The Long and the Short of It: Associations Between 5-HTT Genotypes and Coping With Stress

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Objective: To examine whether the strategies people use to cope with stress were associated with differing serotonin transporter (5-HTT) genotypes. The short (*s*) variant of the 5-HTT promoter polymorphism has been associated with an increased likelihood of depression after significant life stress and greater emotional reactivity to fear-invoking stimuli. **Methods:** Coping strategies were assessed within a longitudinal study in 1993. Ten years later, genomic DNA was obtained for 127 participants and genotypes for the 5-HTT promoter polymorphism were determined. Coping strategies were grouped into coping scales and also using an exploratory factor analysis. Using ordinal regression, associations were then examined between the coping scales and the 5-HTT genotype and gender. **Results:** The short variant of the 5-HTT promoter polymorphism was associated with the use of fewer problem-solving strategies. This genotype effect differed significantly between the sexes and was greatest for males. **Conclusions:** Our results indicate that coping is influenced by 5-HTT genotype, gender, and their interaction. We raise the possibility that a gene-related disposition to greater emotional reactivity may preclude those with the short variant of the 5-HTT promoter polymorphism from drawing on problem-solving strategies to deal with stress. **Key words:** serotonin transporter gene, 5-HTT, genotype, promoter polymorphism, coping, depression.

5-HTT = serotonin transporter; **SCL6A4** = serotonin transporter gene; **MD** = major depression; **ABM** = antidepressive behavior measure; **CUS** = coping under stress.

INTRODUCTION

The serotonin transporter (5-HTT) regulates serotonergic neurotransmission, which is central to many physiologic functions, including appetite, sleep, cognition, mood, and emotions. Transporter functioning is moderated by a polymorphism in the 5-HTT promoter region of the serotonin transporter gene (SCL6A4). In cell lines, the short (*s*) variant (allele) of the 5-HTT genotype reduces transcriptional efficiency of the 5-HTT gene promoter, resulting in reduced 5-HTT expression and serotonin uptake compared with the long (*l*) allele (1). Although an individual's 5-HTT genotype is fixed, it is possible that the regulatory effects imparted on 5-HTT functioning change over time, with genotype differences most evident during development (2,3).

Several recent studies have demonstrated an association between the 5-HTT promoter polymorphism, exposure to a series of adverse life events, and depression onset (2,4–8). Those with the short allele (denoted "*s*" carriers) exhibit a heightened vulnerability to adverse life events, leading to increased rates of onset of major depression (MD) (2). Furthermore, neuroimaging studies by Harriri and colleagues (9–11) and others (12) have revealed that "*s*" carriers respond to fearful stimuli with heightened activity in the amygdala, a brain region implicated in the regulation of emotions such as anxiety and fear.

Stress Response and Coping

There are two distinct, but interdependent, stress response processes that influence our risk to depression. Automatic processes are involuntary cognitive, emotional, and physiological reactions to a stressor, whereas coping strategies are attempts (both cognitive and behavioral) to diminish the physical, emotional, and psychological burden of an event (13).

Coping strategies can be conceptualized as "problem focused," if directed at controlling or changing the problem causing the distress, or "emotion focused," if directed toward managing internal emotional responses to the stressor (14). Whereas problem-focused coping responses are typically seen as a set of problem-solving behaviors (e.g., seeking information, making an action plan), emotion-focused coping strategies cover a range of conceptually distinct sets of behaviors. These are aimed at direct modulation of emotional reactions (e.g., think about the problem in a different light), distraction from the event and the associated distress (e.g., watch TV), engaging emotional support (e.g., seeking sympathy) or emotional release (e.g., breaking something).

Broadly speaking, problem-focused coping has been associated with good psychological adjustment and emotion-focused coping has been associated with poorer adjustment to stressful events (15–17). However, the adaptive utility of coping strategies is likely to depend on the nature of the stressor and factors related to the individual experiencing the event (13,18). Problem-focused strategies are thought to be more adaptive when the stressor is viewed as changeable, whereas emotion-focused strategies may be more helpful when the stressor is unchangeable (19,20). Gender differences on the use of coping strategies and their efficacy have also been reported, with women utilizing more emotion-focused strategies (21–23) and deriving greater benefit from them (24) than men who are more inclined to use problem-solving strategies or avoidance-oriented coping strategies (21,22).

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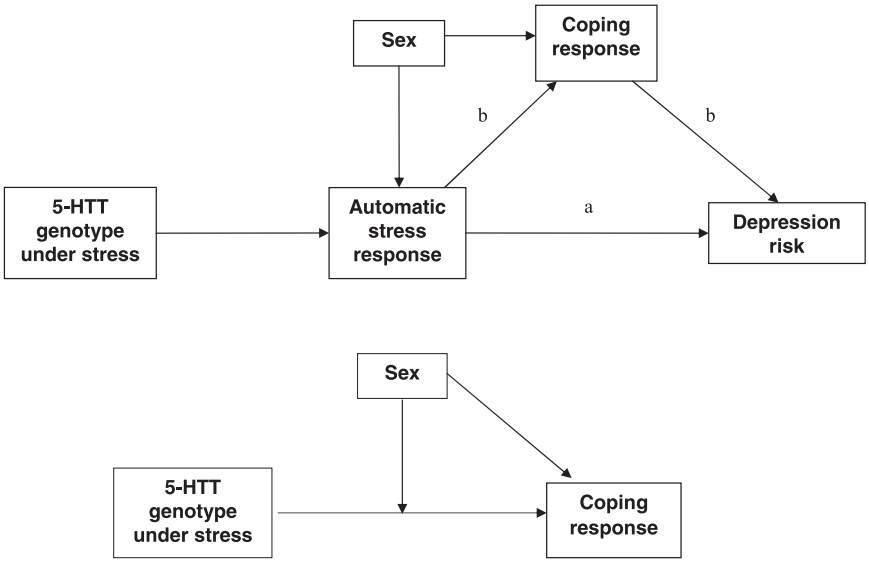

Figure 1. Two hypothetical coping models demonstrating (**A**) the mediating role of coping in the relationship between 5-HTT genotype under exposure to stress and depression, and (B) the relationships between the variables measured in the present study of genotype, gender, and coping. 5-HTT = serotonin transporter.

Coping and a Genetic Vulnerability to Stress

Figure 1 illustrates the hypothesized pathways between 5-HTT genotype, stress responses (automatic and coping processes), and subsequent depression risk. We suggest that a hyperreactive automatic stress response among "*s*" carriers (as observed in neuroimaging studies (9,10) increases depression vulnerability in two ways: directly, via pathway "*a*," and indirectly (pathway "*b*") whereby coping responses mediate the relationship between the automatic stress response and depression risk. Here, high arousal has been associated with avoidance (emotion-focused) coping and lower arousal with approach-oriented (problem-focused) coping (25).

Previously, we replicated Caspi's findings of a vulnerability associated with the short allele to developing depression after life stress within our study cohort (4). In this paper, we explore pathway "*b*"—whether the 5-HTT genotype is associated with the use of different coping responses under stress and whether gender influences this relationship. We anticipated that "*s*" carriers would have developed a greater use of coping strategies intended to lower emotional arousal given their heightened reactivity to stress.

METHOD

Procedure and Materials

In 1978, students completing a 1-year postgraduate teacher training program were invited to participate in a longitudinal study to examine likely psychosocial risk factors contributing to the anticipated evolution of gender difference in rates of depression and anxiety disorders. This cohort was selected as the members were of similar age and had equal career and life opportunities, which helped to minimize the range of possible psychosocial confounders. The 170 students (114 women and 56 men; mean age = 23 years) who gave informed consent formed the study cohort and have been followed up at 5-year intervals (26–28). The participants were primarily Caucasian from European backgrounds (97%) with a small number of participants being from Chinese ($n = 3$) and Indian ($n = 2$) descent.

In 1993, participants remaining in the study completed a coping questionnaire, on which they indicated whether they used each of 48 stated behaviors "when stressed." Coping items were taken from the "Antidepressive Behavior Measure" (ABM) (29); an additional 27 items, relating to emotional expression (particularly irritability and anger) and action-oriented behaviors pertinent to depression, were drawn from the interview schedule for the Mood Disorders Unit (30) (Table 1). These additional coping strategies were chosen because they increased the breadth of the questionnaire and many were similar to those raised by participants during previous assessments. Table 2 describes the ABM scales and development of the new "Coping Under Stress" (CUS) scales derived from the larger item pool.

Genetic Sampling

In 2003, we determined genotypes for the 5-HTT promoter polymorphism for this cohort (4). Of the 156 who had completed the coping questionnaire in 1993, 127 gave informed consent to genetic sampling. One hundred sixteen (91%) participants provided blood samples and 11 (9%) provided buccal swabs.

The following procedure was used to determine participants' 5-HTT promoter genotype (*s/s*, *s/l* or *l/l*) (4). Genomic DNA was extracted from whole blood using a standard salting out method (33). From cheek swabs, buccal cells were pelleted by centrifugation and digested overnight at 42°C in a 420-μl volume containing 1 μg/ml Proteinase K, 6 mmol/L Tris-Cl pH 7.5, 6 mmol/L ethylenediamine tetraacetic acid (EDTA), 3% Na sarkosyl, 1.2 M GuHCl, and 0.5 M ammonium acetate. DNA was purified from the digest by standard chloroform extraction and ethyl alcohol (ETOH) precipitation, and resuspended in dH_2O. The 5-HTT gene-linked promoter region was amplified with the following primers: forward 5′-TGCCGCTCTGAATGCCAGCAC-3′, and reverse 5′-GCGGGATTCTGGTGCCACCTA-3′, to generate a 464bp product for the 16 repeat (*l*) allele, and 420bp for the 14 repeat (*s*) allele. PCR was carried out in 25-μl volumes containing 1x Optiprime mastermix (Stratagene); 1x Optibuffer I (Stratagene), 400 mmol/L Betaine, 160 μM deaza dNTPs; 20 ng template DNA; 20 pmole each primer, and 1 U AmpliTaq Gold DNA polymerase (Applied Biosystems, Carlsbad, CA). Reactions were cycled with initial denaturation at 94°C for 12 minutes, followed by 35 cycles of 94°C for 30 seconds, 65°C for 45 seconds, 72°C for 1 minute, and a final extension of 10 minutes at 72°C. Products were visualized under UV light following electrophoresis in 2% agarose gels.

Statistical Analyses

Factor analysis was performed using MPLUS (34) and ordinal regression was performed using the LOGISTIC procedure in SAS (v. 9) (35). All other statistical procedures were conducted using SPSS for Windows (v. 13) (36).

TABLE 1. Development of the Coping Scales

The coping strategies were categorized in two ways:

(i) Items were congregated into Parker and Brown's (29) ABM scales.

(ii) Using the total pool of 48 items, infrequently used coping strategies were excluded and the dimensions underlying the remaining items were identified using an exploratory factor analysis of the tetrachoric correlation matrix (as variables were binary) followed by oblique rotation. The scales that emerged were designated the Coping Under Stress (CUS) scales.

ABM scales

The ABM (29) is a self-report measure of the coping behaviors used when stressed. It contains 22 items with 6 subscales. Reliability coefficients for the Recklessness ($r = 0.46$), Socialization ($r = 0.37$), Problem Solving ($r = 0.47$), and Self-consolation ($r = 0.44$) scales were reasonable over a 13-week time interval for individuals who were highly or less depressed (29).

For this study, the following changes were made to the format of the ABM coping measure:

(i) Rather than being asked to consider two hypothetical stressful events, participants were asked whether they generally used each coping strategy "when under stress."

(ii) Participants rated their coping using a categorical format (*used* or *not used*) rather than the original five-point scale (from *much less than usual* to *much more than usual*). This revised response format overcame the difficulty posed with the original format in coding for coping strategies that were not used.

(iii) One item (*take on some new work or activity)* was excluded from the questionnaire because it was very similar to another item (*find a challenge in new activities*).

In the current study, the mean interitem correlations were 0.18 for Problem Solving, 0.15 for Recklessness, and 0.18 for Socialization. These correlations were slightly below the recommended optimal range of 0.2 to 0.4 for internal consistency for scales comprising few items (31). The Passivity ($r = 0.13$), Self-consolation ($r = 0.06$), and Distraction ($r = 0.10$) scales contained very few items (≤ 3) and had low mean interitem correlations. These scales were excluded from subsequent analyses. For the remaining scales, intercorrelations were 0.07 between Problem Solving and Recklessness, 0.35 between Problem Solving and Socialization, and 0.10 between Recklessness and Socialization, representing small to small-medium effect sizes according to Cohen's criteria (32).

CUS scales

Exploratory factor analysis was conducted on 39 coping items after 9 were excluded for infrequent endorsement. Twelve factors produced eigenvalues >1.0, however the root mean square error of approximation (RMSEA) supported the use of two (RMSEA = 0.049), three (RMSEA = 0.029), and four (RMSEA = 0.018) factor solutions (with RMSEA values falling below the commonly used criterion of 0.05). The χ^2 value was significant (at $p < .05$) for the two-factor ($\chi^2 = 126.4$ (92), $p = .010$) and three-factor models ($\chi^2 = 117.8$ (94), $p = .049$), but was nonsignificant for the four-factor model ($\chi^2 = 105.5$ (93), $p = .178$). Based on these two criteria, a four-factor model was chosen as an adequate representation of the dimensions of coping strategies. Five items, *spend money on yourself*, *ignore the problem as much as possible*, *go to bed*, *cry by yourself*, and *reassure self that mood will pass*, did not load clearly on any factor. These items were excluded and the factor analysis was rerun.

The four dimensions that emerged were named Distraction, Anger/Tension Release, Emotional Regulation, and Problem Solving, based on the pattern of loadings within each factor (see Table 2). These dimensions accounted for 18.2%, 11.7%, 7.9%, and 7.1% of the variance, respectively, and, in total, explained 44.9% of the variance. Interfactor correlations ranged from 0.04 (between Distraction and Anger/Tension Release) to 0.28 (between Distraction and Problem Solving), representing small effect sizes according to Cohen's criteria (32) and indicating that the factors tap relatively independent sets of coping strategies. In the present study, reports of *taking alcohol* were similarly inversely associated with the use of problem-solving coping strategies. Subsequently, this item was reverse scored on the CUS problem-solving scale. Excepting the item *busy yourself in work*, the CUS scale constructs appear to embody the corresponding items. Problem-focused strategies are often used to manage work-related stress (22,41) and as most of the cohort worked in teaching or other human service-oriented roles that demanded a high rate of problem solving. Increased work involvement may represent an approach strategy that enables them to address the source of the stress. Three of the CUS dimensions were conceptualized as emotion-focused coping as they comprise behaviors that represent attempts to deal with the emotion triggered by the stressful event. The Emotional Regulation factor includes two mechanisms directed at reducing negative affect; one reflects increased attention to feelings (e.g., *isolate yourself and think about your feelings*) and, the other, engagement in self soothing activities (e.g., *seek warmth*). The CUS distraction strategies represent attempts to reduce or avoid emotional distress by focusing on other activities (e.g., *watch TV*, *engage in sport or physical exercise*) and the anger/tension release strategies fell into two groups: those that served to release emotion (eg, *storm around*) and those that internalize emotion (e.g., *stew, clench teeth*).

Coping scale scores were computed from a count of the endorsed coping items. Data for the coping variables did not consistently meet the assumptions of normality nor did they fit distributions for count data. The coping data were thus treated as ordinal data and the appropriate nonparametric tests were used (i.e., Mann-Whitney U test and ordinal regression).

For the dimensions noted in Table 1, the Kruder-Richardson 20 alpha for internal consistency was 0.64 for Problem Solving, 0.57 for Emotional Regulation, 0.63 for Distraction, and 0.72 for the Anger/Tension Release scale. Although modest based on conventional criteria (37), these values are comparable to those reported for previous measures (23). Previous research has shown that increases in problem-solving behavior were associated with reduced drinking behavior (38).

A series of ordinal regression analyses was conducted, using the cumulative logit model, to examine the impact of the 5-HTT genotype, gender and the gender by genotype interaction on each of the ABM and CUS coping scales. The *short* allele has been observed to be functionally dominant in terms of 5-HTT expression and serotonin uptake (2) and amygdala hyperreactivity (11). For these reasons, participants with one or two short alleles (*s/s* and *s/l* genotypes) were combined into a single group ("*s*" carriers) and compared with the *l/l* homozygotes for all regressions.

RESULTS

A total of 156 participants completed the coping inventory in 1993 (age = 38.2 ± 4.2 years, mean ± standard deviation (SD)), including 104 women. In 2003, the mean for those who provided genetic material ($n = 128$) was 47.6 ± 2.7 years; there were 85 women. Genotype frequencies (s/s, $n = 27$,

TABLE 2. Coping Dimensions Derived From Factor Analysis With Item Loadings for the 156 Cohort Members

Coping Dimension	Contributing Items	Factor Loading
Anger/Tension Release	Storm around	+0.93
	Lose your temper	+0.90
	Become argumentative	+0.69
	Yell, raise voice	+0.60
	Be reckless in some activity	+0.51
	Stew	+0.44
	Clench teeth/tense muscles	+0.43
	Bang fist/punch inanimate object	+0.39
	Sleep less	+0.36
	Eat more	+0.34
Emotional Regulation	Do meditation or yoga	+0.88
	Write about your feelings	+0.70
	Isolate yourself and think about your feelings	+0.57
	Eat less	+0.45
	Withdraw from usual social situations	+0.43
	Seek warmth	+0.42
	Sleep more	+0.41
	Use stimulants or coffee	+0.31
Problem-Solving	Take alcohol	−0.67
	Think through the problem	+0.65
	Try to discuss the problem with that person	+0.63
	Seek advice from someone	+0.63
	Tell someone about your anger	+0.56
	Pray	+0.41
	Busy yourself in work	+0.37
Distraction	Spend time with friends	+0.80
	Socialize	+0.69
	Listen to music	+0.52
	Watch TV	+0.48
	Do something to take your thoughts off the problem	+0.47
	Find a challenge in new activities	+0.47
	Care about your physical appearance	+0.42
	Read	+0.38
	Engage in sport or physical exercise	+0.35

20%; *s/l*, $n = 63$, 49%; and *l/l*, $n = 37$, 30%) were in Hardy-Weinberg equilibrium ($\chi^2 < 0.01$ (2), $p = .99$). There were no significant gender differences in genotype frequencies ($\chi^2 = 4.78$ (2), $p = .09$) and frequencies for males (s/s, $n = 10$, 23%; *s/l*, $n = 25$, 58%; and *l/l*, $n = 8$, 19%; $\chi^2 = 1.18$ (2), $p = .55$) and females (s/s, $n = 17$, 20%; *s/l*, $n = 38$, 45%; and *l/l*, $n = 30$, 35%; $\chi^2 = 0.61$ (2), $p = .74$) were in Hardy-Weinberg equilibrium. When genotype groups were dichotomized by presence or absence of a short allele, the gender difference in genotype distribution reached significance ($\chi^2 = 3.81$ (1), $p = .05$), with more male "*s*" carriers than expected.

TABLE 3. Means and Standard Deviations by 5-HTT Genotype on the ABM and CUS Coping Scales for 127 Cohort Members

Coping Scale	5-HTT Genotype		
	s/s	s/l	l/l
ABM scales			
Recklessness	0.74 (1.02)	0.81 (0.93)	0.81 (1.02)
Socialization	0.93 (1.00)	1.02 (1.10)	0.78 (0.82)
Problem-Solving	1.89 (1.25)	2.21 (1.35)	2.84 (1.30)
CUS scales			
Anger/Tension Release	3.67 (2.40)	3.68 (2.48)	4.57 (2.23)
Problem-Solving	3.22 (1.87)	3.79 (1.94)	4.62 (1.61)
Emotion Regulation	1.52 (1.50)	2.00 (1.79)	1.92 (1.74)
Distraction	2.96 (1.95)	3.94 (2.31)	3.54 (1.74)

5-HTT = serotonin transporter; ABM = antidepressive behavior measure; CUS = coping under stress.

There were no significant differences between the groups who did and did not provide genetic material on gender (33% versus 35% female, $\chi^2 = 0.02$ (1), $p = .89$) nor the total number of coping strategies they reported having used (15.3 ± 6.5 versus 14.7 ± 5.8; $z = -0.44$; $p = .66$). Nonproviders were older (50.5 ± 7.5 years) than providers of genetic material (47.6 ± 2.7 years); $t(29.3) = 2.0$; $p = .06$. This difference can be largely attributed to the higher rates of study drop out among older participants before gene sampling for reasons including ill health or death.

Those with one or two copies of the *s* allele (i.e., "*s*" carriers) reported using fewer coping strategies overall ($n = 90$; 14.6 ± 6.8) than those with the *l/l* genotype ($n = 37$; 16.8 ± 5.3), with this difference approaching significance ($z = 1.73$; $p = .09$). Females (16.7 ± 6.2) reported a wider range of coping strategies than males (12.1 ± 5.6), $z = 4.20$; $p < .001$.

Table 3 shows the mean and SD values of the count of coping strategies reportedly used for the ABM and the factor analytically derived CUS scales by 5-HTT genotype (*s/s*, *s/l*, *l/l*). The mean responses for the *s/l* genotype group were increasingly similar to that of the *s/s* group than the *l/l* group on the CUS Anger/Tension Release, ABM Socialization, and each of the problem-solving scales.

Correlations between ABM and CUS scale scores ranged from −0.13, between CUS Problem Solving and Recklessness, to 0.88, between ABM Problem-Solving and CUS Problem-Solving, indicating a high degree of construct overlap between the two problem-solving scales. There were also strong associations between Distraction and Socialization ($r = 0.75$) and a moderate association between Anger/Tension Release and Recklessness ($r = 0.46$).

Ordinal Logistic Regression

Table 4 presents the ordinal logistic regression models testing main effects of the 5-HTT genotype and gender, and the genotype-gender interaction on each of three ABM and

TABLE 4. Ordinal Regressions of the 5-HTT Genotype, Gender, and the Genotype-Gender Interaction on Each Coping Factor for 127 Cohort Members

Coping Scale	5-HTT Genotype[a]				Gender[b]				Genotype × Gender			
	B	SE	χ^2 (1)	*p*	B	SE	χ^2 (1)	*p*	B	SE	χ^2 (1)	*p*
ABM scales												
Recklessness	−0.15	0.24	0.39	.535	−0.38	0.24	2.47	.116	−0.17	0.24	0.48	.489
Socialization	−0.17	0.23	0.50	.478	−0.48	0.23	4.12	.042	0.09	0.23	0.15	.694
Problem-Solving	1.11	0.31	13.04	<.001	0.52	0.30	2.97	.085	1.04	0.31	11.58	.001
CUS scales												
Anger/Tension Release	0.15	0.21	0.53	.465	−0.75	0.22	12.15	<.001	0.04	0.21	0.04	.836
Problem-Solving	0.91	0.23	15.36	<.001	0.43	0.23	3.54	.060	0.77	0.23	11.25	.001
Emotional Regulation	0.09	0.21	0.17	.678	−0.18	0.21	0.70	.403	0.31	0.21	2.13	.144
Distraction	−0.04	0.21	0.03	.858	−0.27	0.21	1.64	.201	0.09	0.21	0.18	.672

5-HTT = serotonin transporter; ABM = antidepressive behavior measure; CUS = coping under stress.
[a] 1 = "*l/l*" genotype; −1 = "*s*" allele group (*s/s* or *s/l* genotype).
[b] 1 = male; −1 = female.

four CUS coping scales. The scale variables were recoded with some extreme categories (high or low counts) aggregated to ensure that the proportional odds assumption was upheld and there were adequate cell numbers for each ordinal regression. For example, those with scores of ≥3 on the 8-item CUS Emotional Regulation scale were aggregated, resulting in a four-category format (i.e., 0, 1, 2, 3). Using the same procedure, eight-category CUS Anger/Tension Release and Distraction scales, and a seven-category CUS Problem-Solving scale were formed. ABM Recklessness, Socialization, and Problem-Solving scales were recoded into three, four, and five categories, respectively.

As shown in Table 4, the "*s*" carriers reported utilizing significantly fewer problem-solving coping strategies on the ABM and CUS scales and there were no other significant associations between genotype and coping scales. On the CUS scales, women reported using significantly more anger/tension release strategies, although there was a trend ($p = .06$) for men to report using more problem-solving strategies. On the ABM scales, women reported using more socialization coping strategies and significantly fewer problem-solving strategies.

Significant gender-genotype interactions were found on both Problem Solving scales (Table 4). The "*s*" allele seemed to be associated with fewer problem-solving strategies for both genders, but this effect was much stronger for the men (as illustrated in Figure 2).

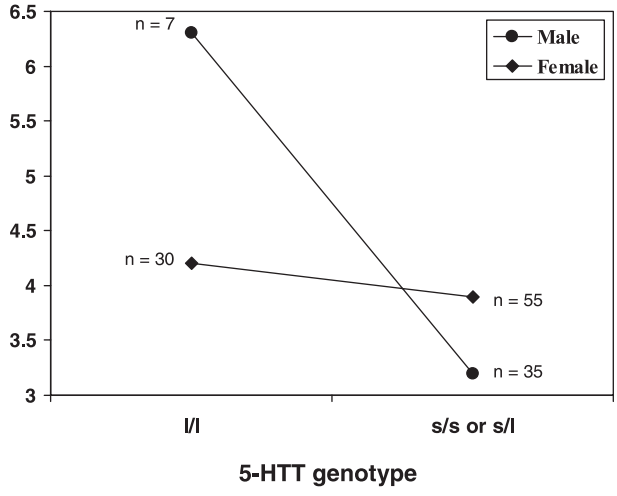

Figure 2. Reported use of CUS problem-solving strategies by gender and 5-HTT genotype. CUS = coping under stress; 5-HTT = serotonin transporter.

DISCUSSION

We have previously shown that the short variant of the 5-HTT promoter polymorphism is associated with an increased vulnerability to developing depression after life stress in this cohort (4). We now report an association between the "*s*" allele and documented use of fewer problem-solving strategies when responding to stress. The present findings may assist in understanding the behavioral mechanisms responsible for the increased risk of developing depression post exposure to stressful events for "*s*" carriers (2).

Gender and Coping

Women reported using more coping strategies overall and significantly more emotion-focused strategies, including anger/tension release and socialization strategies, reflecting gender distributions reported elsewhere (21–24). The trend for men to report the use of more problem-solving strategies is also consistent with past findings (21,22).

Coping and 5-HTT Genotypes

The results did not support our hypothesis that "*s*" carriers would use more emotion-focused responses. Instead, we observed that "*s*" carriers reported using fewer problem-solving strategies.

Problem-focused coping has been reported to be effective in reducing stress and lowering vulnerability to depression (39,40). The use of problem-focused strategies is thought to diminish when people perceive a loss of control in stressful situations they encounter (41). In reconciling our findings, we

speculate that "*s*" carriers perceive stressful situations as more overwhelming and uncontrollable than *l/l* homozygotes and are thus less likely to employ problem-focused coping.

The interaction observed between gender and 5-HTT genotype on problem-solving coping indicates a much stronger association between the "s" allele and the reported use of fewer problem-solving strategies for males than females. As previous research has reported that women tend to use more emotion-focused strategies and demonstrate improved outcomes when using these strategies (24), we speculate that women share a general preference for these emotion-focused strategies and tend to use them regardless of differences in automatic arousal associated with their 5-HTT genotype. In contrast, gene-related hyperreactivity to stressors among males may have a more noticeable inhibitive effect on their use of problem-solving coping responses, given their preference for (and reliance on) this form of coping (21,22).

The assessment of coping was conducted after the first MD onset for most cohort members who developed depression and few reported a depressive episode across the remaining follow-up interval. Thus, we were unable to assess the efficiency of the coping responses (and whether this differed by genotype) in terms of preventing first depression onset as well as any future MD episodes (whether first or recurrent). Additionally, mood state was not controlled for in this study and has been reported to affect coping (29); however, we note that were no differences in lifetime rates of MD by genotype (4).

Sample Characteristics and Genotype Distributions

The genetic and sociodemographic make-up of our study group raises issues that can be addressed via replication studies. Our sample was relatively homogeneous in terms of age, socioeconomic status, education, and ethnicity, thus limiting the generalizability of our findings. The observed associations between genotype and coping may have been influenced by gender differences in genotype distributions as well as population stratification. However, we note that genotype distributions were in Hardy-Weinberg equilibrium (for the total sample and within the sexes) and the sample was comprised almost entirely of Caucasians from European ancestry; hence, ethnic variation in the allelic frequency of the 5-HTT gene promoter (42) was unlikely to have biased our findings.

Coping Scales

The reliability and validity of the CUS measure requires further examination including that of its factor structure within other populations, stability over time, and cross validation against established measures of coping such as the COPE Inventory (43) or Ways Of Coping Questionnaire (44). Our sample was drawn from a very different population to the primary care patients recruited by Parker and Brown (29) and new coping items were added and the response format was modified; hence, substantial differences in the dimensional structures of the CUS and ABM were expected. The similarity of the ABM and CUS Problem-Solving scales therefore suggests a relatively stable, unitary construct.

Summary and Future Directions

This preliminary analysis employed a small, socially homogeneous sample and may not have detected some true associations between gender, genotype, and coping. Nevertheless, we found a significant gender-moderated difference in coping responses reported between the 5-HTT genotype groups. The inhibition of problem-solving via an exaggerated stress response represents a potential mechanism underlying the restricted range of problem-solving coping responses reported among "s" carriers. Replication of these findings, as well as the examination of the causal relationships between 5-HTT gene, coping with stress and depression occurrence, are needed. Further investigation of the genetic link to coping may potentially shed light on why some "at risk" individuals are resilient to the effects of adversity (45).

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