A Serotonin Transporter Gene Polymorphism (5-HTTLPR), Drinking-to-Cope Motivation, and Negative Life Events Among College Students*

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ABSTRACT. Objective: This study was performed to examine whether a polymorphism (5-HTTLPR) in the serotonin transporter gene was related to college students' reports of relief drinking (drinking-to-cope motives) and whether it moderated the associations between negative life events and drinking to cope. We examined reward drinking (drinking-to-enhance motives) as a comparison and to see whether these effects varied across gender. **Method:** Using an Internet-based survey, college students ($N = 360$; 192 women) self-reported on drinking motives and negative life events for up to 4 years. Study participants provided saliva for genotyping the triallelic (L_A vs L_G or S) variants of 5-HTTLPR. **Results:** Among men, individuals with two risk alleles (L_G or S), compared with individuals with the L_A/L_A allele, displayed lower drinking-to-cope

motives. Among women, individuals with one risk allele (either L_G or S), compared with individuals with the L_A/L_A allele, displayed stronger drinking-to-enhance motives. The association between yearly changes in negative life events and drinking-to-cope motives varied across 5-HTTLPR genotype and gender and was strongest in the positive direction for women with the L_A/L_A variant. **Conclusions:** Our findings are not consistent with prior speculation that stronger positive associations between life stress and alcohol use among individuals with the L_G or S allele are the result of increased use of alcohol as a method for coping with stress. The importance of examining gender differences in the relations between 5-HTTLPR, substance use, and related constructs is also noted. (*J. Stud. Alcohol Drugs* 69: 814-823, 2008)

DRINKING TO COPE (DTC) with stress and negative mood is believed to be an important antecedent of alcohol abuse and dependence (Cooper et al., 1995; Greeley and Oei, 1999). To date, researchers examining the predictors of individuals' reports of DTC have focused predominantly on personality factors and Social Learning Theory-based (Bandura, 1969; Maisto et al., 1999) constructs (Cooper et al., 1995; Read et al., 2003; Simons et al., 2005). However, given a growing body of research suggesting a strong genetic component to alcohol use and abuse (Dick and Foroud, 2003), genetic factors may also be important predictors of DTC—especially differences related to the activity of serotonin, a neurotransmitter believed to be involved in a variety of mood and behavior disorders (Mann, 1999). Of particular relevance is the serotonin transporter gene (*SLC6A4*), which encodes the serotonin transporter protein (5-HTT) and plays

a key role in serotonin activity (Greenberg et al., 1999; Lesch et al., 1996). Previous research indicates that variation in *SLC6A4* is related to alcohol dependence (e.g., Feinn et al., 2005) and emotional response to life stress (e.g., Caspi et al., 2003). In the current study, we examined whether variation in the gene (1) predicted DTC levels and (2) moderated the association between life stress and DTC. We examined these questions in a 4-year longitudinal study of college students, a population that exhibits heavy drinking and drinking-related problems (O'Malley and Johnston, 2002; Substance Abuse and Mental Health Services Administration, 2004).

Alcohol-use motivation

Theorists (Cox and Klinger, 1988; Wills and Shiffman, 1985) posit that the desire to relieve negative affective states and the desire to augment positive affective states are important proximal motivational antecedents of discrete drinking behavior. Research also indicates that the propensity toward relief drinking (DTC) and reward drinking (drinking to enhance [DTE]) can be conceptualized as correlated but distinct individual difference factors with unique antecedents (Cooper, 1994; Cooper et al., 1995; Ooteman et al., 2006). For example, studies have found DTC motivation is positively related to tension-reduction drinking expectancies, avoidance coping style, and negative emotionality, whereas

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DTE motivation is positively related to social-enhancement drinking expectancies and impulsivity/sensation seeking (Cooper et al., 1995; Read et al., 2003; Simons et al., 2005).

High endorsement of DTC motivation is also related to greater physiological reactivity to negative stimuli. Colder (2001) found that individuals with stronger DTC motives showed larger increases in respiratory sinus arrhythmia after viewing aversive pictures compared with neutral pictures; DTE motivation was negatively associated to aversive picture-induced respiratory sinus arrhythmia increases. Colder interpreted these findings as evidence that individuals with high DTC responses might allocate more attentional resources to processing aversive stimuli. Colder also found a positive association between recent life stress and DTC motivation (but not DTE motivation) among individuals who showed high and moderate (but not low) levels of aversive picture-induced increases in electrodermal activity, which is purported to measure emotional arousal. In general, these findings suggest a link between high levels of DTC and a tendency to be reactive to stress.

Serotonin transporter gene, alcohol use, stress reactivity, and affect reactivity

A polymorphism in the promoter region of *SLC6A4* (5-HTTLPR) results in long (L) or short (S) alleles, the latter of which is associated with reduced transcriptional efficiency of the 5-HTT promoter (Bradley et al., 2005; Lesch et al., 1996). The presence of an A-to-G single nucleotide polymorphism further subdivides the long allele into L_A or L_G , the latter of which is equivalent to the S allele in terms of reduced functional activity (Hu et al., 2006). Although the S and L_G alleles show reduced gene expression levels in vitro (Hu et al., 2006), in vivo brain imaging studies have provided mixed results related to the effect of these variants on 5-HTT density in the adult human brain (Oquendo et al., 2007; Parsey et al., 2006; Praschak-Rieder et al., 2007; Reimold et al., 2007). Studies of amygdale activation as a function of 5-HTTLPR genotype (e.g., Pezawas et al., 2005) suggest that differences in neural circuits that may arise during development as a function of promoter genotype may be more relevant to adult behavioral correlates than simple effects on transporter density in adult brain of this polymorphism.

Studies generally have found greater alcohol use and dependence among individuals with the S allele (Feinn et al., 2005). For example, Herman et al. (2003) found the presence of S alleles to be related to more frequent heavy episodic drinking and drinking to "get drunk" among college students and suggested that this difference might stem from greater use of alcohol as an anxiolytic. Related to this notion, multiple studies have shown that carriers of the S allele show greater susceptibility to major depression and other conditions of distress in the context of high life stress (e.g., Caspi

et al., 2003; Dick et al., 2007; Mitchell et al., 2004; Taylor et al., 2006). In addition, recent studies have shown S allele carriers to have a stronger positive association between life stress and drinking. Such patterns have been observed among college students with respect to past-year negative life events (Covault et al., 2007), among adolescents with respect to family problems (Nilsson et al., 2005), and among children with respect to maltreatment (Kaufman et al., 2007).

Given these results, one might posit that increased drinking among S allele carriers during times of high stress might represent attempts at relief drinking. Thus, we would predict that S and L_G allele carriers, compared with others, should display greater levels of DTC motivation or demonstrate a stronger positive association between life stress and DTC motivation. However, findings from related areas of research temper such speculation. First, not all studies find greater drinking among S and L_G allele carriers, and other studies report gender-specific effects of 5-HTTLPR. For example, Munafò et al. (2005) found higher alcohol use among S allele homozygotes for males only, and other studies have reported greater consumption levels among L allele homozygotes (e.g., Hinkers et al., 2006; for women only: Skowronek et al., 2006). Similarly, findings from several studies indicate that greater reactivity to life stress among individuals with the S allele regarding alcohol use (see supplemental analyses in Covault et al., 2007) and distress (Eley et al., 2004; Grabe et al., 2005) might be limited to females. Second, drinking levels, especially among college students, tend to be positively associated (uniquely) with DTE motives, not DTC motives (Read et al., 2003; Simons et al., 2005). Moreover, several studies have shown that S allele carriers demonstrate increased impulsivity (Lesch et al., 1996; Steiger et al. 2005), an antecedent of DTE motives (Read et al., 2003). This raises a question as to whether increased DTC or DTE motivation might explain higher drinking levels among S allele carriers who are experiencing increased life stress. Third, studies examining level of response (LR) to alcohol have shown that L allele homozygotes report a need for more drinks to achieve comparable subjective effects (i.e., they have a lower LR; Hinkers et al., 2006; Hu et al., 2005). Moreover, Schuckit et al. (2004) found that lower LR related to higher levels of DTC motivation. This suggests that L allele homozygotes, not S allele carriers, might show evidence of greater DTC motivation. Given these diverse findings, the association between 5-HTTLPR and drinking motives is less than clear and merits further investigation.

Present study

To explicate the psychological mechanism through which 5-HTTLPR genotype influences drinking, we examined whether 5-HTTLPR (1) was directly associated with DTC motivation and (2) moderated the association between recent negative life events and DTC motivation. As a comparison,

we also assessed DTE motivation for the reasons previously cited. We examined these relations in a sample of college students who reported yearly for up to 4 years on their drinking motives and recent negative life events. Repeated measures of motives and life events allowed us to examine how relative *changes* in negative life events were related to motives and whether these associations varied by genotype and gender. We predicted that increases in negative life events would be associated with higher levels of DTC motivation but not DTE motivation. However, given the inconsistent findings across research domains, we made no *a priori* predictions about the direction of the effect of 5-HTTLPR on overall motive levels, the interactive effects of 5-HTTLPR genotype and negative life events, and gender differences in these effects.

Method

Procedure

Five hundred thirty-five college students from one university enrolled in a longitudinal study of college drinking. For 4 years, participants completed an online assessment 1-2 months following the start of the fall or spring semester by logging onto a secure Web site. This assessment included questions about demographics, negative life events, and drinking motives.

During Year 2, we emailed all participants and invited them to participate in a genetics substudy, which was voluntary and did not affect eligibility to continue in the larger study. Four hundred sixteen (77.8%) participants consented to provide samples for genetic analysis, 69 declined (12.9%), 34 did not respond (6.4%), and 16 had moved out of state (3.0%). DNA was collected during small-group sessions of six to eight participants. Following informed consent, participants were asked to "swish" Scope mouthwash (Proctor & Gamble, Cincinnati, OH) for 20-30 seconds and to spit the mouthwash into a collection tube, which was coded with a unique identification number that differed from participants' study identification number.

Genotyping procedure

Genomic DNA was extracted from the mouthwash-stabilized samples using a commercial DNA isolation protocol (Puregene, Gentra Systems, Minneapolis, MN). The 5-HTTLPR polymorphism was genotyped using a TaqMan (Applied Biosystems, Foster City, CA) 5' nuclease assay (see Covault et al., 2007, for details), which was modified from that originally described by Hu et al. (2005). The number of L alleles for each subject was identified by examination of scatter plots of endpoint FAM vs VIC fluorescence levels captured using an ABI 7500 Sequence Detection System (Applied Biosystems, Foster City, CA). Fifteen percent

of samples were repeated with complete concordance in genotype between assays. A second TaqMan 5' nuclease allelic discrimination assay served to distinguish L_A versus L_G alleles by using the same primers and amplification conditions as for the L versus S allele assay but using L_A versus L_G allele-specific probes (6FAM-CCCCCTGCACCCCCAGCATCCC-MGB and VIC-CCCCTGCACCCCCGGCATCCCC-MGB, respectively). Consistent with the findings of Hu et al. (2005), we did not observe the G allele in samples from S allele homozygotes. Given their functional equivalence, the L_G and S alleles were grouped together as S' (lower expressing allele) and the L_A allele was designated as L'.

Measures

Drinking motives. We assessed DTC and DTE motives with corresponding five-item subscales from Cooper's (1994) Motivations for Alcohol Use scale. Participants responded using a 5-point Likert scale (1 = almost never/never, to 5 = almost always/always) regarding how often they have DTC motives (e.g., "to forget your worries," "because it helps you when you feel depressed or nervous") and DTE motives (e.g., "because it's fun," "to get high"). Reliabilities (α) across all years ranged from .88 to .90 for DTC and from .90 to .92 for DTE.

Negative life events. We used 25 items from the Life Events Scale for Students (Linden, 1984). We selected these items because they were unambiguously negative and similar to the items used in Caspi et al. (2003). Participants indicated whether various general stressful life events (e.g., parental divorce, car accident, illness) and events relevant to college students (e.g., broke up with boyfriend/girlfriend, failed a course) occurred in the past year. We used a simple count of the negative events that occurred each year as a yearly index of life stress.

Participants

The 416 participants who consented to provide samples did not differ from the other 119 participants on ethnicity, year in college, or average DTC motivation (across all years). However, participants in the genetic substudy were more likely to be female ($\chi^2 = 7.74$, 1 df, $p = .005$), were younger in age in Year 1 (18.77 vs 18.96 years; $t = 2.58$, 532 df, $p = .01$), had lower levels of negative life events (across all years; 4.55 vs 3.78; $t = 3.28$, 532 df, $p = .001$), and had higher mean levels of DTE motivation (across all years; 3.20 vs 3.01; $t = 1.97$, 531 df, $p = .05$).

To avoid a potential confound owing to population stratification (i.e., racial/ethnic differences in allele frequencies and outcomes) and because our small sample sizes for the specific minority subgroups limited meaningful comparisons (i.e., largest group, $n = 24$ for Asian/Pacific Islanders), we limited

our analysis to non-Hispanic white subjects ($n = 361$), as is common practice (Caspi et al., 2003). In addition, we could not assign a 5-HTTLPR genotype to one participant. Thus, our final sample was 360 subjects (192 women, 53.3%) with a mean (SD) age (in Year 1) of 18.7 years (0.86). Most were freshmen (60.6 %) or sophomores (32.2 %) in Year 1 of the study.

Because we were interested in reasons (motives) for drinking, we did not analyze data from individuals who had never consumed alcohol; however, the data of such individuals were included if they commenced drinking in a later year. In addition, to increase homogeneity and because we were interested in drinking during college, we limited our analyses to years in which participants were still undergraduates. The breakdown for the number of reporting years per person was as follows: 1 (3%), 2 (10%), 3 (33%), or 4 (54%). Participants reported a total of 1,221 person-year observations.

Results

Descriptive statistics

The distribution of participant genotypes was 89 (24.7%) L_A/L_A , 163 (45.3%) S/L_A , 18 (5.0%) L_A/L_G , 17 (4.7%) S/L_G , 1 (0.3%) L_G/L_G , and 72 (20%) S/S . For analyses, we combined the S and L_G alleles (jointly labeled S'), to compare with the L_A allele (L'). Using this categorization, 89 (24.7%) were in the L'/L' group, 181 (50.3%) were in the L'/S' group, and 90 (25.0%) were in the S'/S' group. This triallelic distribution of genotypes was in Hardy-Weinberg equilibrium ($\chi^2 = .011, p = .916$).

Table 1 shows descriptive statistics and correlations. Consistent with past research, we found a moderately strong positive correlation between DTC and DTE motives. DTC motivation, but not DTE motivation, was positively related to average negative life events. We also calculated intraclass correlations for DTC and DTE motives. Approximately half of the variation in both motives was between-person variation (DTE = .53, DTC = .52), indicating substantial year-to-year within-person variation.

Genotype and negative life events as predictors of drinking motives

We used multilevel regressions (Raudenbush and Bryk, 2002; Snijders and Bosker, 1999) estimated with Hierarchical Linear Modeling (HLM) software (Version 6.03;

Raudenbush et al., 2004) to examine the effects of genotype, gender, negative life events, and their interaction on drinking motives. This analytical approach can be conceptualized as estimating a separate regression equation (i.e., the Level 1 model) for each person (e.g., regressing yearly motives on yearly negative life events [Level 1 effects]) and then regressing parameters from these Level 1 equations (e.g., intercepts and slopes) on person-level factors (i.e., the Level 2 model). Thus, this approach allows us to disentangle within-person and between-person variation in the dependent variable and to examine within-person $\times$ between-person interactive effects (e.g., the moderating effect of genotype on the stress-motive relationship). HLM also allows for unbalanced Level 1 data (i.e., not all participants having 4 years of data).

We entered the predictors in several steps. In Step 1 we examined the unique effects of 5-HTTLPR genotype, gender (coded men = -1 and women = 1), participant age (for reporting year), mean levels of negative life events across all years, and person-mean centered yearly negative life events (i.e., each person's average levels of negative life events subtracted from their yearly values). We chose this centering strategy for negative life events because it separates the between- and within-person effects of life events on drinking motives. Two dummy codes represented the 5-HTTLPR genotype with L'/L' serving as the reference group for each: (1) L'/S' versus L'/L' individuals (5-HTTLPR D1: $L'/L' = 0, L'/S' = 1, S'/S' = 0$) and (2) S'/S' vs L'/L' individuals (5-HTTLPR D2: $L'/L' = 0, L'/S' = 0, S'/S' = 1$). Age was grand-mean centered. This centering strategy is analogous to an analysis of covariance approach (Raudenbush and Bryk, 2002), removing both the within- and between-person effects simultaneously. For all models, we estimated only the intercept variance component.

The results for Step 1 are shown in Table 2. For DTC motives, only average negative life events (across all years) and person-centered negative life events were unique predictors. Specifically, (1) individuals who reported higher average levels of negative life events also reported higher levels of DTC, and (2) in years when individuals reported relative increases in negative life events, they reported increased levels of DTC. In contrast, only age was a unique predictor of DTE motives, with older individuals reporting lower levels. None of the genotype dummy codes was significant.

In Step 2, we examined interactions between genotype and negative life events (average level and yearly person-mean centered) and between genotype and gender. The D2 $\times$ Gender interaction in the DTC models was significant. Specifically, the difference between L'/L' individuals and S'/S' individuals differed across men and women. As shown in Figure 1 (top panel), among men, L'/L' individuals were more likely than S'/S' individuals to endorse using alcohol as a means of coping with stress. Follow-up tests for men indicated that this difference was significant ($b = -0.42, p = .005$). In contrast, for women, S'/S' individuals were more

TABLE 1. Descriptive statistics and correlations

	Mean (SD)	Correlations			
		1	2	3	4
1. Gender	—				
2. Drinking to enhance	3.26 (0.84)	-.05			
3. Drinking to cope	2.09 (0.73)	-.01	.48 [†]		
4. Negative life events	3.76 (2.18)	.09	.06	.16 [†]	

[†] $p < .01$.

TABLE 2. Multilevel regression results

Step	Drinking to cope		Drinking to enhance	
	<i>b</i> (SE)	<i>t</i>	<i>b</i> (SE)	<i>t</i>
Step 1				
D1 ^a	-0.07 (0.09)	-0.75	0.12 (0.10)	1.21
D2 ^a	-0.12 (0.10)	-1.14	0.16 (0.12)	1.28
Gender ^a	-0.02 (0.04)	-0.56	-0.05 (0.04)	-1.07
AvgNLE ^a	0.05 (0.02)	3.12 [†]	0.03 (0.02)	1.36
Age ^b	-0.02 (0.02)	-1.09	-0.05 (0.02)	-2.45*
PcNLE ^b	0.04 (0.01)	3.60 [†]	0.02 (0.01)	1.70 [§]
Step 2				
D1 × Gender ^c	0.15 (0.09)	1.53	0.20 (0.09)	2.16*
D2 × Gender ^c	0.29 (0.10)	2.85 [†]	0.18 (0.12)	1.52
D1 × AvgNLE ^c	-0.02 (0.04)	-0.56	0.03 (0.04)	0.70
D2 × AvgNLE ^c	-0.02 (0.05)	-0.50	0.06 (0.06)	0.99
D1 × PcNLE ^d	-0.01 (0.03)	-0.39	0.01 (0.03)	0.21
D2 × PcNLE ^d	-0.03 (0.03)	-1.03	-0.01 (0.03)	-0.28
Step 3				
Gender × PcNLE ^e	0.06 (0.02)	2.70 [†]	0.04 (0.02)	2.09*
Gender × D1 × PcNLE ^e	-0.05 (0.03)	-2.05*	-0.04 (0.03)	-1.67 [§]
Gender × D2 × PcNLE ^e	-0.06 (0.03)	-1.94 [§]	-0.06 (0.03)	-1.98*

Notes: *b* = unstandardized coefficient; SE = robust standard error; AvgNLE = average negative life events; PcNLE = person-mean centered yearly negative life events; Gender: -1 = males, 1 = females; D1: L'/L' = 0, L'/S' = 1, S'/S' = 0; D2: L'/L' = 0, L'/S' = 0, S'/S' = 1. Df's = ^a355, ^b1,214, ^c351, ^d1,208, ^e1,205.

[§]*p* < .10; **p* < .05; [†]*p* < .01.

likely than L'/L' individuals to endorse using alcohol as a means of coping with stress, although this difference was not significant ($b = .16, p = .27$).

The D1 × Gender interaction in the DTE motives model was also significant. Specifically, the difference between the L'/L' individuals and the L'/S' individuals differed across men and women. As shown in Figure 1 (bottom panel), among women, L'/S' individuals had higher DTE levels than L'/L' individuals ($b = 0.29, p = .034$); a similar (but marginally significant) pattern was seen for L'/L' versus S'/S' comparison among women ($b = 0.31, p = .081$). Among men, the difference between L'/S' individuals and L'/L' individuals was in the opposite direction and was not significant ($b = -.12, p = .36$).

In Step 3, we examined the three-way interactions among gender, genotype, and the person-mean centered yearly negative life events variable. We also included the two-way Gender × Negative life events interaction to partial out its effects. All of these interactions were significant or marginally significant. We also examined the three-way Genotype × Gender × Average Negative Life Events interactions. None was significant; for parsimony, we do not report these effects.

To understand the interactive effects, we plotted the simple slopes of the person-centered negative life event–motive associations broken down by gender and genotype (see Figure 2 for DTC model). The simple slope values for all of the subgroups are shown in Table 3. The two-way Gender × Negative Life Events interaction can be seen in that the life events–DTC motive slopes for the three genotype

groups among women (Figure 2, bottom) were more positive in direction—on average—compared with the slopes for men (Figure 2, top). The three-way interactions in the DTC model can be understood as follows. Among women, L'/L' individuals, compared with the other genotypes, had stronger positive associations between negative life events and DTC motives. In contrast, among men, L'/L' individuals had a negative life events–DTC motive association and the other genotype groups showed positive associations. Stated in other words, among women, L'/L' individuals compared with others had more positive slopes, but among men, L'/L' individuals compared with others had more negative slopes. This pattern was similar for DTE motives. As shown in Table 3, only female L'/L' individuals and L'/S' individuals demonstrated significant positive associations between changes in yearly negative life events and DTC motives. Moreover, only the simple slope for female L'/L' individuals was still significant ($p = .001$) after making a Bonferroni adjustment to the α level for 12 simple slope tests ($.05/12 = .004$).

Discussion

Consistent with the notion that alcohol use and related constructs are multiply determined by genetic and environmental factors (Dick and Foroud, 2003), we did not find a simple relationship between 5-HTTLPR genotype and drinking motives. On the contrary, our results indicated that drinking motives are related to genotype, gender, and life stress in a complex interactive fashion. The form of these interactive effects was generally not consistent with previous research

FIGURE 1. Predicted drinking motives means, by gender and genotype. DTC = drinking to cope; DTE = drinking to enhance.

examining the genotype by stress interactions with regard to drinking levels.

Genotype differences in DTC motivation were gender specific and generally at odds with previous findings that have been interpreted as meaning that carriers of the S allele drink more to cope with stress. Instead, we found among men that L' allele homozygotes reported higher DTC motivation than did S' allele homozygotes. These findings are consistent with results from Hinkers et al. (2006) and Hu et

al. (2005), who reported a lower levels of response among L allele homozygotes (vs S carriers), and results from Schuckit et al. (2004) showing that a lower levels of response to alcohol was associated with increased DTC. Given that this effect did not take into account changes in yearly life stress (as did the three-way interaction discussed later), we would speculate that L allele homozygote men might make stronger coping attributions regarding their drinking. One possibility is that, over their lifetimes, L' allele homozygote men are

FIGURE 2. The association between yearly negative life events and drinking to cope (DTC) motives, by gender and genotype.

more sensitive to the negative reinforcing properties (e.g., acquiring relaxation and tension-reduction expectancies) than to the positive reinforcing properties (e.g., acquiring social and physical pleasure expectancies) of alcohol. Such beliefs, which are generally stable over time (Stacy et al., 1991), could manifest into greater endorsement of relief-drinking motives regardless of concurrent stress levels.

We also found among women that S' allele carriers showed a trend for higher levels of DTE motivation. Al-

though this finding is consistent with previous findings showing greater impulsivity among S' allele carriers (e.g., Steiger et al., 2005) and findings showing that impulsivity is related to enhancement motives (e.g., Read et al., 2003), we hesitate to speculate about possible mechanisms until the findings are replicated in independent samples. Nevertheless, our findings for both motives highlight the necessity of examining gender-specific genotype effects regarding alcohol use and related constructs.

TABLE 3. Associations between changes in negative life events and motives across gender and genotype

Genotype	Drinking to cope		Drinking to enhance	
	Men	Women	Men	Women
L'/L'	-0.03	0.08 [†]	-0.04	0.04 [§]
L'/S'	0.03 [§]	0.04*	0.03	0.02
S'/S'	0.02	0.02	0.03	-0.01

Notes: Values represent the unstandardized slopes for the association between person-mean-centered yearly negative life events and drinking motives.

[§] $p < .10$; * $p < .05$; [†] $p < .01$.

Our results are not consistent with previous findings showing that S' allele carriers report more distress and alcohol use in the context of life stress. The only significant positive association between changes in life stress and DTC motivation—after adjustment for multiple comparisons—was for L' allele homozygote women. Discrepant findings in relation to the effects of the 5-HTTLPR polymorphism have also been observed in alcohol-dependence risk (Feinn et al., 2005) and in the growing literature on depressive response to rapid tryptophan depletion (Finger et al., 2007; Moreno et al., 2002; Neumeister et al., 2002, 2006; Pierucci-Lagha et al., 2004; Walderhaug et al., 2007). One possibility is that low levels of response among L allele homozygote women, but less so for others, results in the use of relatively more alcohol to reduce the effects of life stress. However, this increase in coping-related drinking among L allele homozygote women does not seem to translate into greater overall drinking across all contexts (see Covault et al., 2007). Again, replication of these findings in independent samples is needed.

To summarize, our findings do not support the notion that increased alcohol use in the context of life stress among S allele carriers (e.g., Covault et al., 2007) reflects increases in DTC motivation. Similarly, we found no evidence that changes in life stress result in increased enhancement motivation among S' allele carriers. Given these findings, an important question remains as to what processes might underlie the stronger positive association between life stress and alcohol use among S' allele carriers. One possibility is that increased drinking might be indicative of increased externalizing behavior. Studies have shown high levels of aggression and conduct problems to be related to substance use and abuse (Barnow et al., 2002; Sartor et al., 2007) and to be more prevalent among S allele carriers (Cadoret et al., 2003; Gerra et al., 2004). Taken together, S allele carriers might display greater reactivity to life stress in terms of such externalizing behaviors, which in turn cause or co-occur with increased alcohol use. In contrast, L allele homozygotes (specifically women) might engage in relatively more coping-related drinking during times of increased stress, but they also might demonstrate unchanged or reduced levels of externalizing behaviors and thus no overall change in

actual drinking levels. These findings, which have important implications for understanding the gene–environment bases of drinking motives, require evaluation in other studies using different methodologies.

Our study had several limitations. First, limiting our sample to white students from a single university limits the generalizability of our findings. Future studies with adequate minority sample sizes obtained from multiple universities are needed. Second, we found that individuals reporting higher levels of life stress were less likely to participate in the genetics substudy. Although it is logical that individuals with greater life stress might be less likely to volunteer for an additional study, we are unsure how their inclusion might have altered the findings. A third limitation concerns our measures of drinking motives. Although considerable research has shown the DTC measure to be a robust predictor of drinking-related problems (Cooper et al., 1995; Neighbors et al., 2007; Simons et al., 2005), studies examining its relation to daily negative mood-drinking contingencies have produced inconsistent results (Armeli et al., 2005). Thus, it is unclear if retrospective reports of DTC actually reflect attempts to reduce aversive states via consumption. Future studies using close to real-time reports of actual reasons for drinking in discrete episodes are needed.

These limitations notwithstanding, we believe that our findings represent an important contribution to the literature. Strengths of the report include the longitudinal design and our examination of the triallelic 5-HTTLPR genotype that takes into account the additional single nucleotide polymorphism within the L allele that differentiates functionally distinct L_A or L_G alleles (Hu et al., 2006). Our results, at the very least, suggest that the posited self-medication mechanism linking increased life stress and alcohol use among carriers of the S allele might be more complex than previously thought. Moreover, our findings underscore the importance of examining gender differences in these processes. Subsequent studies examining the effects of the 5-HTTLPR polymorphism on drinking motivations should take these factors into account.

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