Refining the candidate environment: Interpersonal stress, the serotonin transporter polymorphism, and gene-environment interactions on major depression

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Abstract:

Meta-analytic evidence has supported a gene-environment interaction between life stress and the serotonin transporter–linked polymorphism (5-HTTLPR) on depression, but few studies have examined factors that influence detection of this effect, despite years of inconsistent results. We propose that the candidate environment (akin to a candidate gene) is key. Theory and evidence have implicated major stressful life events (SLEs)—particularly major interpersonal SLEs—as well as chronic family stress. A total of 400 participants from the Youth Emotion Project (which began with 627 high school juniors oversampled for high neuroticism) completed up to five annual diagnostic and stress interviews and provided DNA samples. A significant gene-environment effect for major SLEs and S-carrier genotype was accounted for significantly by major interpersonal SLEs but not significantly by major noninterpersonal SLEs. S-carrier genotype and chronic family stress also significantly interacted. Identifying such candidate environments may facilitate future gene-environment research in depression and psychopathology more broadly.

Keywords: major depressive disorder | 5-HTTLPR | stressful life events | chronic family stress | interpersonal | young adults | Cox regression | gene-environment

Article:

Following an initial, seminal report by Caspi et al. (2003), the gene-environment (G×E) interaction effect between the serotonin transporter–linked polymorphic region (5-HTTLPR) and stressful life events (SLEs) on onsets of major depressive episodes (MDEs) has been a source of debate among researchers. The polymorphism at the center of this debate, 5-HTTLPR, refers to an insertion/deletion polymorphism in the promoter region of the serotonin transporter gene,

SLC6A4, that yields a transcriptionally less efficient short (S) allele and a relatively more efficient long (L) allele (Heils et al., 1996). The largest and most recent meta-analysis provided support for a significant G×E interaction effect in which individuals with the S allele report greater depression under increasing stress relative to L/L homozygotes (Karg, Burmeister, Shedden, & Sen, 2011), although two smaller, earlier meta-analyses were negative (Munafò, Durrant, Lewis, & Flint, 2009; Risch et al., 2009).

In the context of this debate, the possibility of a significant interaction effect—and the potential for identifying factors that enhance its detection—remains intriguing for several reasons. First, there has been longstanding interest in the serotonin transporter molecule in MDE etiology (e.g., Owens & Nemeroff, 1994). Second, evidence has revealed that this polymorphism alters expression of the serotonin transporter (Heils et al., 1996). Third, meta-analytic evidence has suggested that this polymorphism accounts for up to 10% of the variance in amygdala activation to emotional stimuli (Munafò, Brown, & Hariri, 2008), which is implicated in risk for depression (Monk et al., 2008).

Finally, additional meta-analytic evidence has indicated that stress interviews and other objective measures yield more robust G×E interaction effects compared with lower validity measures (i.e., life stress questionnaires; Karg, et al., 2011), consistent with several reviews (Monroe & Reid, 2008; Uher & McGuffin, 2010). Unfortunately, a majority of investigations of this question have used checklist measures of life stress. Thus, a goal of studies that use interview and objective measures of life stress could be to identify additional factors that influence the detection of the 5-HTTLPR G×E effect. Identifying such factors not only may contribute greater understanding of 5-HTTLPR's role in depression but also may facilitate future G×E research on depression with novel candidate polymorphisms. We propose that an important factor may be the candidate environment (the specific type of stressor, analogous to candidate genes) that is examined.

Many G×E researchers have examined episodic SLEs in keeping with the notion that SLEs are the environmental pathogen most consistently associated with MDE onset (Brown & Harris, 1989; Monroe, 2008), but few researchers have examined characteristics of SLEs that are particularly implicated in the etiology of MDEs. (SLEs are acute, temporary, psychologically threatening experiences that are conceptualized as distinct from chronic stress, which refers to enduring pressures, strains, or quality of life; e.g., Hammen, 2005.) One important characteristic is SLE severity. We refer to SLEs with moderate to severe impact or threat, considering the entire context of the SLE (i.e., long-term contextual threat), as major SLEs and to those with less than moderate impact or threat as minor SLEs, terms used in other stress research (e.g., Monroe & Harkness, 2005). Major SLEs are thought to most increase risk for MDE onset (Brown & Harris, 1978; Kendler, Karkowski, & Prescott, 1998; Monroe, 2008) and may thus be more likely to reveal G×E effects than do minor SLEs.

In contrast to the possibility that major SLEs would not reveal G×E effects if most people became depressed following a major SLE, there is no evidence for such a ceiling effect of major SLEs on depression risk (i.e., even after a major SLE, only a minority of individuals experience an MDE onset; e.g., Kendler et al., 1995). In only one study have researchers examined the influence of SLE severity on the G×E interaction, concluding that the effect was most robust for relatively minor SLEs, in contrast to the authors' own predictions (Kendler, Kuhn, Vittum, Prescott, & Riley, 2005).

Among major SLEs, major interpersonal SLEs (i.e., major events that primarily affect the quality or quantity of one's interpersonal relationships) are a particularly intriguing candidate

environment. Interpersonal SLEs, often representing losses and sometimes representing targeted rejection, may be particularly likely to evoke depression (Brown & Harris, 1978; Hammen, 2005; Slavich, Thornton, Torres, Monroe, & Gotlib, 2009; Tennant, 2002). Numerous other interpersonally relevant findings (Joiner & Timmons, 2009) and the efficacy of interpersonal therapy for treating depression (Beach, Jones, & Franklin, 2009) are consistent with an interpersonal sensitivity in depression.

Furthermore, laboratory-based social stress protocols in which stress responding is differentiated by 5-HTTLPR genotype (Gotlib, Joormann, Minor, & Hallmayer, 2008; Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2012) may derive their stressful quality in part from an interpersonal evaluative component. Indeed, one study showed that only a critical evaluative audience condition (not a supportive evaluative audience condition or a no-audience condition) revealed effects of 5-HTTLPR genotype on stress reactivity (Way & Taylor, 2010a). Finally, G×E research on rhesus macaque infants reared either with peers (a stressor) or with their mothers has provided consistent findings. This consistency may, in part, be due to isolating not only a homogeneous, lab-controlled type of stress but also a potent social stressor. Among the findings most closely related to depression, rearing condition interacted with serotonin transporter genotype to predict both cerebrospinal fluid serotonin metabolite level (Bennett et al., 2002) and higher maternal separation–induced adrenocorticotropic hormone levels (Barr et al., 2004). Despite evidence from independent lines of research for the potential importance of interpersonal stress, to our knowledge, no one has yet examined whether the G×E interaction effect might be present for major interpersonal SLEs but not for major noninterpersonal SLEs.

In addition, in contrast to the focus on SLEs to date, some researchers have suggested that it is important to consider the cumulative nature of long-standing environmental pathogens, such as chronic stress (Moffitt, Caspi, & Rutter, 2005). Among the various forms of chronic stress that can be assessed, several studies have reported specifically that chronic family stress significantly interacts with 5-HTTLPR genotype to predict depressive symptoms in youth and young adults. One report on 346 youth showed a significant G×E interaction, in which greater chronic family stress at age 15 predicted higher levels of depressive symptoms at age 20 among S-carriers but not among their L/L counterparts (Hammen, Brennan, Keenan-Miller, Hazel, & Najman, 2010). Similarly, in a community sample of 200 youth, baseline chronic family stress and 5-HTTLPR genotype produced a significant G×E effect on increases in depressive symptoms during a 6-month prospective period such that greater chronic family stress predicted increasing depressive symptoms in S-carriers but not in L/L youth (Jenness, Hankin, Abela, Young, & Smolen, 2011). However, no one has yet examined whether such an interaction with chronic family stress might predict clinically significant MDE onsets. As such, in addition to episodic SLEs, the present study has considered chronic family stress.

We hypothesized that an interaction would occur between 5-HTTLPR genotype and major SLEs but not minor SLEs, despite one finding to the contrary (Kendler et al., 2005). Among major SLEs, we hypothesized that interpersonal SLEs but not noninterpersonal SLEs would produce a significant G×E effect. Finally, we hypothesized that chronic family stress would also interact with 5-HTTLPR genotype.

Method

Participants

Detailed information regarding recruitment and demographics of the larger Youth Emotion Project (YEP) sample has been reported elsewhere (e.g., Zinbarg et al., 2010). In summary, high school juniors were screened using the Neuroticism scale of the Revised Eysenck Personality Questionnaire (EPQ-R-N; Eysenck, Eysenck, & Barrett, 1985). Those scoring in approximately the top third on this measure were oversampled into the longitudinal sample to increase the number of prospective onsets of emotional disorders. Participants (N = 627) provided informed consent for the longitudinal study and completed the baseline diagnostic and stress interviews described in the Materials and Procedure section. Participants were asked to repeat these interviews annually; five annual interviews (the baseline plus four follow-ups) have been reported here. Beginning in the 6th year of the larger YEP study, participants who were still in contact with the study were invited to provide a DNA sample; 410 participants consented and provided a sample. Ten who had completed at least the baseline interviews and provided a DNA sample were excluded from analyses because of a diagnosis of bipolar disorder (I or II; n = 8), psychotic symptoms (n = 3), or both. The remaining 400 individuals who were included in the study did not differ on demographic variables or EPQ-R-N scores from those who were excluded (see Table 1 for details).

Table 1. Demographic and Genotype Characteristics of Included and Excluded Participants

Characteristic	Participant	
	Included (*n* = 400)	Excluded (*n* = 227)
Female	69.35	68.28
Race and ethnicity		
Asian	4.50	3.96
Black	13.50	12.33
White	48.25	48.02
Hispanic/Latino	14.25	17.18
Pacific Islander	0.75	0.44
Other	5.50	5.29
Multiple	13.25	12.78
Screener risk level (tertile)		
Highest	57.75	60.35
Middle	24.25	21.15
Lowest	18.00	18.50
5-HTTLPR genotype, % (n)		
S/S	19.50 (78)	
S/L	49.50 (198)	
L/L	31.00 (124)	
Age in years at baseline, mean (*SD*)	16.91 (0.38)	16.88 (0.41)
Baseline EPQ-R-N score, mean (*SD*)	11.82 (4.39)	12.01 (4.76)
Hollingshead SES score, mean (*SD*)	48.33 (12.52)	47.62 (13.69)

Note: Data are percentages unless noted otherwise. Individuals from the original Youth Emotion Project sample of 627 who were included in the present analyses did not differ from those who were excluded in gender, $\chi 2(1, N = 627) = 0.06$, $p = .80$, minority racial or ethnic status, $\chi 2(1, N = 627) = 0.00$, $p = .99$, socioeconomic status (SES), $F(1, 611) = 0.42$, $p = .52$ (Hollingshead, 1975), age at baseline, $F(1, 625) = 0.63$, $p = .43$, or score on the Neuroticism scale of the Revised Eysenck Personality Questionnaire (EPQ-R-N), $F(1, 625) = 0.27$, $p = .60$.

Materials and procedure

Assessment of psychopathology We used the nonpatient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 2001) to perform a baseline assessment of lifetime diagnoses of mental disorders. Four subsequent annual follow-up SCID-I/NPs were administered to assess diagnoses of psychopathology occurring during the period since the participant's previous assessment. All interviewers possessed at least a bachelor's degree and had completed an intensive SCID-I/NP administration-and-scoring training program, including demonstrating reliability of diagnoses compared with a set of gold standard ratings. Interviewers were blind to the results of previous assessments and presented cases to a doctoral-level supervisor. MDEs reported here represent clinically significant manifestations. Interrater reliability was assessed for approximately 10% of SCID-I/NPs in the larger study. Across the five assessments, kappa values—adjusted because of departure from equiprobable distributions (i.e., low base rates of diagnoses)—ranged from .82 to .94 (M = .89, SD = .05).

Life stress assessment Chronic and episodic stress during the past year were assessed at the baseline interview using the UCLA Life Stress Interview (LSI; Hammen, 1991; Hammen et al., 1987). The LSI administered at each follow-up interview assessed chronic stress and SLEs occurring in the interim since the previous interview, unless an interview had been missed, in which case only the previous 12 months were assessed. Person-months without LSI information were excluded from the present analyses. In the LSI, chronic stress was measured in 10 life domains: best friend relationship, social circle, romantic relationship, family relationships, academics, work, finances, neighborhood conditions, physical health, and family's health. Ratings for chronic family stress were assigned by the interviewer for each domain on a scale from 1 (best circumstances) to 5 (worst circumstances) in half-point increments. To the extent possible, episodic stressors were excluded from consideration in the evaluation of chronic family stress. Average interrater reliability (intraclass correlation coefficients) for the five time points studied for chronic family stress was a mean of .77 (SD = .07) within site and a mean of .80 (SD = .08) cross-site.

SLEs were assessed throughout the LSI in each of the 10 life domains, with additional SLEs queried at the interview's conclusion. Interviewers gathered information regarding the context, impact, and date of each SLE; this information then was presented to a team of two or more raters who were blind to the participant's diagnoses and reported subjective responses to SLEs. Context-based SLE severity ratings were assigned by the consensus of the independent rating team on a scale ranging from 1 (a nonevent, no significant threat or negative implications) to 5 (a very severe event, maximal negative impact or threat) in half-point increments. Each SLE was assigned a code from a modified list of 77 numeric codes (Paykel & Mangen, 1980) that described the nature of each event (e.g., traffic accident, end of a friendship). Interrater reliability (intraclass correlation coefficients) for SLE severity cross-site for the five interview periods ranged from .69 to .76 (M = .72, SD = .03); due to team rating of SLE severity, no within-site reliabilities are available.

On the basis of an a priori, contextually based decision applied to all previous published LSI analyses in the present sample, we classified events as major SLEs if assigned a severity rating of 2.5 or greater, reflecting events with moderate to severe levels of contextual impact or threat (Adam et al., 2010; Uliaszek et al., 2012; Vrshek-Schallhorn et al., 2013). Events with a severity rating of from 1.5 to 2.0 were classified as minor SLEs. To classify SLEs as interpersonal or

noninterpersonal, two raters with LSI experience (S. Vrshek-Schallhorn and K. Wolitzky-Taylor) assigned a category to each of the 77 Paykel codes. Interpersonal SLEs were defined as those events that in the majority of instances, primarily affect the quality or quantity of the participant's relationships. Agreement was 96% ($\kappa = .92$); three discrepant ratings were resolved by consensus.

To address temporal precedence for SLEs and MDEs (i.e., whether the SLE preceded and potentially triggered the MDE or vice versa), in all instances in which an MDE and an SLE were dated to the same person-month, trained staff examined records to determine the order of occurrence. If the MDE preceded the SLE, or the order was indeterminate, the SLE (but not the MDE or the participant) was excluded from analyses. To determine the influence of excluding SLEs in instances in which the order was indeterminate, we conducted follow-up analyses reincluding these SLEs. The pattern of results did not change (results not presented).

Genotyping After agreeing by phone to provide a DNA sample, participants provided saliva samples using Oragene kits (DNA Genotek, Ottawa, Ontario, Canada) in their homes and mailed them to study offices. Extraction was performed by Kbioscience (Hoddesdon, England). Genotyping of 5-HTTLPR was conducted by the Core Genetics Lab of the University of California, Los Angeles, based on a previously published protocol (Lesch et al., 1996) using modifications described in detail elsewhere (Taylor et al., 2006). Only traditional 5-HTTLPR genotypes have been reported here because of a lack of consensus regarding the single nucleotide polymorphism (SNP) rs25531 (Uher & McGuffin, 2008). Researchers have suggested that this SNP modifies the function of a subset of L alleles (Hu et al., 2005; Wendland, Martin, Kruse, Lesch, & Murphy, 2006). However, several reports have not supported this notion (Martin, Cleak, Willis-Owen, Flint, & Shifman, 2007; Philibert et al., 2008).

Statistical approach

Cox regressions (Cox, 1972) were conducted using person-month data sets.1 MDE onset and offset dates, as well as SLEs, were assigned to the nearest month, with the start of LSI data gathering (1 year prior to the baseline interview date) for each individual marking the beginning of the study period. Individuals experiencing an ongoing MDE at the beginning of the study period were excluded from analyses until the MDE ended; this procedure is consistent with other studies examining dated MDE onsets and SLEs (e.g., Kendler et al., 2005; Kendler, Karkowski, & Prescott, 1999; Kendler, Thornton, & Gardner, 2000). Similarly, after the month in which an individual experienced a new MDE onset, they were excluded from analyses until the MDE ended, at which point the individual reentered analyses. Multiple MDEs with fewer than 2 months of recovery separating episodes were combined into a single, longer episode per Diagnostic and Statistical Manual for Mental Disorders (4th ed., text rev.; American Psychiatric Association, 2000) criteria. The MDE onset variable was coded as 1 (present) in months in which an MDE onset occurred and as 0 (absent) in months in which onsets did not occur.

In our primary analyses, we examined dichotomous occurrences of various types of SLEs rather than dimensional SLE severity for several reasons. Only major (and not minor) SLEs are thought to be significantly associated with MDE onsets, and major SLEs occur infrequently (e.g., in the present data, they occur in less than 5% of months). Our dichotomous but time-specific approach is consistent with a substantial body of previous SLE and depression research (e.g., Kendler et al., 1995; Kendler et al., 1998; Kendler et al., 2000; Kendler, Thornton, & Gardner, 2001). The occurrence of each type of SLE (all major, all minor, etc.) was coded as 0 (absent) or

as 1 (present) for each person-month. The presence of SLEs was lagged to 2 months (e.g., if one occurred in Month 10, it was treated as present for Months 10 and 11), consistent with a previous G×E interaction study that used time-specific analysis (Kendler et al., 2005). We followed this procedure because some evidence has suggested most MDE onsets triggered by an SLE occur within a month of the SLE (Kendler et al., 1995), whereas other evidence has suggested a somewhat longer period is possible (Kendler et al., 1998; Surtees & Wainwright, 1999). To support the primary dichotomous SLE analyses, we also examined dimensional SLE severity secondarily. For these variables, the maximum SLE severity score (1.5–5.0) for each person-month was used, with SLEs lagged to 2 months. Months with no SLEs were coded as 1.0, corresponding to a rating of no threat or impact.

Next, because chronic family stress scores were assigned for each interview period (i.e., ratings did not vary by month), these scores were applied uniformly to all person-months covered by an interview. Dimensional variables (chronic family stress and SLE severity variables) were centered. Genotype was coded as 1 for S-carriers (S/S + S/L) and as 0 for L/L homozygotes. In all models testing a G×E interaction, gender (male = 1, female = 0) was entered as a covariate in a first block (Caspi et al., 2003), genotype and life stress variable or variables were entered in a second block, and the G×E interaction effect was entered in a final block. Hazard ratios (HRs) reported throughout refer to the difference in likelihood of MDE onset associated with a 1-unit increase in the predictor (Singer & Willett, 2003). For all analyses, p values less than or equal to .05 were considered statistically significant. Power to detect a significant G×E interaction effect was estimated to be .775 for a G×E effect size of 4.0 and .589 for a G×E effect size of 3.0 (Demidenko, 2007, 2008).2 In addition to specifying a priori hypotheses, to address multiple testing, we applied false discovery rate adjustments separately to the hypothesized and nonhypothesized primary G×E tests (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001).

Population stratification refers to higher rates of an allele and coincidentally higher rates of disorder in a racial or ethnic subgroup creating a spurious main effect of genotype on risk for disorder. Thus, when significant interactions emerged, we applied a correction similar to those used in other genetic association work (e.g., Wu, DeWan, Hoh, & Wang, 2011). In lieu of an SNP panel to identify ancient geographic ancestry (which is then typically covaried in regressions), we used several self-reported race and ethnicity variables, which other researchers have shown account for nearly all variance identified by such SNP panels (Tang et al., 2005). Specifically, we covaried membership in the sample's largest two racial and ethnic minority groups (Black race and Hispanic ethnicity). Furthermore, to partial out the influence of group membership from an interaction effect (and not only from a main effect of a gene, which is sufficient for case-control genetic association studies), we covaried each of the two-way interactions of Black race and Hispanic ethnicity with S-carrier status and the stressor variable.

Results

Sample demographics and genotype frequencies are presented in Table 1. Zero-order associations of predictors are presented in Table 2. The 400 participants completed a mean of 4.40 (SD = 0.88) of five possible annual diagnostic and life stress assessments, providing 21,340 person-months containing 149 MDE onsets in 100 individuals. These MDEs comprised 56 first onsets, 52 second onsets, and 41 onsets of a third or higher episode number. Genotypes did not depart from the Hardy-Weinberg equilibrium, $\chi 2(1, N = 400) = 0.004$, n.s.

Table 2. Zero-Order Associations as Pearson's rs and Logistic Regression Odds Ratios

Variable	1	2	3	4	5	6	7	8	9	10
Pearson's r										
1. Number of major SLEs (all types)	—									
2. Number of major interpersonal SLEs	.89*	—								
3. Number of major noninterpersonal SLEs	.74*	.35*	—							
4. Number of minor SLEs (all types)	.31*	.29*	.29*	—						
5. Chronic family stress	.39*	.34*	.29*	.13*	—					
6. Number of MDEs in study period	.29*	.28*	.18*	.10*	.22*	—				
Odds ratio										
7. Gender (male = 1, female = 0)	0.92	0.75*	1.14	0.97	0.80	0.71*	—			
8. Black race (yes = 1, no = 0)	1.21*	1.26*	1.33*	0.98	2.24*	1.29	1.13	—		
9. Hispanic ethnicity (yes = 1, no = 0)	1.15*	1.18*	1.23*	1.03	1.59*	0.95	0.52*	1.13	—	
10. *S*-carrier 5-HTTLPR genotype	0.97	0.95	1.00	1.05*	0.86	1.10	1.06	0.41*	1.93*	—

Note: Pearson correlations are presented for associations of continuous variables with other continuous variables. Odds ratios derived from logistic regression are presented for association of any variable with a dichotomous variable. SLE = stressful live event; MDE = major depressive episode.
*$p \leq .05$ (significant one-way associations).

Linear regressions with S-carrier status as a predictor of each life stress variable examined G×E correlations. For these correlations, the number of occurrences of each type of SLE was totaled across the five annual LSIs. Chronic family stress was examined as an average calculated within-person across the 5 years; in contrast, chronic family stress was permitted to vary as a function of interview time point in the G×E analyses. Black race and Hispanic ethnicity were covaried in G×E correlation analyses to prevent population stratification. S-carrier status did not significantly predict any of the stress variables examined, all βs = −0.025 to 0.014, all ps ≥ .620, with the exception of the total number of minor SLEs, $\beta = 0.123$, $p = .015$. S-carriers had more minor SLEs than did their L/L counterparts.

Moderation of SLE effect by 5-HTTLPR

Selected regression results are presented in Table 3; additional results are presented throughout the text. There was a significant interaction of major SLEs and 5-HTTLPR such that S-carriers were at significantly greater risk for MDE onset than were L/L homozygous individuals, given the occurrence of any major SLE. Minor SLEs did not significantly interact with genotype. When all major SLEs were separated into interpersonal and noninterpersonal major SLEs and these were entered into a single model with their respective G×E interaction effects, interpersonal SLEs interacted significantly with S-carrier status, but noninterpersonal SLEs did not interact significantly (see Fig. 1a for model-estimated HRs).3

Table 3. Select Cox Regression Results

Model/Variable	Model −2 log likelihood	χ2(df) change from previous step	β	SE(β)	Hazard ratio	95% Confidence level Lower	95% Confidence level Upper	p	FDR adjusted p
All major SLEs × 5-HTTLPR									
Main effects step	2,594.40	27.17(2)***							
Major SLEs			1.059	0.190	2.884	1.988	4.186	.000***	
5-HTTLPR S-carrier			0.261	0.187	1.299	0.901	1.872	.161	
Interaction step	2,589.96	4.44(1)*							
Major SLEs†			0.312	0.444	1.367	0.572	3.265	.482	
5-HTTLPR S-carrier†			0.045	0.207	1.046	0.697	1.570	.828	
Major SLEs × S-carrier			0.974	0.492	2.649	1.009	6.950	.048*	
Interpersonal vs. noninterpersonal major SLEs (combined dichotomous SLE model)									
Main effects step	2,595.19	26.37(3)***							
Noninterpersonal major SLEs			0.837	0.268	2.309	1.366	3.903	.002**	
Interpersonal major SLEs			0.960	0.226	2.611	1.677	4.063	.000***	
5-HTTLPR S-carrier			0.264	0.187	1.302	0.903	1.877	.157	
Interaction step	2,581.11	14.08(2)***							
Noninterpersonal major SLEs†			1.219	0.480	3.383	1.319	8.676	.011*	
Interpersonal major SLEs†			−1.318	1.016	0.268	0.037	1.962	.195	
5-HTTLPR S-carrier†			0.051	0.205	1.052	0.704	1.573	.803	
Noninterpersonal major SLEs × S-carrier			−0.518	0.578	0.596	0.192	1.849	.370	.733
Interpersonal major SLEs × S-carrier			2.704	1.044	14.946	1.933	115.573	.010**	.020*
Interpersonal vs. noninterpersonal dimensional maximum monthly SLE severity									
Main effects step	2,584.36	37.11 (3)***							
Noninterpersonal SLE severity			0.410	0.133	1.506	1.161	1.953	.002**	
Interpersonal SLE severity			0.610	0.112	1.840	1.477	2.292	.000***	
5-HTTLPR S-carrier			0.276	0.187	1.318	0.913	1.901	.140	
Interaction step	2,571.97	12.39 (2)**							
Noninterpersonal SLE severity†			0.719	0.187	2.052	1.421	2.963	.000***	
Interpersonal SLE severity†			−0.107	0.294	0.899	0.506	1.598	.716	
5-HTTLPR S-carrier†			0.173	0.201	1.189	0.802	1.763	.390	
Noninterpersonal SLE severity × S-carrier			−0.475	0.258	0.622	0.375	1.032	.066	
Interpersonal SLE severity × S-carrier			0.931	0.318	2.538	1.360	4.736	.003**	
All minor SLEs × 5-HTTLPR									
Main effects step	2,619.97	1.59(2)							
Minor SLEs			−0.006	0.174	0.994	0.707	1.397	.971	
5-HTTLPR S-carrier			0.231	0.186	1.260	0.874	1.816	.215	
Interaction step	2,619.85	0.12(1)							
Minor SLEs†			0.094	0.340	1.098	0.564	2.138	.783	
5-HTTLPR S-carrier†			0.275	0.228	1.317	0.842	2.061	.228	
Minor SLEs × S-carrier			−0.135	0.395	0.874	0.403	1.896	.733	.733
Chronic family stress × 5-HTTLPR									
Main effects step	2,551.62	69.37(2)***							
Chronic family stress			0.881	0.103	2.414	1.972	2.955	.000***	
5-HTTLPR S-carrier			0.327	0.187	1.387	0.961	2.003	.081	
Interaction step	2,546.88	4.74(1)*							
Chronic family stress†			0.536	0.195	1.710	1.167	2.505	.006**	
5-HTTLPR S-carrier†			0.122	0.203	1.130	0.759	1.683	.547	
Chronic family stress × S-carrier			0.497	0.232	1.643	1.044	2.587	.032*	.032*

Note: Gender (not shown) was added as a covariate in a first step of all models. Main effects of stress and genotype were added in the second step (main effects step). As such, in the third step (interaction step), stress variables and genotype characterize simple main effects denoted with † (i.e., for reference groups—stress variables refers to stress only for L/L and genotype refers to S-carriers not under stress for models on stressful life events, SLEs, or in dimensional analyses with centered stress variables, at the mean of stress). False discovery rate (FDR) adjustment was conducted separately for hypothesized (i.e., major interpersonal SLEs and chronic family stress) and nonhypothesized (i.e., major noninterpersonal SLEs and minor SLEs) gene-environment interaction effects.
*p ≤ .05. **p ≤ .01. ***p ≤ .001. Effect sizes with p values ≤ .05 are considered significant.

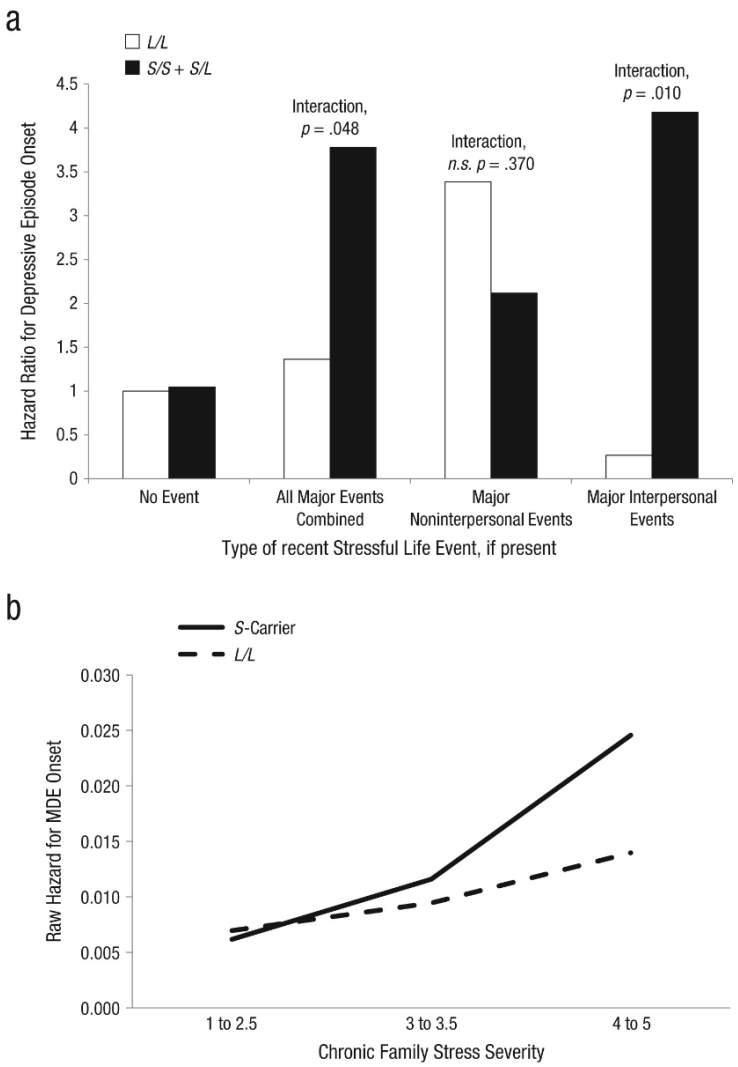

Fig. 1. Model-estimated hazard ratios for (a) major depressive episode (MDE) onset, in the presence or absence of several types of major severity stressful life events (SLEs) within the previous 2 months, separated by 5-HTTLPR genotype. Hazard ratios for major noninterpersonal and major interpersonal SLEs were derived from the combined dichotomous SLE model for these variables reported in Table 3. Standard errors and confidence intervals for each term in the models are presented in Table 3. Raw hazard for (b) MDE onset (number of onsets divided by number of person-months available under a given set of conditions) by severity of chronic family stress and 5-HTTLPR genotype.

We conducted several follow-up tests on the G×E interaction with major interpersonal SLEs. First, to reduce the possibility of population stratification, we covaried Black race, Hispanic ethnicity, and their two-way interactions with S-carrier status and major interpersonal SLEs. The interaction remained significant, $\beta = 2.552$, $SE(\beta) = 1.053$, HR = 12.837, 95% confidence interval = [1.629, 101.171], $p = .015$. Thus, this G×E effect cannot be due to population stratification arising from either of the two largest racial/ethnic minority groups in the sample. Next, a secondary model examining dimensional SLE severity was conducted (see Table 3). Supporting the dichotomous results, a significant G×E interaction of interpersonal SLE severity and S-carrier status emerged, HR = 2.538, $p = .003$, such that those with the S-allele were at significantly

enhanced risk for MDE onsets as SLE severity increased, compared with their similarly stressed L/L counterparts. In addition, the interaction for noninterpersonal SLE severity approached significance in the opposite direction, HR = 0.622, p = .066. This result suggests that when interpersonal SLE severity is accounted for, S-carriers experiencing increasing noninterpersonal SLE severity are slightly (but not significantly) more resilient against MDE onsets than their L/L counterparts under similar stress.

Furthermore, the simple main effects of stress were revealing: L/L individuals were at significant risk for MDE onsets in the context of increasing noninterpersonal SLE severity, HR = 2.052, p < .001, but not in the context of increasing interpersonal SLE severity, HR = 0.899, p = .716. Taken together, this pattern of results suggests that when both types of SLEs are accounted for, genotype may differentiate the type of SLE to which an individual is most sensitive.

Moderation of chronic family stress by 5-HTTLPR

Chronic family stress produced the hypothesized G×E interaction with 5-HTTLPR genotype (see Table 3 and see Fig. 1b for raw hazard for MDE onset). Specifically, although chronic family stress significantly predicted MDE onsets in L/L individuals (simple main effect of family stress in L/Ls: HR = 1.710, p = .006), it predicted MDE onsets in S-carriers with significantly greater strength (G×E effect: HR = 1.643, p = .032). This interaction remained significant after covarying Black race, Hispanic ethnicity, and their two-way interactions with chronic family stress and S-carrier status, $\beta = 0.559$, $SE(\beta) = 0.248$, HR = 1.749, 95% confidence interval = [1.077, 2.842], p = .024.

False discovery rate adjustment

False discovery rate adjustment (Benjamini & Hochberg, 1995) for multiple tests was applied to p values obtained for G×E interactions separately for hypothesized interactions (i.e., major interpersonal SLEs and chronic family stress) and nonhypothesized interactions (i.e., major noninterpersonal SLEs and minor SLEs; see Table 3). After adjustment, the p values for both the major interpersonal SLE G×E interaction (p = .040) and the chronic family stress G×E interaction (p = .032) remained significant.

Discussion

In the present study, we investigated an interaction effect of the serotonin transporter–linked polymorphic region, 5-HTTLPR, and several forms of stress on MDE onsets in 400 individuals during late adolescence to young adulthood, using clinical diagnostic interviews and objectively rated stress interviews. Some researchers have suggested that such stress interviews will produce more valid G×E research (Monroe & Reid, 2008), and other researchers have indeed shown that interviews and other objective measures have produced more robust G×E findings than have questionnaire measures (Karg et al., 2011; Uher & McGuffin, 2010). Although several studies have previously examined an interpersonal form of chronic stress, specifically chronic family stress, the current study is the first to examine major interpersonal and noninterpersonal episodic SLEs separately and to show that among major SLEs, only major interpersonal SLEs significantly contributed to a G×E interaction with 5-HTTLPR.

Importance of interpersonal SLEs

There are several potential implications of the interpersonal SLE G×E finding, pending replication by other studies. First, within the context of G×E interaction research on depression specifically, this finding suggests that distinguishing between major interpersonal and noninterpersonal SLEs may lead to enhanced effect sizes and more consistent results, particularly if interview measures of life stress are employed. More broadly, the finding highlights the potential benefit of examining empirically or theoretically indicated candidate stressors in G×E interaction research. Second, the apparent importance of interpersonal SLEs for detecting a significant G×E interaction effect raises a question of whether the serotonin system is preferentially sensitive to social compared with nonsocial stimuli. There is indeed evidence that the serotonin system mediates the effects of social or interpersonal experiences on a range of health outcomes (for a review, see Way & Taylor, 2010b). However, it is also implicated in an array of other functions, leading some researchers to conclude that its overarching function is to mediate constraint (e.g., Spoont, 1992). Thus, preferential sensitivity of the serotonin system to social conditions may be due to its associations with other neural systems that are particularly sensitive to social threat. Such systems might include the hypothalamic-pituitary-adrenal axis (Dickerson & Kemeny, 2004; Doane & Adam, 2010) and the oxytocin system (e.g., Jørgensen, Riis, Knigge, Kjaer, & Warberg, 2003).

Influence of SLE severity

Major SLEs, particularly interpersonal ones, but not minor SLEs produced a significant G×E interaction. In this regard, our results concerning the level of SLE severity that produces a significant interaction diverged from those of Kendler et al. (2005), possibly because of important differences between the two samples. The present sample is younger and would be expected to have a higher proportion of first-onset cases of depression than would the Kendler et al. sample. There is evidence that with successive episodes of depression, as individuals putatively become more sensitive to stress, they are paradoxically less often observed to succumb to recurrences due to major SLEs, which occur relatively infrequently (Kendler et al., 2000, 2001). Instead, they may succumb to recurrences after minor severity SLEs (Stroud, Davila, Hammen, & Vrshek-Schallhorn, 2011), supporting a stress sensitization model (Monroe & Harkness, 2005) of Post's (1992) kindling hypothesis. It may be that in relatively older samples, such as that of Kendler et al., with a higher proportion of recurrences, the peak of the G×E interaction shifts from more major SLEs toward more minor SLEs.

Findings for chronic family stress

We also reported a significant association of chronic family stress and 5-HTTLPR, which was consistent with two prior reports that obtained significant chronic family stress G×E interactions with 5-HTTLPR genotype on depressive symptoms (Hammen et al., 2010; Jenness et al., 2011). We extend these earlier findings to the prediction of clinically significant MDEs. Few G×E researchers have examined objectively rated enduring stressors, such as chronic family stress, and the present results suggest that examining chronic family stress may be a promising approach for future work.

Limitations

Although this study has several notable strengths, including a prospective design using repeated measures, clinical diagnostic interviews, objective stress interviews, and a time-specific statistical approach, it also has limitations. First, the present sample size of 400 participants is modest relative to certain other genetic studies; however, this sample is larger than the median sample size of 345 participants per study from 103 G×E publications reported in one review (Duncan & Keller, 2011). Furthermore, unlike most such studies, the present study included repeated measures assessments of both stress and depression. Second, the sample is also racially and ethnically diverse, rather than homogeneous, which might have resulted in population stratification. Beyond what we were able to address in follow-up analyses, population stratification could potentially arise from latent ancient geographic ancestry groups. Moreover, the G×E interaction may be stronger in certain racial or ethnic groups than in others, just as it may be stronger in males compared with females. Unfortunately, the present sample is underpowered to compare G×E effect magnitude between subgroups (i.e., to test three-way interactions).

Finally, in contrast to our hypothesis that interpersonal SLEs are important to the G×E interaction because depression is characterized by interpersonal sensitivity, it is possible that interpersonal SLEs appear important only for obtaining the G×E interaction due to certain characteristics of this sample. These characteristics could include the predominance of female participants, a large proportion of participants with high levels of neuroticism, and the developmental stage of participants (i.e., the transition to adulthood). However, regarding the larger YEP recruitment strategy of oversampling participants with high levels of neuroticism, a simulation study demonstrated that such oversampling (and corresponding higher rate of prospective disorder onsets) does not bias regression effect size estimates but does ameliorate other problems that occur when predicting to a low number of disorder onsets (Hauner, Revelle, & Zinbarg, 2013).

Conclusions

The present study indicates a significant interaction between major SLEs and having one or two S alleles of the serotonin transporter–linked polymorphic region, 5-HTTLPR, on risk for MDE onset. This result was accounted for by the interaction of 5-HTTLPR and major interpersonal events. Evidence also supports a G×E interaction of chronic family stress with 5-HTTLPR genotype, consistent with previous reports. These results emphasize the importance of the careful measurement and selection of candidate environments (analogous to candidate genes) first for G×E research on depression and perhaps also for other forms of psychopathology.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Notes

1. Although person-months are technically nonindependent of one another, Allison (1982) demonstrated that an assumption of independence is reasonable because the estimated standard errors closely approximate the true standard errors.
2. For both power estimations, alpha was set to .05, sample size was set to 400, and the option to examine two binary variables, x and z, with their interaction, x*z, was selected. The likelihood that x, genotype, was 1, Prx = Pr(x = 1), was set to .7, with a main effect of genotype (x) on depression (y), odds ratio (OR) = 1.1. The likelihood that z, the environment or stress variable, was 1, Prz = Pr(z = 1), was set to .5 for the likelihood of exposure to major SLEs during a duration of several years, with a main effect of stress (z) on depression (y), OR = 4.0. The G×E correlation, ORxz, was set to 1.0 (none), and disease prevalence rate was set to .20.
3. This simultaneous test of the G×E effect for major noninterpersonal SLEs and major interpersonal SLEs demonstrates that the major interpersonal SLE G×E effect possesses significant unique variance beyond the major noninterpersonal SLE G×E effect, which neither possesses significant unique variance in this model nor reaches significance on its own (model not reported). That is, the major interpersonal SLE G×E effect significantly predicts over and above the noninterpersonal SLE G×E effect. However, this test is not the same as testing for a significant difference between the two G×E effects. Unfortunately, the conclusive test for this difference, given by a Gene × Major SLE × Event Type (interpersonal vs. noninterpersonal) three-way interaction, is impossible to conduct in a person-month model. The event type variable can be specified only for months in which an event of interest (a major SLE) occurred. All months without such events would be missing this specifier, and Cox regression would omit those months from the analysis, leaving in the model only months in which major SLEs occurred. The closest approximation is to isolate months in which a major SLE occurred and test for a two-way Gene × Event Type (major interpersonal SLE vs. major noninterpersonal SLE) interaction. This test provided a significant result, $\beta = 2.524$, $SE(\beta) = 1.161$, HR = 12.484, 95% confidence interval = [1.283, 121.443], $p = .030$, consistent with the notion that the G×E effect for major interpersonal SLEs is indeed significantly larger than the G×E effect for major noninterpersonal SLEs. However, this is still not a strict test of whether one G×E effect is significantly larger than is the other because months without any major events are necessarily omitted.

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