

Chronic and acute stress, gender, and serotonin transporter gene–environment interactions predicting depression symptoms in youth

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Background: Many recent studies of serotonin transporter gene by environment effects predicting depression have used stress assessments with undefined or poor psychometric methods, possibly contributing to wide variation in findings. The present study attempted to distinguish between effects of acute and chronic stress to predict depressive symptoms at age 20 among 346 youth varying in polymorphisms of the 5HTT gene who had been assessed at ages 15 and 20. **Methods:** Interview measures assessed major acute life events between 15 and 19, and multiple interviews and questionnaires with youths and their parents at youth age 15 provided an index of chronic family stress. Lg alleles were reclassified as S. **Results:** Chronic family stress at age 15 predicted higher depression scores at 20 among those with one or two S alleles, and the effects of genetic moderation were significant only for females. Gene–environment interactions with acute stress were nonsignificant. **Conclusions:** Careful measurement and separation of the effects of chronic and acute stress, and gender, are encouraged in the study of mechanisms of the stress–depression association. **Keywords:** Depression, serotonin transporter gene, acute stress, chronic stress, gender differences, gene–environment interactions.

Most depressions are triggered by stressful experiences (Mazure, 1998). Therefore, considerable attention has focused on why some people become depressed when exposed to negative circumstances and others do not. Various psychosocial and biological factors have been studied as modifiers of depressive reactions to stressors. A rapidly proliferating body of research implicates the short allele variants of the functional polymorphism (5-HTTLPR) in the promoter region of the serotonin transporter gene (5HTT) as a contributor to the negative emotional effects of stressors. Caspi and colleagues (2003) reported that past 5-year acute stressors and childhood maltreatment predicted depression, depressive diagnoses, and suicidality, especially among carriers of one or two S polymorphisms.

These basic findings have been replicated inconsistently (reviewed in Monroe & Reid, 2008; Risch et al., 2009; Uher & McGuffin, 2008; Zammit & Owen, 2006), suggesting that further study of the G × E effect is warranted. Several investigations have failed to find significant gene–stress interactions in relation to depression or even have found patterns opposite to predictions (e.g., Chipman et al., 2007; Gillespie, Whitfield, Williams, Heath, & Martin, 2005; Surtees et al., 2006). Also, several studies have focused only on females (Jacobs et al., 2006) or

have reported that the G × E effect is specific to females (Eley et al., 2004; Grabe et al., 2005; Sjöberg et al., 2006). While recent reviews have cast doubt on the robustness of the serotonin transporter gene by environment patterns of prediction of depression, it is expected that findings will be affected by statistical and methodological considerations, especially given the well-established likelihood that genetic effects on psychopathology are small. Nevertheless, seeking the moderators of the effects of stress on depression remains an important goal.

An important issue in gene–environment interaction studies is the considerable variability in the nature and quality of measures of stress. A recent review by Monroe and Reid (2008) noted the methodological insufficiencies of measures of stress in gene–environment studies. Only a small number of studies used comprehensive interview assessments of stressors, and reported psychometric properties of the methods (e.g., Caspi et al., 2003; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005). Many studies have relied on self-report checklists of negative life events, which have significant limitations such as reliance on memory, and subjective interpretation of items and their impact. Such judgments may be biased by the effects of current or past depressed mood. Questionnaire methods rarely probe the timing of events, and lacking contextual information about each event's unique circumstances, the meaning and severity of the event

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cannot be known (Brown & Harris, 1978). The few studies that do provide psychometric evidence of soundness of their stress questionnaires or other methods of assessment, nonetheless typically do not distinguish between major and minor events or chronic and acute duration of impact.

The varied findings and diverse methods of stress assessment may confuse understanding of the mechanisms linking stress and depression and the role played by genetic factors. Notably, the majority of the 5HTTLPR G × E interaction studies do not distinguish between chronic and acute stressors. It is likely that chronic and acute stressors predict depression by somewhat different psychosocial and biological mechanisms, possibly engaging different neuroendocrine and neurobiological processes (e.g., de Kloet, Joëls, & Holsboer, 2005), as well as different psychosocial mediators or moderators such as cognitions, coping strategies, and social support resources. In order to advance understanding of mechanisms of the stress–depression relationship, it is important to consider separately the effects of acute and chronic stress, and to employ well-developed methods of assessment.

The present study tests the moderation of the stress–depression relationship by 5HTTLPR polymorphisms with separate analyses by chronic and acute stress exposure based on psychometrically sound stress assessment methods. Participants come from a longitudinal community sample of youth at risk for depression due to varying courses of maternal depression (or no depression). The youth were assessed at ages 15 and 20 and provided blood samples for genotyping between 22 and 25. The chronic stress variable is chronic family discord at age 15, a multimethod, multivariable construct indexed by diverse measures of marital, parenting, and family functioning over at least a six-month period. An acute stress variable was derived, based on contextual threat interview procedures covering major discrete life events in the 4-year period of ages 15–19 (to parallel Caspi et al., 2003). Level of depressive symptoms at age 20 was the measure of outcome. The effects of gender were also explored.

Method

Participants

The current study is based on 346 youth (132 males, 214 females), mean age 23.7 (S.D. = .89) who met the following criteria: A) They participated in a study of youth at age 15 who had been selected for study of children of depressed or never depressed mothers ($n = 815$; details in Hammen & Brennan, 2001, 2003); B) They had been followed up at age 20 (described in Keenan-Miller, Hammen, & Brennan, 2007); C) They provided a blood sample for genotyping between ages 22 and 25, and D) were randomly selected for

5HTTLPR genetic analyses from among all who gave DNA samples.

All participants initially had been part of the Mater University Study of Pregnancy (MUSP) birth cohort study of health and development in families with children born between 1981 and 1984 at the Mater Misericordiae Mother's Hospital in Brisbane, Australia (Keeping et al., 1989). Four hundred and eighty-two participated in all phases of the study, and 384 of these were randomly selected for genotyping (381 valid readings). This number represented a single full plating holding 384 samples; the entire available sample was not genotyped for 5HTTLPR due to economic and procedural constraints, and was batched with platings from unrelated studies.

The sample was 93% Caucasian, and predominantly middle and lower middle income. The current study is based on 346 youth (132 males, 214 females), mean age 23.7 (S.D. = .89) who met the following criteria: 44% of the youth had mothers ($n = 151$) who met diagnostic criteria for major depression or dysthymic disorder by youth age 15; the other mothers had no history of depression.

Those in the age 15 and 20 follow-ups who provided blood samples 8–10 years later were compared with those who refused or could not be located. The groups did not differ in youth depression history by age 15, or maternal history of depression by age 15, but were less likely to be male ($\chi^2(1, 815) = 21.29, p < .001$). Although randomly selected for genotyping of the serotonin transporter gene among all those who met inclusion criteria, by chance fewer males were tested ($\chi^2(df = 1, n = 512) = 16.49, p < .001$), but again the genotyped and not-genotyped samples did not differ in terms of maternal depression status, youth depression by 15, or youth depression between ages 15 and 20.

Procedures

Youth and mothers and available fathers completed interviews and questionnaires separately and independently in their homes when the youth turned 15. Subsequently, youth and mothers were again studied when the youth turned 20 years of age, and as noted above, youth were re-contacted for the DNA collection in 2006 when they were between the ages of 22 and 25. Participants gave informed consent for each procedure, and all protocols were approved by the institutional review boards of the University of Queensland, UCLA, and Emory University. Maternal depression (major depression and dysthymic disorder during the child's lifetime to age 15) was diagnosed using the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995). Further details of mothers' diagnoses are reported in Hammen and Brennan (2001).

Measures

Youth depressive symptoms. Current self-reported depressive symptoms at age 20 were based on the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). BDI scores provided a continuous dependent

variable in analyses, and were used in lieu of diagnoses owing to a very small number of cases of current major depression ($n = 33$) based on administration of the SCID for DSM-IV. The BDI has excellent psychometric properties and is highly sensitive and specific for the detection of depressive disorders (e.g., Lasa et al., 2000).

Negative acute life events. A semi-structured life stress interview for adults (UCLA Life Stress Interview) was modified for adolescents (Hammen, Henry, & Daley, 2000). Modeled after the contextual threat assessment of stressful life events (Brown & Harris, 1978), the interviewer probed the occurrence of each reported acute event, elicited careful dating of the occurrence, and obtained information about the nature of the event and the circumstances in which it occurred. Written narratives of each event were scored by a rating team of 5 or more interviewers who were blind to youth and mother depression status and actual reactions to the event, using a 5-point *severity* scale ranging from 1 (no impact) to 5 (extremely severe). Studies of adolescents have supported the validity of the measure of acute events as a predictor of depression (e.g., Hammen et al., 1995; Shih, Eberhart, Hammen, & Brennan, 2006).

The interview covered the four-year period between ages 15 and 19, to predict to age 20 depression, a similar time period covered by Caspi et al. (2003). To minimize forgetting over this period by focusing only on the most significant and threatening events, participants were asked if they had experienced any one of a list of 11 severe acute life event examples (e.g., major academic failure such as expulsion or quitting school; termination of serious committed relationship or marriage; victim of crime). If an event was acknowledged to have occurred, the interviewer probed the context of its occurrence. Only events that were rated by the team as at least 3 (moderately severe) on the 5-point scale and acute in onset and duration were included. Inter-rater reliabilities comparing Australian and US rating teams on acute life events yielded an intraclass correlation of .95.

Some overlap of acute and chronic stress occurs, particularly if an acute event has a long duration such as a divorce or major illness. However, multiple occurrences of the same situation or multiple elements of the same enduring event were considered chronic stress and were not included in the acute stress measure. In statistical analyses, effects of acute stress were evaluated controlling for chronic family stress, and effects of chronic family stress were evaluated controlling for acute events.

Chronic family stress at age 15. A summary family discord variable was formed from 11 measures across different informants of the quality of marital and parental functioning quality obtained at the age 15 interview. Three variables were interviewer-rated scores from the youth and mother versions of the UCLA Chronic Stress Interview (Hammen et al., 1987) covering quality of family relationships in at least the past six months: mother's intimate/romantic relationship, and her relationship with the youth, and the youth's relationship with immediate family members. Reliabilities based on ratings by independent raters yielded

intraclass correlations of .82 for the mother-child relationship, .88 mother's intimate relationship, and .76 for youth's report of family relationship quality. Validity data for adults and youth have been reported elsewhere (e.g., Hammen et al., 1987; Hammen, Brennan, & Keenan-Miller, 2008).

Four questionnaire measures of parents' relationship quality included items from the Satisfaction subscale of the Dyadic Adjustment Scale (DAS; Spanier, 1976), administered to women currently in relationships, and those husbands who were available; the scale has good levels of reliability and validity and is useful as a measure of overall relationship quality (Kurdek, 1992). Additionally, mothers and fathers completed a self-report version of the Modified Conflict Tactics Scale (MCTS; Pan, Neidig, & O'Leary, 1994) covering frequency of seven items of psychological or physical coercion (argued heatedly; yelled/insulted; sulked and refused to talk; threw something; pushed, grabbed or shoved partner; tried to hit partner; hit partner).

Four questionnaire measures of youth-rated quality of parent-child interactions included two subscales of the revised Children's Report of Parental Behavior Inventory (CRPBI; Schludermann & Schludermann, 1988), parental acceptance versus rejection (e.g., 'gives me a lot of care and attention') and psychological control versus psychological autonomy (e.g., 'tells me all of the things she has done for me') completed for each parent separately. Coefficient α 's ranged from .77 to .91. Measures of the CRPBI have been shown to have good reliability and validity (e.g., Safford, Alloy, & Pieracci, 2007).

Each of the 11 scores was standardized across the entire age 15 sample, and were averaged across each participant in the current sample to form a summary score ($\alpha = .78$), ranging from -1.25 to 1.99 ($M = -.01$, $SD = .57$), with higher scores indicating greater chronic discord. Evidence that family discord is chronic is supported by significant correlations between this measure at age 15 and both an interview-based rating of family relations at age 20 ($r = .31$, $p < .001$) and an early family adversity composite (Hazel, Hammen, Brennan, & Najman, 2008) based on data in the first five years of the youth's life ($r = .23$, $p < .001$).

Genotyping

Participants who agreed to the blood collection study were mailed consent forms, a blood collection pack, and questionnaires, and were instructed to have the blood drawn at a local pathology lab. The blood samples were picked up by courier from the individual and transported to the Genetic Epidemiological Laboratory of the Queensland Institute of Medical Research, where the genotyping procedures were conducted.

The 43 bp deletion polymorphism was genotyped by agarose gel analysis of PCR products spanning the central portion of the repeats in the 5HTTLPR. PCR employed Qiagen enzyme and buffer except for the use of 30% deazaguanine and with 10 cycles of Touchdown protocol beginning at 67°C and finishing at 62°C with a further 32 cycles. Samples were subject to independent duplicate PCR with primer set 1 (acgttgatgTCCTGCATCCCCCAT, acgttgatgGCAGGGGGGATACTGCGA,

lower case sequence is non-templated) that gave products of 198 and 154 bp for Long and Short versions respectively and primer set 2 (acgttgatgTCCTGCATCC CCCAT, acgttgatgGGGGATGCTGGAAGGGC) for products of 127 and 83 bp. Most samples were subject to triplicate gel analysis. A minimum of two independent results in agreement was required for inclusion, which gave a final call rate of 96.4%. To estimate accuracy duplicate samples were genotyped for 829 individuals in a different study using these procedures, with discordance rates of .36%. Overall, in the present sample the proportions were: L/L = .32, L/S = .46, and S/S = .22, and in Hardy-Weinberg equilibrium.

There were no significant associations between maternal depression status and genotyping (χ^2 (362, df = 2) = .30, p = .86).

In view of evidence of variants of the L allele designated as L_A and L_G (SNP rs25531), in which L_G and S are functionally similar (Hu, Zhu, Lipsky, & Goldman, 2004), analyses were performed reclassifying L_G variants as S.

Data analytic plan

Two regression models were estimated predicting depressive symptoms at age 20 (BDI). Because the sample was a high-risk sample defined by maternal depression, presence of maternal depression diagnoses prior to the target child's age 15 was entered as a covariate in all analyses. The first model used number of severe acute events between ages 15 and 19, genotype, gender, and their interactions as predictors. Following Caspi et al. (2003), the number of acute life stressors between ages 15 and 19 were recoded into categories of 0, 1, 2, 3, and 4 or more events. Chronic family discord at age 15 was also included to control for the effects of chronic stress. The second model was identical to the first model, but included chronic family discord as the stress variable, while controlling for acute life stressors between 15 and 19. Genotype was dummy coded using the LL group as the reference, resulting in two variables representing the SS/LL contrast and the SL/LL contrast. Each interaction of genotype and another variable thus resulted in two interaction terms. Each model was estimated once and all simple effects were derived from those models using the LINCOM command in Stata 10.0. Sample sizes may differ somewhat due to missing data.

Results

Gene-environment correlations

Overall, the number of acute stressors in the last four years, $F(2, 343) = 2.26$, $p = .11$, and BDI score, $F(2, 343) = 1.03$, $p = .36$, did not differ by genotype. However, there was a significant difference between genotypes on family discord, $F(2, 343) = 6.66$, $p < .01$, with the SL genotype reporting significantly higher discord ($M = .10$, $SD = .60$) than the LL ($M = -.08$, $SD = .56$, $p = .04$) and SS ($M = -.15$, $SD = .45$, $p < .01$) groups. A correlation matrix (Table 1)

Table 1 Descriptive statistics and correlation matrix

Variable (Mean/SD)	1	2	3
1. Four-year acute stress (1.02/1.10)	–		
2. Chronic family stress (–.01/.57)	.29*	–	
3. BDI score at age 20 (7.71/8.75)	.25*	.33*	–

Note: * = Significant at or below .05 level. BDI = Beck Depression Inventory II.

indicates mild-moderate associations among stress and depression variables.

Gene \times acute stress interaction in predicting BDI at age 20

Number of severe stressors in the four years between ages 15 and 19, gender, genotype, and their interactions were used to predict BDI at age 20 controlling for maternal history of depression and family discord at age 15. The overall regression was significant, $F(13, 332) = 5.54$, $p < .001$, $R^2_{Adj} = .15$, 95% CI: (.05, .25). Although number of four-year acute stressors was correlated with BDI at age 20, it did not predict BDI at 20 after controlling for the interaction terms. None of the interaction terms were significant (all $ps > .05$). Thus, genotype does not appear to moderate the influence of severe acute stressors between ages 15 and 19 and BDI at age 20.

Gene \times chronic stress interaction in predicting BDI at age 20

Prediction of BDI from the chronic stress model is presented in Table 2. The overall regression was significant, $F(13, 332) = 6.24$, $p < .001$, $R^2_{Adj} = .16$, 95% CI: (.06, .27). A joint test of the two three-way interaction terms revealed a significant three-way interaction, $F(2, 332) = 4.47$, $p = .01$. A joint test of the two-way interaction terms for females suggested a significant interaction between family discord and

Table 2 Results of multiple regression analyses to predict G \times E interactions with chronic family stress

	Chronic family stress		
	<i>b</i>	<i>SE</i>	<i>p</i>
Maternal depression	2.84	.85	<.01
Acute events	1.15	.38	<.01
Gender	.36	1.54	.81
Family discord	–.73	1.89	.70
LL/SS	1.31	1.49	.38
LL/SL	.50	1.27	.69
Discord \times LL/SS	8.39	3.00	.01
Discord \times LL/SL	5.45	2.17	.01
Gender \times LL/SS	–4.00	2.38	.09
Gender \times LL/SL	–2.03	1.97	.30
Discord \times Gender	4.21	2.72	.12
Discord \times Gender \times LL/SS	–11.84	4.62	.01
Discord \times Gender \times LL/SL	–8.89	3.50	.01
Constant	1.17	1.15	<.01

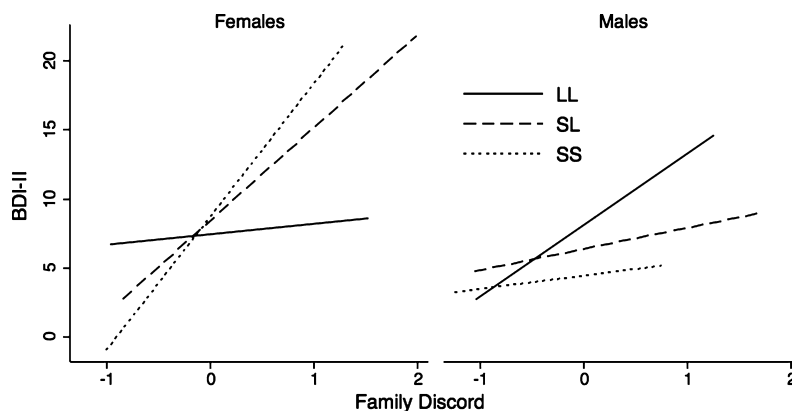


Figure 1 Association between age 20 Beck Depression Inventory scores and chronic family discord at age 15 as a function of 5HTTLPR genotype (with L_g reclassified as S) and gender. Females with one or two S alleles had significantly higher BDI scores under high chronic stress, but there were no associations between chronic stress and genetic factors predicting depression for males

genotype, $F(2, 332) = 4.65, p = .01$, whereas there was no significant interaction between family discord and genotype among males, $F(2, 332) = .92, p = .40$ (see Figure 1). The effect of family discord on BDI was stronger in SL females compared to LL females, $b = 5.45, 95\% \text{ CI: } (1.18, 9.73), p = .01$, and also in SS females compared to LL females, $b = 8.39, 95\% \text{ CI: } (2.48, 14.30), p = .006$. In LL females, family discord did not predict BDI, $b = -.73, p = .56$, but it did in SL, $b = 4.71, 95\% \text{ CI: } (2.42, 7.02), p < .001$, and SS, $b = 7.66, 95\% \text{ CI: } (2.96, 12.37), p = .001$, females. There was no difference in the strength of the family discord–BDI relationship between SS and SL females, $b = -2.94, p = .20$.

Discussion

In the present study the effects of chronic stress, but not severe acute stress, on depression were moderated by the 5HTTLPR polymorphisms consistent with several studies showing that those with at least one S allele were most susceptible to the depressogenic effects of stress (e.g., Caspi et al., 2003; Kendler et al., 2005; Wilhelm et al., 2006). The effects were obtained controlling for maternal depression and acute stress, based on the reclassification of L_g as S. Also consistent with several studies, the effects were significant for females but not males (Eley et al., 2004; Grabe et al., 2005; Sjöberg et al., 2006). Increasingly, research has shown that females are generally more reactive to the depressive effects of stress than males are (Shih et al., 2006), and such effects appear to be amplified or partly accounted for, at least for chronic stress, by genetic factors – finding with implications for understanding the well-known higher rates of depression in women than men.

The results based on chronic family stress are notably consistent with studies showing elevated rates of depression among those exposed to

adverse family conditions in childhood and at least one S allele (e.g., Caspi et al., 2003; Taylor et al., 2006; Gibb, McGeary, Beevers, & Miller, 2006). However, several conceptual issues remain to be explored: whether the $G \times E$ effects are particularly specific to family discord, or to the feature of exposure early in life implying critical developmental processes, or to continuing, chronic exposure to stress. The issue of whether content of stress is crucial (e.g., interpersonal vs. noninterpersonal) is also an unresolved issue. Furthermore, because adverse childhood experiences are commonly chronic and predictive of acute events (Hazel et al., 2008), what may appear to be effects of acute events in $G \times E$ interactions might actually in part reflect chronic stress exposure (Brown & Harris, 2008). Although it is potentially difficult to entirely separate acute from chronic stress, fuller understanding of the mechanisms by which genes and stressful experiences trigger depression likely depends on efforts to distinguish the effects of each. Although the two types may overlap, they are also likely to involve somewhat different neuroendocrine, neurobiological, and psychosocial mechanisms. Thus, differentiating between chronic and acute stress exposure may help to further clarify the processes by which stress eventuates in depression.

It is noted that chronic family discord differed by genotype, possibly reflecting gene–environment correlations of some kind. The S/S group had the lowest and the S/L group the highest levels of chronic family stress exposure overall. Nevertheless, the S/S females at high levels of discord were at greatest risk for depressive symptoms. At this point we cannot offer explanations for the association of S/L with high family discord, and if replicated, further study of this pattern would be warranted.

Several limitations of the study are acknowledged. The actual genotyped sample was relatively

small, and a larger sample might have yielded different results. The limited sample size also prohibited direct comparisons of acute versus chronic stress and their interactions with gender and genotype. A large sample size would be ideal for testing interactions among chronic and acute stress and genotype. It is also possible that a larger sample would yield greater power to detect potentially significant but small effect sizes associated with acute stress by genotype interactions. By chance the genotyped sample under-represented males, and the relatively smaller sample of males compared to females might have limited the ability to detect gene by stress interactions among men. On the other hand, as Figure 1 suggests, males' patterns of depressive responses to chronic stress do not appear to reveal trends suggestive of a robust two-way interaction. The sample was limited to depression outcomes at age 20, and samples of different ages might yield dissimilar findings owing to likely developmental variations in gene–environment effects. Some of the youth were at increased risk for depression owing to maternal depression. However, distributions of maternal depression history were not different across the genotypes, although mothers' history of depression was associated with higher levels of chronic family discord. The reported results were obtained when maternal depression status was statistically controlled, but results did not differ if maternal depression was omitted from the models. The evaluation of acute severe stressors included a four-year period prior to assessment of depression outcomes, generally similar to the work of Caspi et al. (2003). This time period may be too lengthy to capture effects of acute stressors on depression (unless, as argued by Brown and Harris (2008), multiple events might actually reflect chronically stressful conditions). Further, as acknowledged, acute and chronic stress may overlap, and the boundaries between them may be far from exact. The analyses examined effects of each controlling for the other, but further work is needed to refine and distinguish acute and chronic stress.

Results were based on depressive symptoms rather than diagnoses, because only a small number of youth met diagnostic criteria for major depression at age 20, and continuous outcome variables may be less susceptible to artifactually significant interactions, compared to dichotomous outcomes like diagnostic status (Eaves, 2006). BDI scores do not lack clinical relevance (e.g., Gotlib, Lewinsohn, & Seeley, 1995), particularly if persistently elevated. However, such scores may be transitory, suggesting the need for further studies using clinical diagnoses.

The measure of chronic family discord had the advantage of a multivariable, multi-informant

method, and indicated modest but significant stability over the life course of the youth in relation to conceptually similar but different indicators. As noted, further work is needed to discern what features of chronic family discord are relevant to the mechanisms of the genetic consequences of stress on depression.

Additionally, it is important to acknowledge increasing questions about the potential role of the 5HTTLPR gene in depression and the meaningfulness of findings with this genotype (e.g., Munafó, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). We expect that as the field develops, other genes that modify how individuals respond to stressful experiences will doubtless invite close attention in gene–environment studies.

The current results argue for greater refinement in the measurement of stressful conditions when studied in association with genetic factors to predict depressive reactions. The results imply that the influence of chronically adverse family conditions on depressive symptoms among young adult females may be especially affected by serotonin transporter functions, but also indicate that further studies of the patterns and mechanisms of stress reactivity dependent on acute and chronic stress are needed.

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Key points

- Prior studies indicate that the effects of stress on depression may be modified by the serotonin transporter gene (5HTTLPR), but inconsistencies require further clarification.
- The study explored the roles of psychometrically sound measures of severe acute life events and chronic family discord as moderators of the association between genotype and depressive symptoms, and also examined gender differences in a sample of youth with depressed or never-depressed mothers.
- Results indicated that young women with one or two s-alleles were more depressed in the face of chronic family discord. Chronic stress by genotype interactions were not found for males, and the interaction of genotype and acute stress was not significant.
- The combination of chronic family discord and s-alleles of the 5HTTLPR genotype put females at risk for depressive symptoms. Further study is needed to explore whether such stress has its effects because it concerns family relations, is chronic rather than acute, or may create vulnerability associated with stress exposure from early childhood.

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