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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 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.

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,

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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