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The moderating effect of FKBP5 and 5-HTTLPR polymorphisms on the day-level association between drinking to cope motivation and negative affect

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Abstract

Daily levels of drinking to cope (DTC) have been found to be related to negative outcomes such as increased negative affect, and these effects vary across person. We examined whether daily-level effects of DTC motivation were related to two genetic polymorphisms (rs1360780 in the *FKBP5* gene and 5-HTTLPR in *SLC6A4*) thought to be associated with maladaptive drinking and stress-reactivity. We also examined whether these associations changed during the transition from college to post-college life. Participants ($N = 839$, 55% women) completed an Internet-based 30-day daily diary during college and again five years later in which they reported their previous night's drinking and drinking motivation, and their current day's negative affect. Saliva was collected at wave 1 to provide DNA for genotyping. The within-person association between nighttime DTC motivation and next-day anxiety and depression was stronger (more positive) for *FKBP5* rs1360780 T-allele carriers, compared C/C-allele individuals. We also found that 5-HTTLPR L'/S' subjects (but not S'/S' homozygotes), compared to L'/L' homozygotes, showed stronger positive

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Author Statement

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Declaration of interests

None of the authors (Jonathan Covault, Stephen Armeli and Howard Tennen) have any financial or personal relationships with other people, business or organizations to disclose that could inappropriately influence their contributions, execution of the research, analysis or writing related to this manuscript "The moderating effect of FKBP5 and 5-HTTLPR polymorphisms on the day-level association between drinking to cope motivation and negative affect"

¹The participants used in Armeli et al. (2018) were also part of the analyses for Armeli et al.(2014) and one of the samples used in Armeli et al. (2016).

²Because our sample is a subsample from Armeli et al. (2018), we again report the time and DTC motivation effects. This allows us to examine whether removal of individuals with Asians and unidentified ethnicities altered the core findings results reported. Results with our sub-sample were the same.

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associations between DTC and anxiety. Results for *FKBP5* T-allele carriers are discussed in terms of past findings indicating that such individuals tend to demonstrate increased attention toward stressors, thus possibly intensifying the deleterious effects of DTC-motivated drinking.

Keywords

drinking to cope; SLC6A4; serotonin transporter; glucocorticoid receptor chaperone; daily processes

1.) Introduction

Drinking to cope (DTC) is a maladaptive emotion-regulation strategy that predicts long-term development of alcohol use disorders (AUDs) independent of drinking level (Cooper et al., 2016; Littlefield et al., 2010). To better understand this connection, recent studies utilizing micro-longitudinal research designs have examined the dynamic processes linking discrete instances of DTC-motivated drinking and proximal negative health outcomes (Armeli et al., 2014, 2016, 2018).

Drawing on attention allocation (Steele & Josephs, 1990) and self-control (Francis et al., 2018; Inzlicht & Schmeichel, 2012) theories, Armeli and colleagues posited that DTC, in some instances, might exacerbate negative affect, thus resulting in prolonged or more intense emotion regulation efforts. Sustained emotion dysregulation could, in the near-term, result in reduced self-control and increase the probability of commonly reported drinking-related problems such as neglected responsibilities, reduced self-care and interpersonal conflict. Consistent with several of these assertions, Armeli et al. (2014) found in a cohort of college students that independent of drinking level, high levels of nighttime DTC motivation predicted higher levels of negative affect and symptoms of reduced self-control the following day. In addition, Armeli et al. (2016) found that stress-reactivity in Armeli et al.'s (2014) sample, and in a separate predominately African American college student sample, was stronger on days following drinking episodes characterized by high levels of DTC motivation. Finally, a five-year post-college follow-up of moderate to heavy drinkers from Armeli et al.'s (2014) sample showed that the positive association between episode-specific levels of DTC and next-day anxiety and symptoms of reduced self-control increased in strength over time (Armeli et al. 2018), raising the possibility that DTC might become more problematic as individuals progress through early adulthood.

Armeli et al. (2018) also found that long-term changes in the day-level association between DTC motivation and daily depressive affect were related to contextual factors such as life stress and adult social role attainment. Specifically, the positive association between nighttime DTC motivation and next-day depressive affect decreased across time (i.e., DTC motivation had a less deleterious effect) among individuals who (a) attained more adult roles and (b) who reported lower levels of post-college life stress. In the present study, we examined whether the deleterious effects of DTC motivation on proximal health-related outcomes in the wave 1 and 2 assessment periods for the college student sample examined in Armeli et al., (2018) were related to two genotypes thought to be associated with emotion

regulation and problematic alcohol use: rs1360780 in the gene *FKBP5* and the promoter polymorphism 5-HTTLPR in the gene *SLC6A4*.

FKBP5 and 5-HTTLPR genetic variants as risk factors for DTC-related negative outcomes

To the extent that the deleterious outcomes from DTC-motivated drinking are due, in part, to DTC's exacerbation of negative affective states, individuals who have a genetic predisposition toward poor emotion regulation might be predisposed to react more intensely to discrete instances of DTC-related drinking. In the present study, we focused on two genotypes that might account for some of the between-person variation in the deleterious effects of DTC-related drinking. First, we examined a single nucleotide polymorphism (SNP) rs1360780 in the gene *FKBP5* encoding a glucocorticoid receptor (GR) chaperone that negatively regulates GR signaling. Polymorphisms in a *FKBP5* haplotype block tagged by the rs1360780 SNP have been linked to a number of stress-related conditions, including depression and PTSD (Binder, 2009; Wang et al., 2018). The rs1360780 T-allele has been associated with stress and anxiety related endophenotypes, including increased amygdala activation to emotional stimuli (Holz et al., 2015), reduction in cingulate cortex gray matter volume and white matter integrity (Fujii et al., 2014) and increased cortisol response during the Trier Social Stress Test (Buchmann et al., 2014). In addition, Fani et al. (2013) found that T-allele carriers showed increased attentional bias and hippocampal activation for threatening face images (Fani et al., 2013). T-allele carriers' greater tendency to focus on threatening stimuli could place them at greater risk for the posited attention allocation processes experienced during coping-motivated drinking (i.e., an increased likelihood of ruminating on stressful events), thus, increasing the negative emotion intensification posited to underlie the deleterious effects of DTC. In contrast to these studies that identify the T-allele as a "risk" allele for stress adaptation, the rs1360780 C-allele has been associated with heroin addiction (Levrán et al., 2014) and with risk for suicide attempts in substance dependent adults (Roy et al., 2010). Roy et al. (2010) speculated that different hypothalamic pituitary axis sensitivities in PTSD vs. chronic drug use (sensitization vs. blunted respectively) may relate to associations of opposite *FKBP5* alleles in these two conditions emphasizing the potential contribution of *FKBP5* genetic variation to differences in subjects' response to stressors.

We also examined a polymorphism in *SLC6A4*, which encodes the serotonin transporter protein (5-HTT) that regulates the magnitude and duration of serotonergic synaptic responses. A common 46-bp insertion/deletion in the promoter region of the serotonin transporter gene (5-HTTLPR) is characterized by a lower transcriptional activity S-allele compared with the L-allele (Heils et al. 1996) and has been associated with greater emotional reactivity, trait anxiety, neuroticism, and maladaptive emotional reactivity (Lesch et al. 1996, Schinka et al. 2004, Sen et al. 2004; Juhasz, Gonda et al. 2015) and risk of psychopathology (Kenna, Roder-Hanna et al. 2012). Since serotonin plays important roles in neurite growth and patterning, biochemical effects of the 5-HTTLPR variant may influence developmental processes as well as adult synaptic signaling (Trakhtenberg & Goldberg, 2012).

Relevant to emotional reactivity and alcohol use, S'-allele carriers have shown a stronger positive association between recent life stress and alcohol use (Covault et al., 2007; Kranzler et al., 2012), with S'-allele homozygotes generally showing the strongest relations between stress and outcomes such as drinking frequency, heavy drinking, and other drug use (Covault et al. 2007). In contrast, 5-HTTLPR was unrelated to the association between yearly changes in life stress and overall levels of DTC motivation among college students (Armeli et al., 2008). Thus, 5-HTTLPR S'-allele carriers, compared to others, are not more likely to resort to DTC-motivated drinking when experiencing distress. However, this finding does not preclude the possibility that 5-HTTLPR S'-allele carriers might experience worse outcomes from discrete instances of DTC-related drinking. To the extent that S'-allele carriers exhibit poor emotion regulation in general, they might demonstrate a more pronounced negative affect exacerbating effect of DTC-related drinking.

The present study

We reanalyzed data from Armeli et al. (2018)¹ to examine whether the within-person daily association between episode-specific levels of DTC motivation and next-day levels of anxious and depressive affect were related to *FKBP5* and 5-HTTLPR genotypes. We focused on these forms of affect given their relevance to our genotypes of interest (Binder, 2009; Kenna, Roder-Hanna et al. 2012). Specifically, we predicted that *FKBP5* rs1360780 T-allele carriers and 5-HTTLPR S'-allele carriers (especially, S' homozygotes) would show stronger positive associations between DTC motivation and next-day negative affect. In an exploratory fashion, we examined whether change in the strength of the daily DTC-negative outcome association from college years to post-college years (approximately 5 years later) was stronger among individuals with 5-HTTLPR S' or those with *FKBP5* T-alleles.

2.) Methods

2.1 Participants and procedure

As detailed in Armeli et al. (2018), this sample was part of a larger longitudinal study of college student daily alcohol use and well-being first examined in Armeli et al. (2014). At wave 1 we recruited college students for a study of daily life and alcohol use from the psychology department subject pool and through campus-wide email announcements at a northeastern state university. Prospective participants had to be at least 18 years of age, consumed alcohol at least twice in the previous month (measured at pre-screening) and have no previous (or current) treatment for alcohol or drug abuse.

Approximately five years after completing wave 1, we recruited a sub-sample of participants with moderate to heavy drinking during Wave 1 for the follow up assessment (see Armeli et al. 2018 for detailed description of the selection criteria). At both time points, individuals were instructed to log in to a secure website where they acknowledged the informed consent process and completed an initial baseline survey assessing demographics and retrospective reports of alcohol use. Participants commenced the daily diary portion of the study approximately two weeks after completing the baseline survey at both time points. Specifically, for 30 days between 3:30 and 7:00 p.m. participants were instructed to complete a brief survey (5–7 minutes long) on the secure Internet website. This time window

was selected to coincide with naturally occurring end of daytime responsibilities (undergraduate at wave 1; graduate school or professional school/work day at wave 2), but before typical evening activities began.

The daily survey first asked participants about any drinking that occurred the previous evening (after the prior day's survey [or after 7:00 pm for the first day]). If they reported any alcohol use, they were administered the drinking motives items. The second section of the daily survey asked about their current affective states any physical ailments they experienced that day and any drinking that occurred that day up to the reporting time. To maximize daily survey adherence, the system sent a reminder email at 6 pm.

Using a minimum daily adherence (15 days), we obtained baseline survey and daily data from 927 participants (81.2% of the targeted sample). Daily diary adherence was high in both waves, with participants completing the daily survey on 87.8% (wave 1) and 93% (wave 2) of the days. Armeli et al. (2018) examined comparisons between the final sample and individuals we attempted to, but failed to recruit for wave 2 and found no differences in age or drinking levels at wave 1 (college years). However, compared to those who participated in wave 2, those excluded were more likely to be men (60% of excluded vs. 46% of completers) and minorities (22% of excluded vs. 14% of completers). See Armeli et al. 2018 for more detailed demographic information.

For the current report, 24 participants who did not have genotype results were also excluded. In addition, studies of Asian samples suggest the 5-HTTLPR L- rather than the S-allele may be the stress-related risk-allele (Ming et al., 2015). Therefore, we did not include 57 Asian participants and 7 participants who reported unspecified ethnic background. This resulted in a final sample size of 839 that was 55% women, 94% Caucasian (2.8% African American, 3.2% Hispanic) and had a mean age of 19.2 years ($SD = 1.3$) during college and 24.6 years ($SD = 1.3$) post-college.

2.2. Measures

2.2.1 Daily alcohol and drinking motives.—Participants reported how many drinks (responses: 0 to >15) they had in social (interacting with others) and non-social (alone; not interacting with others) contexts separately for the previous evening (i.e., after they completed the prior day's survey) and for today (up to the reporting time). One drink is listed as “one 12-oz. can or bottle of beer, one 5-oz. glass of wine, one 12-oz. wine cooler or 1-oz. of liquor straight or in a mixed drink.”

On days when participants reported drinking, they were queried about their reasons for drinking using an adapted version of Cooper's (1994) drinking motives scale. Participants were asked, “Why did you drink last night?” DTC motivation was assessed with the items: “to forget my ongoing problems/worries,” “to feel less depressed,” “to feel less nervous,” “to avoid dealing with my ongoing problems,” “to cheer up,” “because I was angry,” and “to feel more confident/sure of myself.” Enhancement motivation were assessed with two items (“Because I like the pleasant feeling” and “to have fun”) derived from two of the higher-loading items described by Cooper (1994). Responses were made on a 3-point scale (0 = *no*,

1 = *somewhat*, 2 = *definitely*). Cronbach's alphas at for wave 1 and 2, respectively, were .82 and .80 for coping and .63 and .59 for enhancement.

2.2.2. Daily affect.—Participants were asked to rate how they felt today (from the time you woke up until now) using a 5-point scale (1 = *not at all* to 5 = *extremely*). We assessed anxious affect with two items (“nervous” and “anxious”) and depressive affect with two items (“sad” and “dejected”) adapted from the Positive and Negative Affect Schedule-Expanded (Watson et al., 1988) and Larsen and Diener's (1992) mood circumplex. Cronbach's alphas at wave 1 and 2, respectively, were .69 and .75 for anxiety and .70 and .69 for depressive affect.

2.2.3. Daily physical ailments.—Participants rated how stressful today (from the time you woke up until now) was in terms of “*feeling ill: cold, flu, headache, etc.*” using a 7-point scale (0 = “not at all” to 6 = “extremely”). Participants could also respond “did not occur” which was coded 0. We assessed physical ailments to include as a control for any physical side effects from alcohol use.

2.3. Genotyping

Saliva samples for DNA were collected during the wave 1 baseline assessment. Salivary DNA was purified using a commercial kit per vendor protocol (Oragene, DNA Genotek, Ottawa, Ontario, Canada). The *FKBP5* SNP rs1360780 was genotyped as previously described (Lieberman et al., 2016) using an Applied Biosystems TaqMan Assay On-Demand probe and primer set (C_8852038_10; Life Technologies, Carlsbad, CA) per the manufacturer's instructions. The rs1360780 genotype (C/C, C/T and T/T) frequencies were: Caucasian 0.48, 0.42, 0.10; and African Americans 0.30, 0.65, 0.04). Genotypes for each radical group were consistent with Hardy-Weinberg equilibrium expectations ($p=0.69$ and 0.63 respectively). The minor T-allele frequencies (Caucasians 0.31 and African American 0.37) were consistent with that reported in the 1000 genomes data set for this SNP (European ancestry 0.29 and African ancestry 0.39).

The serotonin transporter (*SLC6A4*) promoter region 22-bp insertion/deletion VNTR polymorphism (5-HTTLPR, 14-repeat S-allele vs. 16 repeat L-allele) was genotyped using a TaqMan 5' nuclease allelic discrimination assay incorporating a probe for the L-allele specific repeat. A second TaqMan assay was used to distinguish the L-allele linked rs25531 single nucleotide A to G polymorphism located 18 bp upstream from the L-specific repeat (Perroud et al., 2010). The long repeat / G-allele haplotype (L_G) has a reduced transcriptional activity similar to the short repeat 5-HTTLPR S-allele (Hu et al., 2006). Based on their similar in vitro transcription activity, the S and L_G alleles are grouped together as S' -alleles and the L_A identified as L' -allele. The TaqMan allelic discrimination assays were conducted using conditions, probes and primers as we previously described (Kranzler et al., 2012) which were modified from those originally published by (Hu et al, 2005). The tri-allelic genotype distributions were consistent with Hardy-Weinberg equilibrium expectations ($p=0.51$ for EA and 0.59 for AA). The frequency of $L'L'$, $L'S'$ and $S'S'$ genotypes were 0.25, 0.52, and 0.23 for Caucasians and 0.44, 0.30, and 0.26 for AA and are comparable with the frequencies reported by Hue et al. (2006). Genotyping quality

controls included assaying at least 10% of samples in duplicate, use of no-template controls and use of known standard DNA samples for each assay run. Sanger sequencing was used to confirm all L_G/L_G genotypes, *FKBP5* was coded with a single dummy code contrasting rs1360780 C/C (coded 0) vs. T-carriers (coded 1). Similar to Covault et al. (2007), 5-HTTLPR locus was coded with two dummy codes, with L'/L' as the reference group coded zero being compared to L'/S' and S'/S' (coded 1 for the relevant contrast).

3.) Results

3.1. Descriptive statistics

Drinking motives were assessed only on days that drinking occurred, thus analyses focused on daily reports in which nighttime alcohol use was reported. Our total number of daily observations for analysis was further reduced because we controlled for previous day's affect in our models (described below), thus requiring consecutive days of complete data. This resulted in a total of 11204 person-days for analysis over the two reporting waves, with 815 participants contributing 4131 person-days at wave 1 (i.e., 5.07 nighttime drinking episodes per person, $SD = 3.22$) and 784 participants contributing 7073 person-days at wave 2 (i.e., 9.02 nighttime drinking episodes per person, $SD = 5.72$). Given that our analytic procedure allows for missing data across waves, all 839 participants were included in the analyses.

3.2. Multi-level regressions results

We tested the hypotheses with 3-level (days [level 1] nested within assessment wave [level 2] nested within persons [level 3]) multi-level models estimated with HLM software (Raudenbush et al. 2004). A key advantage to this approach is that the maximum likelihood estimation provides more precise parameter estimates, compared to other approaches, when missing data is present (Hedeker & Mermelstein, 2007).

We estimated separate models for anxiety and depressive affect. In the level 1 portion of the model we specified current day (day t) affect as the dependent variable and DTC motivation from the previous night (also reported on day t) as a predictor. All models controlled for previous day's level of the dependent variable (reported on day $t-1$), previous night's social and non-social drinking amounts, drinking to enhance motivation, and current day's physical ailments and drinking level in level 1; all predictors were person-mean centered. A weekday-weekend dummy code was also included (0 = weekdays; 1 = Friday and Saturday). In the level 2 portion we included a dummy code for wave (0 = college, 1 = post-college). In the level 3 portion of the model, we included mean levels of the level 1 predictors (except for the lag-day outcome), sex, the genotype contrasts and two dummy codes comparing Black and Hispanic participants to Caucasians (the reference group). Given that Armeli et al. (2018) reported the additive effects of all of these predictors except genotype, we report only the genotype effects along with the other predictors involved in their hypothesized interactions.² All models included variance components for the level 1 and level 2 intercepts and for the level 1 slopes for DTC and enhancement motivation predictors.

We estimated the model in two steps. In the first step, we entered all of the predictors across all levels without modeling the interactions. The results for the predictors of interest (daily deviations from mean levels of DTC; genotype contrasts and study wave) are shown in Table 1 under step 1. The genotypes were unrelated to mean levels of the outcome variables except for *FKBP5*; specifically, T-carriers reported lower mean levels of depressive affect compared to C/C individuals. Mean levels for depressive affect were lower post-college versus college years, and relative increases in previous night's DTC motivation levels were positively related to both outcomes.

In the second step, we tested the hypothesized interactions between the genotypes and episode specific levels of the DTC motivation (i.e., we entered the relevant product terms into the models). We also controlled for the genotype $\times$ drinking to enhance motivation and the ethnicity $\times$ DTC motivation interactions (effects not shown; results presented were substantively identical with these interaction effects omitted from the model). The results for the hypothesized genotype $\times$ DTC motivation interactions are shown in Table 1 under step 2. We found several significant interactions; as predicted, we found significant interactions between the *FKBP5* genotype contrast and DTC motivation in predicting anxiety and depressive affect. Specifically, the association between DTC motivation and these two types of affect were stronger in the positive direction for *FKBP5* T-carriers compared to C/C allele individuals. The form of this interaction for depressive affect is shown in figure 1; the pattern was similar for anxiety.

We also found that the associations between DTC motivation and anxiety was stronger in the positive direction for 5-HTTLPR L'/S' individuals, compared to L'/L' individuals. However, none of the other interaction involving the 5-HTTLPR contrasts were significant. Finally, for all models we tested the wave $\times$ drinking motive $\times$ genotype interactions; all relevant 2-way interactions were also included in this model. None of the 6 interactions (3 per model) were significant.

4.) Discussion

We found some evidence that genetic risk factors were related to the degree to which individuals experience proximal deleterious effects of coping-motivated alcohol use, independent of the amount of alcohol consumed. Our findings showing a stronger effect of DTC on anxiety among *FKBP5* T-allele carriers is consistent with results showing this genotype related to attentional bias toward threatening stimuli (Fani et al., 2013). Consistent with Armeli et al.'s (2014) contention, when individuals drink to cope, their attention might become more focused on the precipitating stressor in accordance with the attention allocation model (Steele & Josephs, 1990). *FKBP5* T-carriers' reduced ability to disengage from negative stimuli – especially stressors high in threat appraisals – might further exacerbate affective reactions in such situations. Our similar findings with depressive affect raises the possibility that the greater attentional bias among T-carriers might not only apply to threats, but might be a general tendency to focus on a variety of negative stimuli that vary in appraisal/attribution and the type of negative affect they elicit. Future research examining the types of events underlying DTC would aid in understanding this effect.

The findings for 5-HTTLPR were less supportive of our hypotheses. We only found that the L'/S' individuals, compared to L'/L' individuals, showed a stronger positive association between prior night's DTC motivation and current day anxiety. Although the coefficients for the contrast comparing S'/S' to L'/L' was in the predicted direction in the anxiety model (i.e., greater reactivity for S'/S'), it was not significant. In addition, there was little evidence for a moderating effect of 5-HTTLPR in the depressive affect model. The inconsistent and null findings for 5-HTTLPR are generally consistent with recent evidence pointing to low replicability concerning risks associated with for S' alleles carriers (Culverhouse, Saccone et al. 2018; Bleys, Luyten et al; 2018).

We did not find that the genotype moderating effects differed across time (college versus post-college). One possibility is that the vulnerabilities conferred by these genotypes are relatively stable; that is, they set a baseline level of reactivity to DTC that does not fluctuate across developmental stage. However, we examined only one portion of the high-risk developmental window. Future research examining these processes in individuals through their late twenties and early thirties are needed to better evaluate this premise. More generally, we should acknowledge that our observed gene effects – i.e., the differential effects of DTC motivation on negative affect – are quite small. However, this does not necessarily imply that our findings are of little importance. Indeed, these effects might accumulate over time and represent a constant drain coping ability, especially among individuals who engage in coping-motivated drinking often.

Several limitations of our study should be noted. First, our non-experimental design does not allow for causal conclusions. One possibility is that current affective states bias recall of previous night's drinking motives; this distorted recall could be exacerbated by *FKBP5*-allele carriers lesser ability to disengage from negative stimuli, thus causing them to attribute negative affect to DTC more strongly. Second, we did not adjust for multiple significance tests, thus increasing the chance that our observed effects might be type 1 errors. However, we made a priori predictions based on theory and related empirical findings for these genotypes and our observed effects were consistent with these predictions. Nevertheless, replication is warranted. Third, although distress from drinking is a commonly assessed drinking-related problems (Read et al., 2006), we did measure other problems that are posited to arise from these factors, such as impulsive behavior, poor self-care, etc. Finally, we examined only two candidate genes selected based on strong prior literature regarding their involvement in various aspects of stress and threat appraisal. Our sample is too small to consider a genome wide association approach.

These limitations notwithstanding, we believe our findings advance previous research. Specifically, our findings suggest that research focus not only on how genetic risk factors might affect drinking level, research should also focus on whether such factors affect how individuals react to alcohol and to drinking for different reasons. Our findings suggest that some individuals might experience exacerbated distress from DTC, which in turn could result in commonly reported drinking-related problems.

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Highlights

- Drinking to cope is a maladaptive emotion-regulation strategy
- DTC is associated with increased next day negative affect and stress reactivity
- Polymorphisms in the FKBP5 gene have been linked to stress-related conditions
- Association of DTC and next-day anxiety is stronger for *FKBP5* risk-allele carriers

Figure 1.

The moderating effect of FKBP5 on the DTC-motivation-Next Day depressive affect association (Low and high values of DTC motivation correspond to the 5th to 95th percentile of relative levels [i.e., deviations from mean levels]).

Table 1.*FKBP5* and 5-HTTLPR Genotype and daily DTC motivation predicting next day negative affect

<i>Step</i>		<i>Anxiety</i>			<i>Depressive affect</i>		
		b	SE	<i>p</i>	b	SE	<i>p</i>
<i>1</i>	DTC	.482	.046	<.001	.630	.049	<.001
	C/C vs. T-carriers	-.040	.026	.132	-.050	.018	.007
	L'L' vs. L'S'	-.010	.031	.752	-.010	.021	.654
	L'L' vs. S'S'	-.045	.036	.203	-.050	.024	.058
	Wave	-.015	.021	.487	-.079	.017	<.001
<i>2</i>	DTC × C/C vs. T-carriers	.196	.087	.025	.205	.080	.011
	DTC × L'L' vs. L'S'	.192	.097	.048	.038	.102	.708
	DTC × L'L' vs. S'S'	.140	.136	.301	-.002	.126	.987

Note. Step 1 shows unique effects for hypothesized predictors; Step 2 shows hypothesized 2-way interactions among DTC and genotype contrasts that were added to the model. DTC = daily deviations from mean levels. Wave: 0 = college assessment, 1 = post-college.