HTTLPR increase risk for four alcohol-related outcomes.

One potential mechanism of risk transmission is level of response to alcohol, which refers to the subjective intensity of the effects of consuming alcohol. This response varies among individuals (Schuckit, Tipp, Smith, & Bucholz, 1997b) and may account for up to 60% of variance in hereditary alcohol dependence risk (Schuckit, 1999). This construct is particularly relevant because an individual with a low level of response to alcohol is likely to consume more alcohol on any given occasion (in order to obtain the desired effects) and is therefore at greater risk for developing an alcohol use disorder (AUD; Schuckit & Smith, 1996; Ray, Hart, & Chin, 2011; though see Newlin & Thomson, 1990). Given strong evidence for an association between the S allele and alcohol risk, it is likely that S carriers exhibit a low level of response. However, some studies have found that the LL genotype is associated with a low level of response to alcohol (Hu et al., 2005; Schuckit et al., 1999), indicating that more work is needed. To our knowledge, no studies have directly assessed level of alcohol response as a potential mediator in the relationship between genes and behavior. Thus, we aimed to determine whether level of response to alcohol may be a potential mechanism through which 5-HTTLPR predicts later alcohol outcomes.

The additional question of *under what circumstances* these associations hold remains. Addressing this issue may explain some of the discrepancies in the literature on 5-HTTLPR and alcohol outcomes to the extent that previously unmeasured variables exert a moderating effect on the association between genotype and alcohol outcome. That is, the strength and/or direction of the association between 5-HTTLPR and alcohol use outcomes via SRE may depend on other variables. A likely moderator of the proposed mediation effect is parental monitoring. Broadly defined, parental monitoring comprises behaviors that parents and guardians use to attend to and track the whereabouts, activities, and social affiliations of their children (Dishion & McMahon, 1998). It has been shown to exert a substantial influence over alcohol-related risk, including consumption and sustained use (Becker et al., 2012; Kristjansson, James, Allegrante, Sigfusdottir, & Helgason, 2010; Steinberg, Fletcher, & Darling, 1994) and number of intoxication incidents (Kristjansson et al., 2010). One study found that adolescents who reported high levels of parental monitoring were more likely to be in a *moderate and decreasing alcohol use* trajectory group than in either of two *heavy use* groups (Becker et al., 2012). Further support for the role of parental monitoring comes from a study that found poorly monitored adolescents to be more likely to use drugs and seek out like-minded peers, thereby increasing the risk of transitioning from experimentation to regular use (Fallu et al., 2010; Steinberg et al., 1994). Finally, a program designed to increase parental monitoring and parent-adolescent engagement led to decreased adolescent alcohol consumption and fewer incidents of intoxication (Kristjansson et al., 2010). Thus, greater parental knowledge and/or vigilance about the activities and social affiliations of their children may limit opportunities to access alcohol. Indeed, if the proposed effect of 5-HTTLPR on alcohol outcomes through level of response to alcohol is moderated by parental monitoring, this would provide a feasible target for prevention efforts that seek to reduce the prevalence and negative consequences of problematic alcohol use, particularly among high-risk youth. To our knowledge, no studies have tested whether the impact of level of response

to alcohol (acting either as a mediator or predictor) on alcohol outcomes is moderated by environmental factors.

Here we sought to elucidate how and under what circumstances genetic risk for alcohol-related outcomes in young adulthood is transmitted by testing a prospective model that integrates variation in 5-HTTLPR, level of response to alcohol, and parental monitoring in adolescents (N = 218). The goal of this work was to better characterize the link between an established genetic alcohol risk factor and negative alcohol outcomes by examining both physiological (i.e., level of response to alcohol) and contextual (i.e., parental monitoring) factors in a prospective design. Based on prior research examining 5-HTTLPR and alcohol use as well as work that links a low level of response to alcohol and negative outcomes, we hypothesized that carriers of the 5-HTTLPR S allele would exhibit lower levels of response to alcohol, which in turn would make them more likely to drink more alcohol, have more occasions of binge drinking, experience more alcohol-related problems, and be diagnosed with an alcohol use disorder (AUD). We further hypothesized that the association between level of response to alcohol and alcohol-related outcomes would be moderated by parental monitoring. Specifically, we proposed that the mediated effect would be stronger among individuals with low levels of parental monitoring.

2. Material and methods

2.1. Participants and procedure

Participants were 218 adolescents/young adults (63 [28.9%] female) enrolled in the Michigan Longitudinal Study (MLS; Zucker, Ellis, Fitzgerald, Bingham, & Sander, 1996, Zucker, Fitzgerald, Refior, Puttler, Pallas, Ellis, 2000), an ongoing, multi-wave, community-recruited study investigating the development of substance use and substance use disorder. Recruitment targeted high-risk families in which the father was convicted of driving under the influence of alcohol and met criteria for an AUD (one-third of the sample). Contrast families recruited from the same neighborhoods where the high-risk families lived comprised moderate-risk (i.e., fathers with an AUD diagnosis but no conviction; one-third of the sample) and low-risk families (i.e., neither parent with an AUD; one-third of the sample). Accordingly, 79.8% of participants in the present study had at least one parent with a lifetime AUD. As part of the MLS, assessments are conducted every three years starting when the children are aged 3–5; beginning at age 11, participants are assessed every year. Families are excluded if the target child displays evidence of fetal alcohol effects or the mother reports drinking during pregnancy. Full details on the MLS can be found elsewhere (Zucker et al., 1996; 2000). In order to avoid problems with population stratification, only data from non-Hispanic White participants were included. This racial/ethnic class constitutes 82.5% of the MLS sample from which this study sample was drawn. See Table 1 for demographic and behavioral variables.

Participants underwent genotyping and, at regular intervals, completed measures of level of response to alcohol, parental monitoring, quantity and frequency of alcohol use, and number of alcohol-related problems, and were assessed for alcohol abuse and dependence using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 1994) criteria. Participants and parents/guardians provided written informed assent and/or consent. Study

materials and procedures were approved by the University of Michigan Medical School Institutional Review Board.

2.2. Assessment

2.2.1. Genotype—DNA was isolated from whole blood or saliva using the Puregene kit and its protocols (Qiagen, Venlo, Netherlands). Polymerase chain reaction and agarose gel electrophoresis were used to determine the length as previously described (Sen, Burmeister, & Ghosh, 2004a). Genotypes SS, LS, and LL were in Hardy Weinberg equilibrium. Based on prior evidence that the L allele is recessive (Hariri et al., 2002; Heinz et al., 2000), we used a dominant model and thus compared the LL genotype to S carriers (LS/SS). Among European-Americans, the frequency of the S allele is 0.43 (Odgerel, Talati, Hamilton, Levinson, & Weissman, 2013).

2.2.2. Level of response to alcohol—The Self-Rating of the Effects of Alcohol (SRE; Schuckit, Smith, & Tipp, 1997a) is a 12-item questionnaire that asks how many standard drinks it took to reach each of four outcomes during three different periods in one's life. The four questions ask how many drinks it took to: 1) begin to feel different; 2) feel a bit dizzy or to begin to slur speech; 3) begin stumbling or walking in an uncoordinated manner; and 4) pass out or fall asleep when not wanting to. The SRE score is typically calculated as the sum of the total number of drinks divided by the number of endorsed outcomes. Recent work indicates that this method may downwardly bias SRE scores for participants with more unendorsed outcomes, however (Lee, Bartholow, McCarthy, Pedersen, & Sher, 2015). Therefore, we used the *standardized person-mean imputation* method suggested by Lee et al. (2015), in which items are converted to *z*-scores before averaging. A higher score is indicative of a low level of response to alcohol (i.e., more drinks are required to feel the effects). The SRE is administered at three-year intervals beginning at age 12; we selected the first available score after the initiation of alcohol use to minimize confounding due to inaccurate memory. We also restricted analyses to the set of questions pertaining to an individual's first five drinking occasions as we were interested in innate physiological responses to alcohol before tolerance developed (herein referred to as "SRE-5"). Thus, the timing of the SRE-5 assessment was contingent on each participant's age of alcohol use initiation. Mean age at SRE-5 completion was 17.6 (*SD* 1.5, range 13.8–20.0). See also Supplemental Material.

2.2.3. Body mass index (BMI)—BMI measured within one year of SRE-5 assessment was included as a covariate to control for the association between body size and sensitivity to the effects of alcohol. BMI is calculated as weight in kilograms divided by height in meters squared (kg/m^2). Mean age at BMI assessment was 17.6 (*SD* 1.5, range 13.6–20.3).

2.2.4. Parental monitoring—The Parent Monitoring–Youth Form (Chilcoat & Anthony, 1996) is a self-report measure that focuses on the supervision and monitoring provided by parents or other responsible caretakers. Seven questions ask the participant to respond on a 5-point Likert-type scale (1 = *all of the time*, 5 = *never*) how often his/her parents are involved, are present, and are aware of his/her behavior or whereabouts. Scores were reverse-coded, summed, and averaged such that higher scores indicate higher (i.e., tighter)

monitoring. Mean age at parental monitoring assessment was 16.5 (*SD* 0.9, range 13.4–18.7). In 53.2% of participants, parental monitoring and SRE-5 were assessed at the same wave. For all other participants, we used the next closest parental monitoring assessment (SRE-5 assessment was contingent on age of alcohol use initiation). This parental monitoring age range corresponds to the SRE-5 age range as well as to the time period during which adolescents typically live at home and attend high school. Reliability (Cronbach's α) for this sample was 0.76. Items can be found in Supplemental Material.

2.2.5. Alcohol outcomes—Drinking histories were obtained from each participant by trained research staff as part of the regular MLS assessment schedule. Beginning at age 6 and occurring at three-year intervals, a health and daily living questionnaire was used to assess the use of alcohol (more than a sip) and, if applicable, the age at which use occurred and the quantity/frequency of use. Beginning at age 9 and occurring at three-year intervals, the child version of the Diagnostic Interview Schedule for the DSM-IV (DISC; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) (and beginning at age 18, the adult version [DIS-IV; Robins et al., 2000]) was used to make diagnoses of alcohol abuse and dependence based on DSM-IV criteria. Finally, at annual assessments beginning at age 11, the Drinking and Drug History Questionnaire (DDH; Zucker & Fitzgerald, 1994) was used to assess the quantity and frequency of alcohol use as well as the number of times each of 27 alcohol-related problems occurred (see Supplemental Material for examples). From these assessments, the following alcohol outcomes were calculated by dividing the respective cumulative totals by the number of years of drinking and performing a square root variance-stabilizing transformation to address the fact that they could be considered count data: mean number of drinks consumed per year, days on which binge drinking occurred (defined as ≥ 5 drinks) per year, and times alcohol-related problems were experienced per year (mean age at assessment was 24.2 [*SD* 2.7, range 17.0–31.0]). In addition, in light of recent changes to the definition of alcohol and other substance use disorders in DSM-5 (APA, 2013), we combined DSM-IV abuse and dependence into one lifetime AUD outcome (absent/present); mean age of most recent AUD assessment was 23.4 (*SD* 3.2, range 15.7–30.8). The mean number of drinking years was 11.5 (*SD* 3.5, range 3.3–23.0). Mean age at first drink (i.e., more than a sip) was 13.7 (*SD* 2.4, range 5.0–19.3). Despite using SRE scores from only the first five drinking occasions to reduce the potential confounding effect of acquired tolerance, we included *drinks before SRE-5 assessment* as a covariate to control for prior drinking.

2.2.6. Other assessment—The DDH was used to determine number of years of drinking, as well as cumulative uses of nicotine, cannabis, and other illicit drugs, respectively. Prior functioning was also assessed with DSM-IV attention deficit hyperactivity disorder (ADHD) diagnosis, anxious/depressed symptomology from the Youth Self-Report (Achenbach, 1991), and perceived social competence from the Harter Perceived Competence Scale for Children (Harter, 1982).

2.3. Analytic plan

We used the PROCESS macro v2.15 (Hayes, 2013) in SPSS v22.0 (IBM Corp., 2013) to test the conceptual conditional process model found in Fig. 1. Specifically, we tested whether the mediated effect of *X* (5-HTTLPR genotype; LL vs. LS/SS) on *Y* (alcohol outcomes) through

M (level of response to alcohol [SRE-5]) is contingent on *V* (parental monitoring), controlling for drinks before SRE-5, sex, age at SRE-5 assessment, and BMI. This model (PROCESS model 14) was run separately for each of the four alcohol outcomes. The two variables involved in the interaction, SRE-5 and parental monitoring, were mean-centered prior to entry into the model in order to avoid problems with multicollinearity (Aiken & West, 1991). Bootstrapping with 10,000 resamples was performed to determine bias-corrected (asymmetric) 95% confidence intervals for the conditional indirect effects (Preacher & Hayes, 2004), which are the focus of these analyses. Bootstrapping is based on random sampling of the data and does not make assumptions about the shape of the sampling distribution. Bootstrapping also allows for the construction of more accurate confidence intervals than those derived from normal theory methods, and has been recently advocated (e.g., Edwards & Lambert, 2007; Hayes, 2013). We opted not to correct for multiple comparisons as the four outcomes are highly correlated and measure the same phenomenon (i.e., alcohol use), but in different ways.

3. Results

3.1. Correlations

Table 2 shows correlations for variables in the conditional process models. Briefly, there was a trend-level correlation between 5-HTTLPR genotype (where 1 = LL and 2 = LS/SS) and SRE-5 score ($r = 0.12$, $p = 0.085$). There was a significant correlation between SRE-5 score and drinks per year ($r = 0.25$, $p < 0.001$), binge drinking days per year ($r = 0.18$, $p = 0.007$), BMI ($r = 0.20$, $p = 0.003$), and sex (where 1 = female and 2 = male; $r = 0.30$, $p < 0.001$). Genotype was not significantly correlated with parental monitoring, $r = -0.06$, $p = 0.395$.

3.2. Conditional process analysis (moderated mediation)

Conditional process analysis was used to investigate the conditional indirect effect of 5-HTTLPR on alcohol outcomes through SRE-5, conditioned on parental monitoring and controlling for drinks before SRE-5, sex, age at SRE-5 assessment, and BMI. This model was tested separately for each of the four alcohol outcomes. 5-HTTLPR was a significant predictor of SRE-5 ($a = 0.31$, $p = 0.014$), indicating that the LS/SS genotypes were associated with higher SRE-5 scores. This effect was not mediated or moderated and is thus the same for all models. See Fig. 2 for a statistical diagram of the models and Table 3 for model statistics.

Conditional indirect effects (with 95% bias-corrected bootstrapped confidence intervals) can be found in Table 4. Briefly, the conditional indirect effect of 5-HTTLPR on both alcoholic drinks consumed and binge drinking days through SRE-5 was significant at low levels of parental monitoring. In addition, the conditional indirect effect on drinks consumed continued to be significant at moderate levels of parental monitoring. These effects were positive, indicating that higher SRE-5 scores were associated with a greater number of alcoholic drinks and binge drinking days at lower levels of parental monitoring, but not at high levels of monitoring.

For alcohol-related problems, the conditional indirect effect was significant at high levels of parental monitoring, whereby higher SRE-5 scores were significantly related to fewer problems. There were no significant effects for lifetime AUD diagnosis. See Fig. 3–5 for visual depictions of the interaction effects (Preacher, Curran, & Bauer, 2006).

4. Discussion

The goals of this prospective study were to clarify how and under what circumstances variation in 5-HTTLPR confers risk for alcohol-related outcomes. In three of the four models tested, level of response to alcohol, operationalized as scores on the Self-Rating of the Effects of Alcohol (First-Five) questionnaire (SRE-5; Schuckit et al., 1997a), was found to be a significant mediator, suggesting one mechanism by which variation in 5-HTTLPR transmits alcohol-related risk. In addition, parental monitoring was found to be a significant moderator of this effect, indicating that the strength and direction of this effect varies with levels of monitoring.

Specifically, youth with the S allele reported lower responses to alcohol (i.e., higher SRE-5 scores). This in turn predicted more drinks consumed and more binge drinking days when parental monitoring levels were low (i.e., looser monitoring), but not when parental monitoring levels were high (i.e., tighter monitoring). In addition, for drinks consumed, this effect was also present at moderate monitoring levels. These results are consistent with prior studies finding that the 5-HTTLPR S allele is associated with negative alcohol behaviors and outcomes (Chen et al., 2014; Covault et al., 2007; Herman et al., 2003), as well as those indicating that poorly monitored adolescents are more likely to use drugs (Steinberg et al., 1994). Results also showed that at high levels of parental monitoring, the lower level of response to alcohol associated with the 5-HTTLPR S allele was *negatively* associated with alcohol-related problems. These results suggests that even in the presence of genetic (i.e., S allele) and physiological (i.e., low level of response to alcohol) risk factors, parents have the ability to influence the likelihood of their offspring developing problem alcohol use.

The results presented here are consistent with a substantial portion of the work involving alcohol outcomes, level of response, and variation in 5-HTTLPR. Several empirical studies and two meta-analyses point to S carriers being at increased risk for negative alcohol outcomes (e.g., Chen et al., 2014; Feinn et al., 2005; Herman et al., 2003; McHugh et al., 2010). However, other studies have reported that L carriers are at increased risk (e.g., Hu et al., 2005; Schuckit et al., 1999). Here we did not find a significant direct effect from 5-HTTLPR variation to alcohol outcomes, but did find an indirect effect whereby S allele carriers were at increased risk via SRE-5; this held in those with moderate to low parental monitoring. High monitoring was also protective, particularly against alcohol-related problems. These findings suggest that prior conflicts in the literature may have been due to unmeasured variance in other factors, including parenting.

Results across the different outcomes are also consistent in pattern. That is, an examination of the slopes found in Figs. 3–5 shows that outcomes are generally worse at low and moderate levels of parental monitoring but better at high levels of monitoring. Furthermore, high parental monitoring appears to have more of an effect as the severity of the outcome

increases (i.e., from drinks consumed to binge drinking to alcohol-related problems); lifetime AUD diagnosis also trended in this direction, but a non-significant interaction term precluded more definitive interpretation. These results can be interpreted in the context of the differential susceptibility model put forth by Belsky and Pluess (2009). Contrary to a diathesis-stress model—in which some individuals are vulnerable only to the negative influence of adversity—differential susceptibility posits that some individuals are susceptible both to the positive influence of nurturing environments as well as the negative influence of adverse environments. In this way, it is possible that genetic variants reflect *plasticity factors* rather than *vulnerability factors*. Under this view, parental monitoring interacts with the combined genetic/physiological endophenotype (i.e., S allele and low sensitivity to the effects of alcohol) to lead to positive or negative outcomes, depending on whether the monitoring is low, moderate, or high. Future work is necessary to directly test the differential susceptibility hypothesis (see, for example, Widaman et al., 2012).

Of note, we found significant effects for all outcomes except lifetime AUD. One possible reason is that, as a binary variable (present/absent), AUD diagnosis may not be sensitive enough for young and/or high-risk samples (Chassin, Bountress, Haller, & Wang, 2014) and/or dichotomizing variables reduces power. Whereas we did obtain a bootstrapped 95% confidence interval that did not contain zero for lifetime AUD diagnosis at high levels of parental monitoring, the interaction term was not significant, indicating that the effect should not be interpreted as significant. Therefore it is possible that with a larger sample this effect may be found significant in future work. It is also important to note that our measure of AUD is not the same as DSM-5 AUD (APA, 2013), given that DSM-IV abuse or dependence do not include craving and DSM-5 AUD does not include legal problems. Future studies that utilize DSM-5 criteria, which include craving and define AUD as *mild*, *moderate*, or *severe*, may be more informative.

4.1. Parental monitoring

Our finding that high levels of parental monitoring were protective against alcohol-related problems—even in the presence of genetic and physiological risk factors—is consistent with previous research (Beck, Shattuck, Haynie, Crump, & Simons-Morton, 1999; Becker et al., 2012; Steinberg et al., 1994). Our finding of significantly increased drinks and binge drinking days under conditions of low monitoring is also consistent with the literature. Adolescents raised by parents low on monitoring may be more likely to associate with deviant peers, thus increasing their own exposure and access to substances. Another possibility is that low parental monitoring increases the opportunities for adolescents to use on their own. Here we did not assess drinking context (i.e., whether participants were drinking alone, with friends, etc.), but future work should attempt to answer this interesting question.

Some researchers have argued for a different interpretation of parental monitoring, however, namely that what is often measured is parental *knowledge*—conveyed primarily by child disclosure—rather than overt monitoring behaviors (e.g., Stattin & Kerr, 2000). Perhaps adolescents who do not disclose freely to parents are more likely to do the types of things that they would not want their parents to know about (e.g., drink alcohol). In either case, low

monitoring implies a different relationship between parents and child than one of high monitoring, though the details of how this monitoring gets played out remain to be articulated. These findings suggest that the nature of the relationship between parents and adolescents may be particularly important.

Regardless of whether the harm conferred by low parental monitoring is due to negative peer relationships, more opportunity to use alone, a parent-adolescent relationship characterized by poor communication, or all three, the present results support previous research highlighting the benefits of interventions aimed at increasing parental monitoring and knowledge (e.g., Kristjansson et al., 2010). These results also support previous work showing that the effects of monitoring and/or knowledge may extend years into the future (Laird, Pettit, Bates, & Dodge, 2003). One specific area to target, as previously suggested (Becker et al., 2012; Spirito et al., 2011), is adolescents already in treatment for AUD, who could benefit from an additional component that targets increasing the parental connection via monitoring.

4.2. Strengths and limitations

To our knowledge, this is the first study to test the indirect effect of 5-HTTLPR on alcohol-related outcomes through level of response to alcohol. By using a relatively young sample (i.e., SRE-5 and parental monitoring were measured during the teenage years) and including only SRE items that pertain to the first five drinking occasions, we were able to capture a purer subjective response that was less likely to be confounded by acquired tolerance (Corbin et al., 2013; Morean & Corbin, 2008). We made this choice because there is evidence that acquired tolerance and early level of response (i.e., innate tolerance) are distinct (Higgins, Le, & Sellers, 1995; Morean & Corbin, 2008). Yet, one study found that participants with high tolerance were 2.8 times more likely to have the SS relative to the LL genotype (Turker et al., 1998), pointing to the possibility that acquired tolerance and early level of response are related. The extent to which these constructs are linked—and the nature of the possible mechanism that connects them—are interesting questions that should be addressed in future work.

The results presented here should be interpreted with some limitations in mind. First, by using the SRE questionnaire we were not able to address the “differentiator model” (Newlin & Thomson, 1990). That is, it has been proposed that some individuals at high-risk for alcohol-related problems are *more* sensitive to the effects of alcohol during the ascending limb of intoxication (characterized primarily by stimulation and euphoria) and *less* sensitive during the descending limb (characterized primarily by sedation). Support for this model has been mixed (see Morean & Corbin, 2008), so future studies may want to address this model directly. Second, by using moderated mediation models and including genes, level of response to alcohol, parental monitoring, and four covariates, we did not have the statistical power to examine sex differences. However, in order to address the fact that males typically have greater body mass and therefore require more drinks to feel the effects of alcohol, we statistically controlled for sex and BMI. It will be important for future work to examine the role of biological sex as a potential moderator. Third, given that the sample came from a high-risk community study and all participants had experience with alcohol, the results may

not generalize to low-risk and/or healthy community populations. At the same time, because drinking levels would be anticipated to be substantially lower in such populations, it is also likely that any findings would be considerably attenuated because of lack of variance. Finally, some methodological caveats should be noted. Our assessments were largely self-report measures completed by the adolescent/young adult participants, introducing the possibility that shared method variance played a role in the results. Additionally, measuring early (i.e., innate) sensitivity to alcohol in a sample with substantial variability in drinking age initiation meant that there was large variability in assessment ages, though we statistically controlled for age. Finally, though a sample size of 218 would be considered large for many types of studies, this represents a small sample for testing a conditional process genetics model; despite being consistent with much of the previous work examining this genetic variant and alcohol outcomes, considerable caution is warranted when interpreting these findings until this work is replicated using a larger independent sample.

5. Conclusions

In conclusion, the findings presented here help elucidate the mechanism of transmission from the 5-HTTLPR S allele to a variety of alcohol-related outcomes. That is, adolescents with the S allele may be at greater physiological risk to engage in detrimental substance use behaviors by way of lower sensitivity to the effects of consuming alcohol. However, our findings also demonstrate that this risk is not deterministic, and that adaptive social supports, such as parental monitoring, may minimize effects of these innate risk factors. Alternatively, under the view of differential susceptibility, those with the S allele, which leads to lower sensitivity to alcohol, may be especially vulnerable to environmental influences (e.g., parental monitoring), both for the better and for the worse. Intervention programs that emphasize increasing parental monitoring and knowledge of their child's whereabouts and affiliations are likely to have a profound impact on youth at high risk for alcohol problems based on genetic and physiological factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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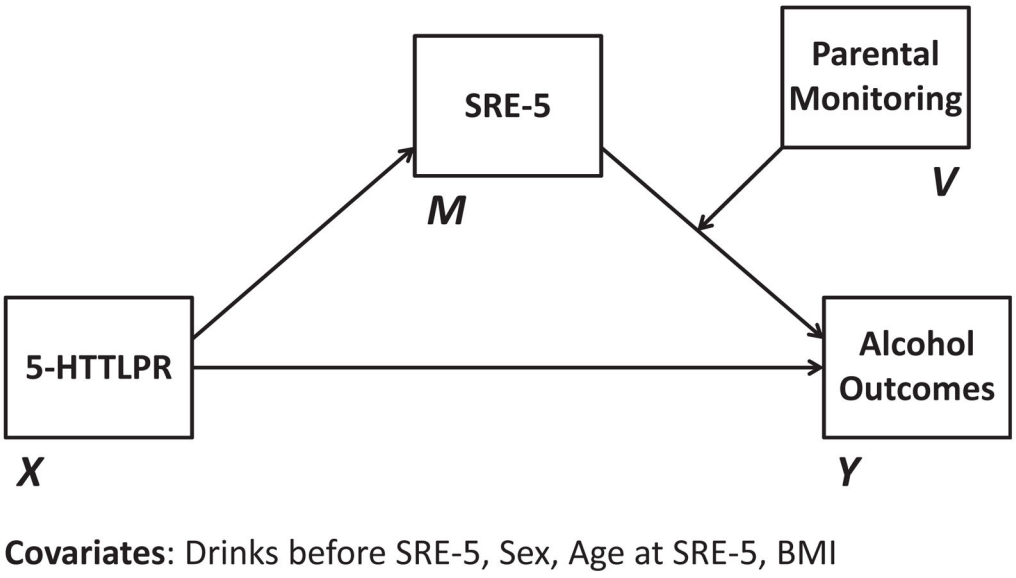

Fig. 1. Conceptual diagram of conditional process model

A conceptual diagram of the model testing whether the mediated effect of 5-HTTLPR genotype on alcohol outcomes through level of response (SRE-5) is contingent on parental monitoring, controlling for drinks before SRE-5 assessment, sex, age at SRE-5 assessment, and BMI. 5-HTTLPR, serotonin transporter-linked polymorphic region of the serotonin transporter gene (*SLC6A4*); SRE-5, Self-Rating of the Effects of Alcohol (first five drinking occasions; standardized person-mean imputation method [Lee et al., 2015]); BMI, body mass index.

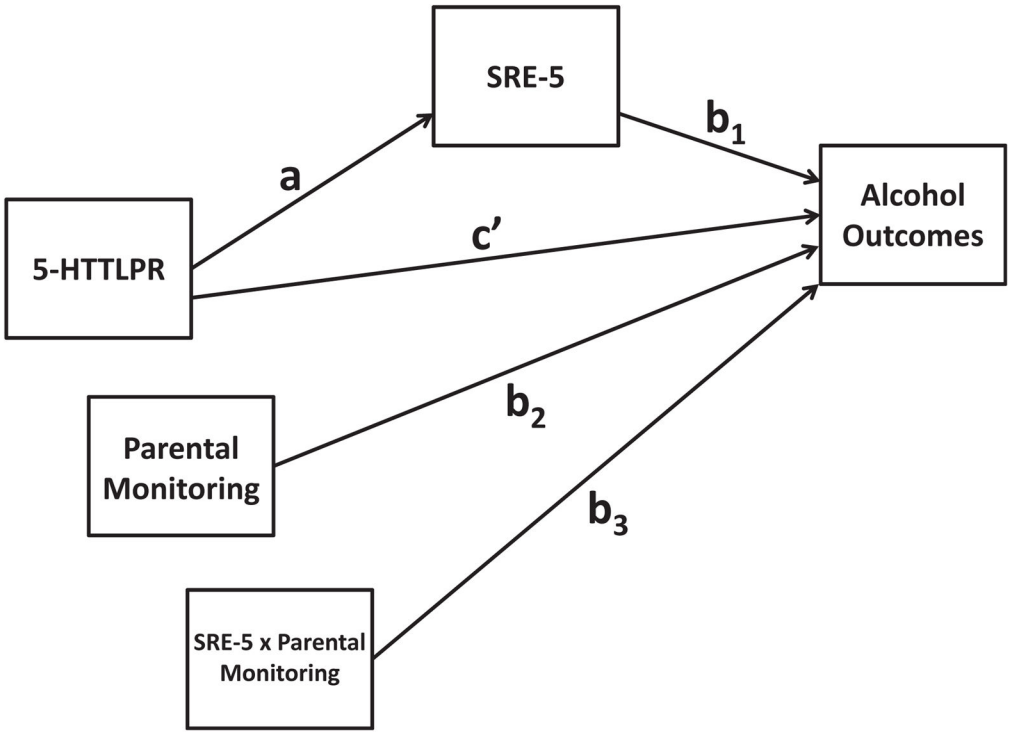

Fig. 2. Statistical Diagram of Conditional Process Model

A statistical diagram of the model testing whether the mediated effect of 5-HTTLPR genotype on alcohol outcomes through level of response (SRE-5) is contingent on parental monitoring, controlling for drinks before SRE-5 assessment, sex, age at SRE-5 assessment, and body mass index (BMI; covariates not depicted in figure). Letters correspond to path labels in Table 3. 5-HTTLPR, serotonin transporter-linked polymorphic region of the serotonin transporter gene (*SLC6A4*); SRE-5, Self-Rating of the Effects of Alcohol (first five drinking occasions; standardized person-mean imputation method [Lee et al., 2015]).

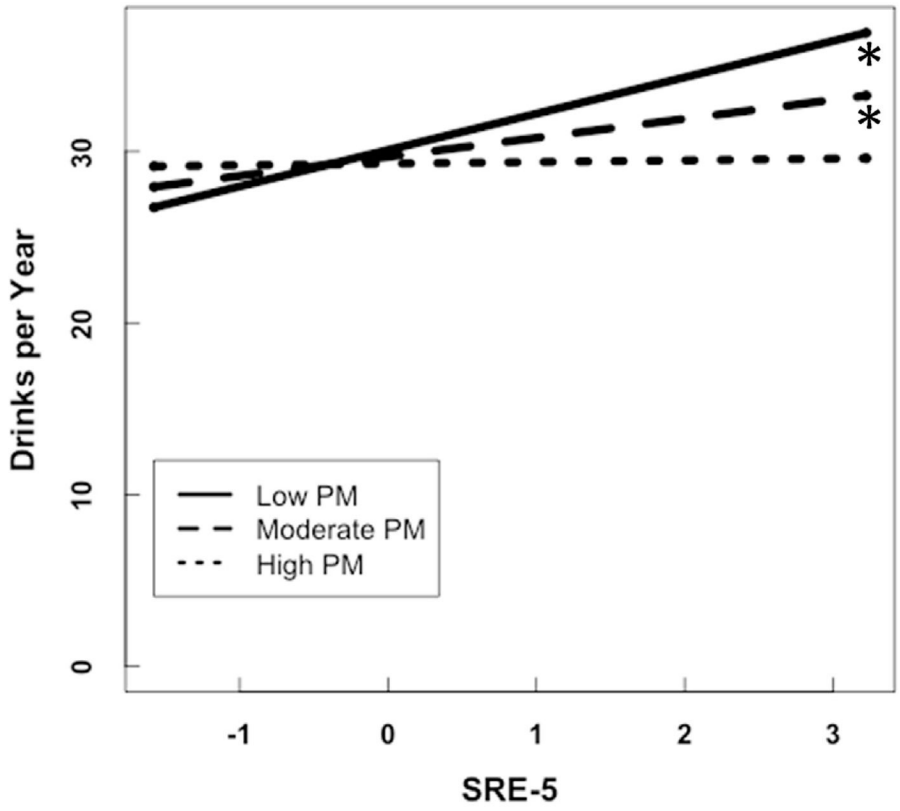

Fig. 3. Interaction of SRE-5 × Parental Monitoring Predicting Drinks per Year

A visual depiction of the moderated mediation effect (interaction only; i.e., the simple slopes of SRE-5 predicting drinks per year at low, moderate, and high levels of parental monitoring, controlling for 5-HTTLPR and drinks before SRE-5 assessment, sex, age at SRE-5 assessment, and body mass index). Using the PROCESS macro, the conditional indirect effect of 5-HTTLPR was significant at *low* and *moderate* levels of parental monitoring (effects denoted with an *), with higher SRE-5 scores associated with a greater number of drinks per year. Drinks per year was square root transformed. 5-HTTLPR, serotonin transporter-linked polymorphic region of the serotonin transporter gene (*SLC6A4*); SRE-5, Self-Rating of the Effects of Alcohol (first five drinking occasions; standardized person-mean imputation method [Lee et al., 2015]).

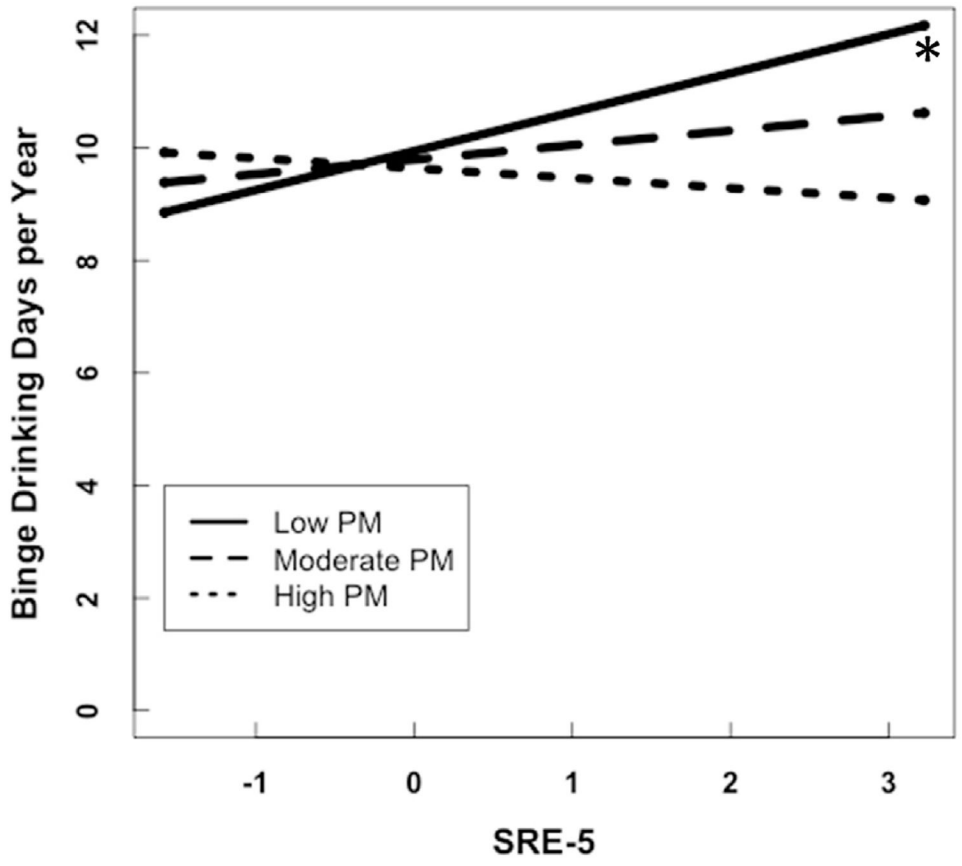

Fig. 4. Interaction of SRE-5× Parental Monitoring Predicting Binge Drinking Days per Year

A visual depiction of the moderated mediation effect (interaction only; i.e., the simple slopes of SRE-5 predicting binge drinking days per year at low, moderate, and high levels of parental monitoring, controlling for 5-HTTLPR and drinks before SRE-5 assessment, sex, age at SRE-5 assessment, and body mass index). Using the PROCESS macro, the conditional indirect effect of 5-HTTLPR was significant at *low* levels of parental monitoring (effect denoted with an *), with higher SRE-5 scores associated with a greater number of binge drinking days per year. Binge drinking days per year was square root transformed. 5-HTTLPR, serotonin transporter-linked polymorphic region of the serotonin transporter gene (*SLC6A4*); SRE-5, Self-Rating of the Effects of Alcohol (first five drinking occasions; standardized person-mean imputation method [Lee et al., 2015]).

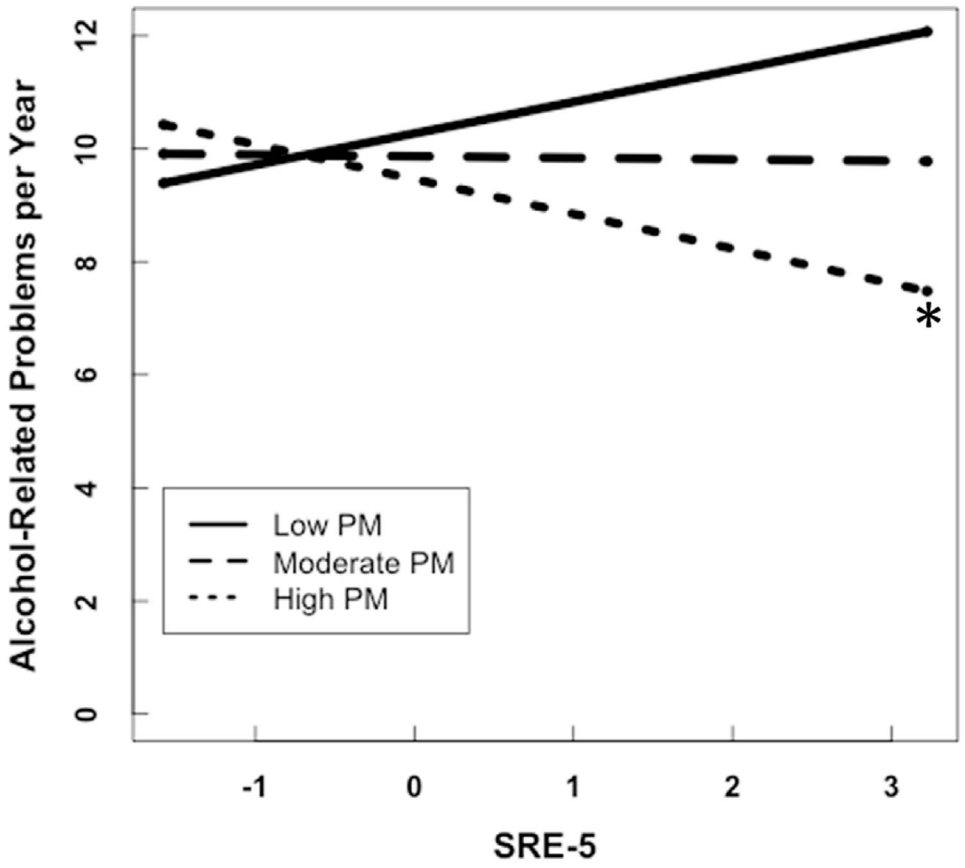

Fig. 5. Interaction of SRE-5 × Parental Monitoring Predicting Alcohol-Related Problems per Year

A visual depiction of the moderated mediation effect (interaction only; i.e., the simple slopes of SRE-5 predicting alcohol-related problems per year at low, moderate, and high levels of parental monitoring, controlling for 5-HTTLPR and drinks before SRE-5 assessment, sex, age at SRE-5 assessment, and body mass index). Using the PROCESS macro, the conditional indirect effect of 5-HTTLPR was significant at *high* levels of parental monitoring (effect denoted with an *), with higher SRE-5 scores associated with fewer alcohol-related problems per year. Alcohol-related problems per year was square root transformed. 5-HTTLPR, serotonin transporter-linked polymorphic region of the serotonin transporter gene (*SLC6A4*); SRE-5, Self-Rating of the Effects of Alcohol (first five drinking occasions; standardized person-mean imputation method [Lee et al., 2015]).

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Table 1

Demographic and behavioral variables within 5-HTTLPR allelic groups.

	LL (*n* = 68)	LS/SS (*n* = 150)	Full Sample (*N* = 218)	Statistic[a]	*p*-value[a]
Covariates					
Sex (% female)	26.5	30.0	28.9	–	0.632[b]
SRE-5 age of assessment (years)	17.8 (1.5)	17.5 (1.5)	17.6 (1.5)	$t(216) = 1.18$	0.241
BMI	24.3 (4.8)	23.4 (4.5)	23.7 (4.6)	$t(216) = 1.36$	0.177
Drinks before SRE-5 assessment	489.4 (1263.5)	305.7 (767.8)	363.0 (951.3)	–	0.522[c]
Mediator					
SRE-5 (standardized person-mean imputation)	−0.14 (0.81)	0.09 (0.97)	0.02 (0.93)	$t(216) = 1.73$	0.085
Moderator					
Parental monitoring	3.9 (0.7)	3.8 (0.7)	3.9 (0.7)	$t(216) = 0.85$	0.395
Alcohol Outcomes					
Drinks per year	17.3 (8.0)	18.0 (8.2)	17.8 (8.1)	$t(216) = 0.59$	0.554
Binge drinking days per year	4.4 (2.3)	4.5 (2.5)	4.5 (2.4)	$t(216) = 0.28$	0.780
Alcohol problems per year	4.1 (3.8)	4.2 (3.1)	4.1 (3.3)	$t(216) = 0.01$	0.989
Lifetime AUD (count; absent/present)	42/26	90/60	132/86	–	0.881[b]
Other Variables Not Included in Statistical Models					
BMI age of assessment (years)	17.8 (1.5)	17.5 (1.5)	17.6 (1.5)	$t(216) = 1.12$	0.265
Parental monitoring age of assessment (years)	16.4 (1.0)	16.5 (0.9)	16.5 (0.9)	$t(216) = 0.86$	0.393
Years drinking	11.4 (3.9)	11.5 (3.3)	11.5 (3.5)	$t(216) = 0.16$	0.874
Parental lifetime AUD diagnosis (count; absent/present)[d]	14/54	30/120	44/174	–	>0.999[b]
SRE-5 (conventional unstandardized person-mean imputation)	4.7 (2.5)	5.4 (2.8)	5.2 (2.7)	$t(216) = 1.84$	0.067
Other Substance Use (cumulative uses)					
Nicotine	942.6 (945.4)	980.2 (1115.0)	968.5 (1063.0)	–	0.608[c]
Cannabis	572.2 (860.5)	533.9 (901.5)	545.8 (887.1)	–	0.547[c]
Other illicit drugs	37.3 (92.7)	75.2 (229.2)	63.4 (197.6)	–	0.453[c]
Prior Functioning					
ADHD diagnosis (count; absent/present)	62/5	145/5	207/10	–	0.291[b]
YSR anxious/depressed (T-scores)	53.4 (5.6)	53.1 (5.7)	53.2 (5.7)	$t(216) = 0.26$	0.792

	LL (*n* = 68)	LS/SS (*n* = 150)	Full Sample (*N* = 218)	Statistic[a]	*p*-value[a]
HPCS social competence	17.3 (2.9)	16.7 (3.2)	16.9 (3.1)	*t* (216) = 1.31	0.190

Note. Numbers given are means with standard deviations in parentheses, unless otherwise noted. Drinks per year, binge drinking days per year, and alcohol-related problems per year were square root transformed prior to testing the models. Lifetime AUD refers to the presence/absence of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 1994) abuse or dependence in the lifetime. 5-HTTLPR, serotonin transporter-linked polymorphic region of the serotonin transporter gene (*SLC6A4*); SRE-5, Self-Rating of the Effects of Alcohol (first five drinking occasions; standardized person-mean imputation method [Lee et al., 2015]); BMI, body mass index; AUD, alcohol use disorder; ADHD, attention deficit hyperactivity disorder; YSR, Youth Self-Report (Achenbach, 1991); HPCS, Harter Perceived Competence Scale for Children (Harter, 1982); LL, long/long genotype; LS/SS, long/short or short/short genotype.

[a]Two-tailed *t*-test for unpaired samples with equal variances assumed, unless otherwise noted.

[b]Two-tailed Fisher's exact test.

[c]Mann-Whitney *U* test for independent samples.

[d]One LL participant was missing parental AUD diagnosis.

Table 2

Correlations among study variables.

Variable	1	2	3	4	5	6	7	8	9	10	11
1.5-HTTLPR (1 = LL, 2 = LS/SS)	–										
2. SRE-5	0.12$^{\wedge}$	–									
3. Parental monitoring	−0.06	−0.05	–								
4. Drinks per year	0.04	0.25**	−0.16*	–							
5. Binge drinking days per year	0.02	0.18**	−0.13$^{\wedge}$	0.75**	–						
6. Alcohol-related problems per year	0.00	0.08	−0.18**	0.64**	0.65**	–					
7. Lifetime AUD (1 = absent, 2 = present)	0.02	−0.05	−0.11$^{\wedge}$	0.38**	0.40**	0.42**	–				
8. Drinks before SRE-5 assessment	−0.09	0.15*	−0.17*	0.41**	0.12$^{\wedge}$	0.16*	0.07	–			
9. Sex (1 = female, 2 = male)	−0.04	0.30**	−0.11	0.30**	0.29**	0.21**	0.18**	0.10	–		
10. Age at SRE-5	−0.08	0.12$^{\wedge}$	0.03	−0.08	−0.20**	−0.17*	−0.15*	0.28**	0.09	–	
11. BMI	−0.09	0.20**	0.02	−0.04	−0.05	−0.01	−0.07	0.02	0.08	0.20**	–

Note. For the SRE-5, higher scores indicate lower level of response to alcohol. Drinks per year, binge drinking days per year, and alcohol-related problems per year were square root transformed prior to testing the models. Lifetime AUD refers to the presence/absence of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 1994) abuse or dependence in the lifetime. 5-HTTLPR, serotonin transporter-linked polymorphic region of the serotonin transporter gene (*SLC6A4*); SRE-5, Self-Rating of the Effects of Alcohol (first five drinking occasions; standardized person-mean imputation method [Lee et al., 2015]); LL, long/long genotype; LS/SS, long/short or short/short genotype; BMI, body mass index.

$^{\wedge}p < .10$,

$^{*}p < .05$,

$^{**}p < .01$.

Table 3

Unstandardized path coefficients for the conditional process models (moderated mediation).

	5-HTTLPR to SRE-5 (a)	SRE-5 to Alcohol Outcomes (b_1)	Parental Monitoring to Alcohol Outcomes (b_2)	Interaction (SRE-5 × Parental Monitoring) to Alcohol Outcomes (b_3)	Direct Effect (5-HTTLPR to Alcohol Outcomes) (c')	Model Summary
Drinks per year	0.31 * (0.13)	1.11 * (0.54)	−0.60 (0.69)	−1.46 * (0.70)	0.92 (1.02)	R^2 = 0.32 F(8,209) = 12.52 p < 0.001
Binge drinking days per year	0.31 * (0.13)	0.26 (0.18)	−0.23 (0.22)	−0.63 ** (0.23)	0.04 (0.33)	R^2 = 0.21 F(8,209) = 6.94 p < 0.001
Alcohol-related problems per year	0.31 * (0.13)	−0.03 (0.25)	−0.60 ^ (0.31)	−0.85 ** (0.32)	0.06 (0.46)	R^2 = 0.16 F(8,209) = 5.09 p < 0.001
Lifetime AUD[a]	0.31 * (0.13)	−0.30 (0.18)	−0.22 (0.22)	−0.22 (0.23)	0.13 (0.32)	Nagelkerke R^2 = 0.13 Model log-likelihood = 21.46 p = 0.006

Note. AUD, alcohol use disorder; 5-HTTLPR, serotonin transporter-linked polymorphic region of the serotonin transporter gene (*SLC6A4*); SRE-5, Self-Rating of the Effects of Alcohol (first five drinking occasions; standardized person-mean imputation method [Lee et al., 2015]). Numbers given are unstandardized coefficients with standard errors in parentheses. Drinks per year, binge drinking days per year, and alcohol-related problems per year were square root transformed prior to testing the models. Lifetime AUD refers to the presence/absence of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 1994) abuse or dependence in the lifetime. See Fig. 2 for a statistical diagram of the path coefficients.

^ p < .10,

* p < .05,

** p < .01.

[a] Model summary results refer to logistic regression.

Table 4

Conditional indirect effects of X (5-HTTLPR) on Y (alcohol outcomes) at values of the moderator (parental monitoring).

Outcome Variable	Parental Monitoring	Effect	SE[a]	95% LLCI, ULCI[a]
Drinks per year	***low***	***0.66***	***0.36***	***0.10, 1.52***
	moderate	***0.35***	***0.25***	***0.01, 1.06***
	high	0.03	0.36	−0.66, 0.82
Binge drinking days per year	***low***	***0.22***	***0.11***	***0.05, 0.49***
	moderate	0.08	0.07	−0.02, 0.28
	high	−0.06	0.10	−0.29, 0.12
Alcohol-related problems per year	low	0.18	0.14	−0.05, 0.50
	moderate	−0.01	0.08	−0.19, 0.15
	high	***−0.19***	***0.12***	***−0.51, −0.02***
Lifetime AUD	low	−0.04	0.08	−0.25, 0.09
	moderate	−0.08	0.07	−0.26, 0.02
	high[b]	−0.14	0.10	−0.41, −0.00

Note. Drinks per year, binge drinking days per year, and alcohol-related problems per year were square root transformed prior to testing the models. Lifetime AUD refers to the presence/absence of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 1994) abuse or dependence in the lifetime. The moderator (parental monitoring) was mean-centered prior to testing the conditional process models. Classifications of low, moderate, and high parental monitoring refer to 1 standard deviation below the mean (−0.69), the mean (0.00), and 1 standard deviation above the mean (0.69), respectively. Actual range of mean-centered parental monitoring scores was −2.00 to 1.14. Significant effects (i.e., effects for which the 95% bias-corrected bootstrapped confidence intervals do not contain zero) are in bold and italics. 5-HTTLPR, serotonin transporter-linked polymorphic region of the serotonin transporter gene (*SLC6A4*); AUD, alcohol use disorder; SE, standard error; LLCI, lower limit of the confidence interval; ULCI, upper limit of the confidence interval.

[a]Bootstrapped values.

[b]The interaction term for the lifetime AUD model is not significant (see Table 3), and therefore the high parental monitoring effect is not interpretable as significant.