Early Family Environment, Current Adversity, the Serotonin Transporter Promoter Polymorphism, and Depressive Symptomatology

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Background: *Mixed evidence has suggested that homozygous carriers of the short allele (s/s) of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) may be at increased risk for depression, if they have also been exposed to early or current adversity/stress. We address this debate by examining the relation of a stressful early family environment, recent adversity/stress, and the 5-HTTLPR to depressive symptomatology in a normal sample.*

Methods: *A nonclinical sample of 118 young adult men and women completed assessments of early family environment, recent stressful events, psychosocial resources, and psychological distress, including depressive symptomatology. The 5-HTTLPR was genotyped using a standard protocol with DNA extracted from oral fluid.*

Results: *A stressful early family environment was significantly related to depressive symptomatology. In addition, gene-by-environment (G×E) interactions were observed between the 5-HTTLPR and both early family environment and current adversity/stress. Individuals homozygous for the short allele had greater depressive symptomatology if they had experienced early or recent adversity but significantly less depressive symptomatology if they reported a supportive early environment or recent positive experiences, compared with participants with the s/l or l/l genotype.*

Conclusions: *Early or current environment, in conjunction with the serotonin transporter polymorphism, predicts depressive symptomatology.*

Key Words: Serotonin transporter, depression, stress, early family environment, 5-HTTLPR, gene/environment interaction

Recent investigations have found conflicting evidence concerning the relationship between a polymorphism in the promoter of the serotonin transporter gene (SLC6A4) and risk for depression. This polymorphism (5-HTTLPR) consists of a 20–23 base pair sequence that is repeated either 14 (short) or 16 (long) times, with the presence of the short (s) allele putatively conferring greater risk for depression, particularly for people who have experienced stress recently or early in life. Caspi et al (2003) found that childhood maltreatment predicted adult diagnosed depression among individuals carrying at least one copy of the s allele. They also found that people with one or more s alleles who were exposed to adult stressful life events were more likely to develop depression than those homozygous for the long allele. Partial to full replications of this pattern have been reported by Eley et al (2004), Grabe et al (2005), Kaufman et al (2004), Kendler et al (2005), and Wilhelm et al (2006). However, Surtees et al (2005) reported that adversity in childhood and adulthood was associated with major depressive disorder, defined by DSM-IV diagnostic criteria, but these relations did not interact with the 5-HTTLPR genotype. Gillespie et al (2005) also reported no replication of the pattern identified by Caspi et al (2003).

We report on research designed to replicate the gene-by-environment (G×E) interactions between the 5-HTTLPR and the stressful early family environment and between the 5-HTTLPR and current stress/adversity on depressive symptomatology, as assessed by the Beck Depression Inventory (BDI; Beck et al 1961), in a nonclinical sample of young adult men and women participating in a study of stress processes. In addition, we assessed whether depressive symptomatology is modulated by psychosocial resources, including personal mastery, dispositional optimism, self-esteem, and social support. Previous investigations have found such resources to buffer people against psychological distress (Taylor et al 2003).

Methods and Materials

Participants

After obtaining approval from the Institutional Review Board from the University of California, Los Angeles, members of the UCLA campus community responded to an advertisement offering $60 for participation. Prospective participants with the following conditions were excluded: serious physical or mental health problems; current treatment from a mental health professional; diagnosis of PTSD; and current use of mental health-related medication (e.g., selective serotonin reuptake inhibitors).

A sample of 118 participants (51 men and 67 women) participated. All were affiliated with UCLA as either employees, students, or both. Participants ranged in age from 18 to 29 years, with a median age of 20.6 years.

Participants reported to a computer laboratory where they completed informed consent forms and individual difference measures of psychosocial resources and psychological distress. Psychosocial resource measures included the Life Orientation Test, a measure of dispositional optimism (LOT; Scheier and Carver 1985), the Rosenberg Self-Esteem scale (Rosenberg 1965), the Pearlin Mastery Scale (Pearlin and Schooler 1978), and measures of social support (Schuster et al 1990). Measures of psychological distress included the BDI (Beck et al 1961), the trait anxiety scale of the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al 1970), and the neuroticism scale of the Big Five International Personality Scale (Goldberg 1999).

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Deoxyribonucleic acid (DNA) was obtained using the Orasure oral specimen collection device (Orasure Technologies Inc., Bethlehem, Pennsylvania). Samples were immediately placed on ice in a cooler and transferred within the next few minutes to a freezer. The samples were stored at –20°C for 12–18 months before being extracted using the Puregene DNA purification kit (Gentra Systems, Inc., Minneapolis, Minnesota).

Assessment of Early Family Environment and Current Stress

Early life stress was assessed via the Risky Families questionnaire. This questionnaire (Taylor et al 2004) was adapted from an instrument originally developed by Felitti et al (1998) to assess the relation of family stress to mental and physical health outcomes in adulthood. In previous research, we validated this questionnaire against clinical interviews conducted and coded by trained clinical interviewers; the dual assessments (questionnaire and interview) demonstrated high agreement and reliability (Taylor et al 2004).[1] The scale has been reliably tied to adverse mental and physical health outcomes, including diagnosed depression and depressive symptomatology (Felitti et al 1998; Lehman et al 2005; Taylor et al 2004).

Participants rated aspects of their early family environment on 4-point scales ranging from 1 (rarely or none of the time) to 4 (most or all of the time), with items including whether the individual felt loved and cared for; was insulted, put down, sworn at, or made to feel threatened; was shown physical affection; was pushed, grabbed, shoved, or slapped; was verbally abused; was physically abused; observed quarreling or shouting between parents; observed violence or aggression between family members; lived with a substance abuser; lived in a well-organized, well-managed household; and whether family members knew what the child was doing. Positively worded items were reverse-coded. Cronbach's alpha was .86. Average scores ranged from 1.00 to 3.54, with higher values representing a riskier family environment.

To assess current adversity/stress, participants were asked to list up to 10 major life events that had occurred in the past 6 months and rate their impact on a 7-point scale with labeled endpoints ranging from –3 "very negative" to +3 "very positive." A total score was calculated for each subject across all events by summing the participant's ratings. Average total scores ranged from –21 to 13, with lower values representing more negative events.

Genotyping

The 5-HTTLPR was identified using a protocol modified from Lesch et al (1996). Briefly, the forward primer was 5′-GGC GTT GCC GCT CTG AAT GC-3′ (labeled with 6-carboxyfluorescein fluorophore), and the reverse primer was 5′-GAG GGA CTG AGC TGG ACA ACC AC-3′, which yielded 484-bp (short) and 527-bp (long) fragments. Polymerase chain reaction (PCR) was performed in a total volume of 25 μL, containing 100 ng of DNA; 160 nM of each primer; 1 mM Tris-HCL (pH 8.3); 5 mM KCl; 1.5 mM $MgCl_2$; 2% DMSO (v/v); 2.5 U Amplitaq Gold DNA polymerase (Applied Biosystems, Foster City, California); 200 μM of dATP, dCTP, and dTTP; 100 μM of dGTP; and 7-deaza-2′-dGTP. Cycling conditions consisted of 1) an initial 5 min denaturation at 94°C; (2) 8 cycles with denaturation for 30 sec at 94°C, varied annealing temperatures consisting of 30 sec at 66°C (2 cycles), then 65°C (3 cycles), then 64°C (3 cycles), followed by hybridization for 1 min at 72°C; (3) 35 cycles with an annealing temperature of 63°C and the same denaturation and hybridization parameters; and (4) a final extension for 20 min at 72°C. The PCR products were electrophoresed on an ABI 3700 DNA analyzer (Applied Biosystems) with a Mapmaker size standard (Bioventures, Murfreesboro, Tennessee). Data collection and analysis used GeneScan and Genotyper software (Applied Biosystems).

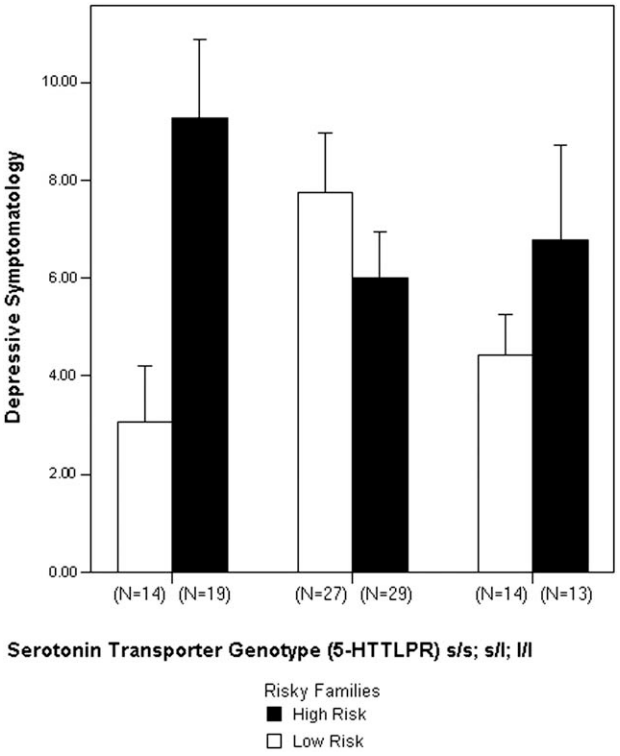

Figure 1. Relationship of risky family environment and 5-HTTLPR genotype to depressive symptomatology.

Results

Participants were divided according to genotype (s/s 27%, s/l 48%, l/l 25%), which conformed to Hardy–Weinberg equilibrium. An analysis of variance with genotype group (s/s, s/l, and l/l) and risky families (split at median of 2.00) as the two independent variables was conducted on depressive symptomatology, as assessed by the BDI. Results revealed no main effect for genotype but a significant main effect for risky families, such that participants from a risky family environment had higher levels of depressive symptomatology, $F(1, 110) = 4.07$, $p < .046$, replicating findings from our previous investigations.

In addition, there was a significant interaction between 5-HTTLPR and early family environment, $F(2, 110) = 4.99$, $p < .008$. As Figure 1 shows, s/s participants were at greater risk for depressive symptomatology if they came from an early adverse environment and at reduced risk for depressive symptomatology if they came from an early supportive environment ($t(31) = 2.932$, $p < .006$), relative to participants with the s/l ($t(54) = 1.131$, $p < .263$) and l/l variants ($t(25) = 1.128$, $p < .270$); that is, family environment did not significantly moderate risk for depressive symptomatology among s/l or l/l individuals. In addi-

[1]The clinical interviews revealed that exposure to family conflict, especially fighting between parents, was a common family stressor. This stressor did not appear in the original Felitti et al (1998) questionnaire, and so items addressing this dimension of family life were added to the assessment.

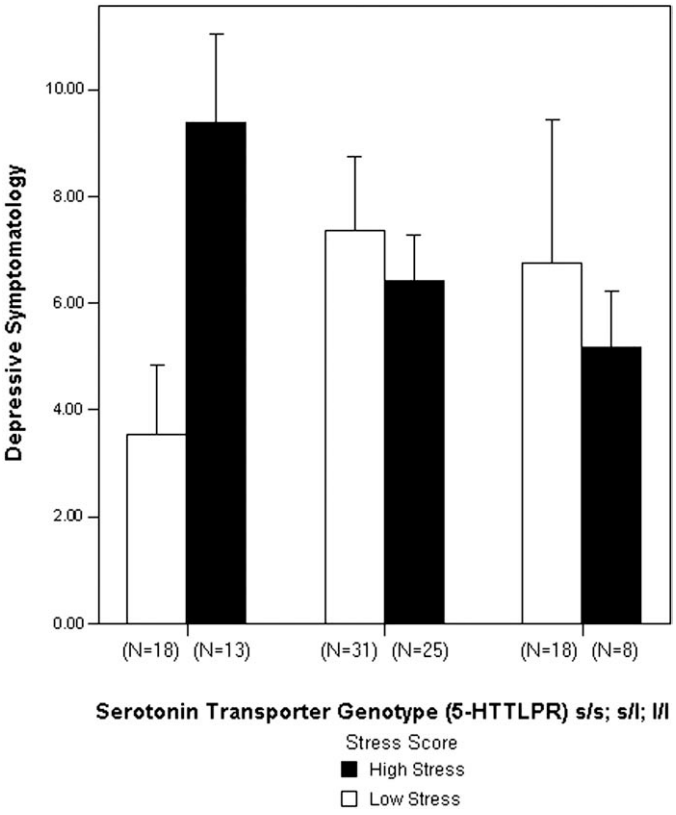

Figure 2. Relationship of current stress and 5-HTTLPR genotype to depressive symptomatology.

tion, individual comparison tests within the supportive family environment groups revealed that the apparent protective effect of the s/s genotype is significant (comparing s/s versus combined s/l and l/l groups within supportive families $t(60) = 2.049$), $p < .045$). Comparisons of the harsh family environment groups revealed a marginally significant difference between the s/s genotype and the combined s/l and l/l groups ($t(66) = 1.696$, $p < .095$). We repeated the analyses with scores on the Spielberger et al (1970) state-trait anxiety measure as the dependent variable; there were no main effects for risky families or genotype and no interaction (all ps $> .10$). No psychological resource measures showed this distinctive interaction either, and no psychosocial resources significantly moderated the interaction.

An analysis of variance with genotype (s/s, s/l, l/l) and recent adversity/stress (split at median of –1.00) as the two independent variables was conducted on the BDI scores. Results revealed no main effect of stress or genotype. However, there was a significant interaction that mirrors the results for early family environment, $F(2, 107) = 8.88$, $p < 0.024$;[2] specifically, as Figure 2 shows, participants with the s/s genotype were at greater risk for depressive symptomatology if they had experienced more negative events during the previous 6 months and at lesser risk for depressive symptomatology if they had experienced more positive events ($t(29) = 2.596$, $p < .015$), relative to those with the s/l ($t(54) = .603$, $p < .549$) or the l/l variant ($t(24) = .670$, $p < .509$) genotype (see Figure 2). In addition, individual comparison tests revealed that the apparent protective effect of the s/s genotype in low stress environments is significant (comparing s/s versus combined s/l and l/l variants in low stress condition $t[68] = 2.179$, $p < .033$). Comparisons of the high-stress environment groups revealed a marginally significant difference between the s/s genotype and the combined s/l and l/l groups ($t[48] = 1.745$, $p < .087$). Recent adversity/stress was not significantly correlated with early risky family environment ($r = 0.23$, $p < .22$), indicating that these two sets of analyses are largely independent of each other. We repeated these analyses with the Spielberger et al (1970) anxiety measure as the dependent variable, and there were no significant effects (all ps $> .10$).

We examined whether there were differences in these patterns as a function of gender and ethnicity. Men and women both showed this interactive pattern, although the effects are significant only for women because of the reduced sample sizes. Two large ethnic subgroups comprised approximately two thirds of the sample, specifically Asian-Americans ($n = 45$) and European-Americans ($n = 40$). There were no significant differences between these two groups on risky family scores, current stress, or depressive symptomatology. However, there were significant ethnic differences in allelic variation of the serotonin transporter gene, such that Asian-Americans were overrepresented in the s/s category and European-Americans were overrepresented in the l/l category, $X^2(2) = 13.163$, $p = 0.005$. To ensure that the G×E interaction between 5-HTTLPR and early family environment was not explained by ethnicity, we compared the depressive symptomatology of Asian versus Non-Asian s/s participants from risky (Asian = 10.10; Non-Asian = 8.88) versus non-risky (Asian = 3.88; Non-Asian = 2.40) early environments. As these means suggest, the difference in depressive symptoms as a function of risky family background was present for both ethnic groups at approximately the same magnitude and did not differ between the two groups ($p = 0.958$). To ensure that the G×E interaction between 5-HTTLPR and current stress was not explained by ethnicity, we compared the depressive symptomatology of Asian versus Non-Asian s/s participants with high (Asian = 10.50; Non-Asian = 8.00) versus low (Asian = 3.88; Non-Asian = 3.80) current stress scores. As these means indicate, the difference in depressive symptoms as a function of current stress was present for both Asians and Non-Asians at approximately the same magnitude and did not differ between the two groups ($p = .662$).

Discussion

This investigation identified a significant G×E interaction between a stressful early family environment and the 5-HTTLPR on depressive symptomatology. A similar significant interaction was found between current adversity and the 5-HTTLPR on depressive symptomatology. The specific form of these G×E interactions indicates that the s/s genotype of the 5-HTTLPR appears to be protective against depressive symptomatology in a supportive early or current environment but enhances the risk for depressive symptomatology in a high-stress early or current environment. The pattern was distinctive to depression, as opposed to other forms of psychological distress. Specifically, anxiety as assessed by the Spielberger et al (1970) anxiety measure did not show these same interactions. The fact that the s/s genotype is implicated in depression but not anxiety or other assessments of psychological distress is consistent with Kendler et al's (2005) findings. In addition, the interactions were not significantly modulated by psychosocial resources, including optimism, self-esteem, personal mastery, or social support. An early stressful environment by itself predicted depressive symptomatology, consistent with previous investigations (Lehman

[2]Degrees of freedom very slightly due to missing data; three participants reported no major life events during the previous 6 months.

et al 2005; Taylor et al 2004). Neither current adversity/stress nor 5-HTTLPR genotype alone predicted depressive symptomatology. Overall, these patterns are notable not only for demonstrating a true crossover interaction between adversity and the 5-HTTLPR genotype, but also because they occurred in families in which the degree of adversity was fairly mild, consisting of some conflict, moderate household chaos, and/or cold, unaffectionate and distant behaviors. No instance of physical or sexual abuse was identified, for example.

Inconsistencies among previous efforts to demonstrate G×E interactions between an early or current stressful environment and the 5-HTTLPR on risk for depression or depressive symptomatology may be attributable to several factors. First, the interaction appears to implicate only those with the s/s and not the s/l genotype. Thus, studies in which s/s and s/l participants are grouped together could reduce or obscure the interaction.

Second, studies that use a dependent variable with a restricted range (such as diagnosed depression), rather than a more continuous variable (such as depressive symptomatology), would identify only the fact that the s/s genotype in conjunction with stress enhances risk for depression; depending on the specific statistical techniques used, it would not necessarily identify the protective effects of the s/s genotype in the context of a supportive or low-stress environment. Essentially, then, the statistical test on a dependent variable with a restricted range would test only half of the interaction. Moreover, if the sample is a normal sample that includes lots of supportive families, then the baserate for s/s variant individuals with diagnosed depression would include two contributing factors that could potentially offset each other; that is, the number of cases demonstrating the protective effect of the s/s variant in a low-stress environment could offset the number of cases, demonstrating the enhanced risk of diagnosed depression among s/s variant participants in high-stress environments.

A third factor contributing to irregular results relating stress and 5-HTTLPR genotype to depression or depressive symptomatology concerns whether the predictor variables have a restricted or continuous range. The protective effects of the s/s genotype are most evident in people who report a supportive early environment or recently experienced positive life events. If only predictors associated with risk are included (i.e., only stressors in early childhood or adulthood and not beneficial experiences), then the strength of the interaction will be underestimated.

Fourth, in the current study, the assessment of early family environment was based on a standardized measure that has been found in previous studies to predict both depressive symptomatology and diagnosed depression (Felitti et al 1998; Lehman et al 2005; Taylor et al 2004). Moreover, it assesses a chronically stressful early environment, which may be more likely to reveal a G×E interaction than exposure to discrete stressful events, a measure that has been used in some previous studies (e.g., Caspi et al 2003; Surtees et al 2006).

An additional factor that may have accounted for the significant results of this investigation was the relative youthfulness of the sample. Previous investigations (Surtees et al 2006; Gillespie et al 2005) have speculated that gene-environment interactions may be more evident in younger than in older samples. Moreover, because our young adult participants had lived at home with their families until relatively recently, the assessment of early family environment may also have been more reliable, relative to reconstructions made by older adults.

A few prior investigations present graphic data suggestive of the same cross-over interaction we report, but they do not comment on the protective effects of the s/s in low-stress environments (e.g., Eley et al 2004; Wilhelm et al 2006). These articles, along with the statistically significant protective effect in the current study, suggest that this crossover interaction is reliable. The protective effects of the s/s genotype in the context of a supportive family environment and the reversal in the context of an adverse early family environment also mirror findings from animal research. For example, Suomi (1999) reported that temperamentally impulsive rhesus monkeys raised in the tumultuous environment of the peer group show adverse psychosocial outcomes, including poor social skills, labile emotionality, and low position in the dominance hierarchy, whereas those raised by their mothers achieve greater than average psychosocial outcomes, often rising to the top of the dominance hierarchy. The crossover G×E interaction reported here may reflect similar dynamics.

This crossover interaction has potentially important implications for the study of the 5-HTTLPR gene because it suggests that the s/s genotype is not a risk factor for depression so much as it reflects a sensitivity to environmental influence; in benign environments, that sensitivity assumes a protective form, and in harsh environments, it confers risk for depression. As the 5-HTTLPR polymorphism lies within the upstream regulatory region of the serotonin transporter gene, it may be poised to modulate transporter expression in response to environmental factors. For example, in vitro, cells (B-lymphoblastoid) homozygous for the short allele have a greater increase in transporter expression in response to glucocorticoid exposure than cells homozygous for the long allele (Glatz et al 2003).

These findings may have implications for the search for other "disease" genes or "psychopathology" genes as well, in that a narrow search for a risk factor may obscure the broader behavioral implications of a genetic variant. This point also underscores the fact that, without considering the full range of predictor and outcome variables, the multiple forms and meaning of phenotypes associated with a particular genotype may be obscured (c.f., Manuck et al 2004).

A complicating factor in the interpretation of these results is the ethnic difference in allelic distribution in the serotonin transporter genotype (Gelernter et al 1997). Although the pattern of increased depressive symptomatology in a stressful early or current environment and lower levels of depressive symptomatology in supportive or less stressful environments held for both Asians and Non-Asians with the s/s genotype, it is not entirely clear what ethnicity may contribute to the dynamics of these processes, and so these differences warrant additional investigation. The ethnic differences in the distribution of the serotonin transporter polymorphism do raise an intriguing question as to whether cultural conventions may develop to modulate genetic variations such as these. Asian cultures have been referred to as interdependent, characterized by viewing the individual as part of encompassing social relationships and subject to the thoughts, feelings, and actions of others in the social group (Markus and Kitayama 1991). This characterization is in contrast to the independent self, more common among European-Americans, which is characterized as a more distinctive independent functioning unit. It is conceivable that this robust cultural difference may have developed at least in part to modulate potential genetic risk conferred by s/s, given its high frequency in Asian populations, by ensuring a strong family and social environment (see Laland

1993, for a discussion of gene-culture co-evolution). Currently, these are merely intriguing speculations.

Limitations

A first potential limitation consists of the fact that we measured depressive symptomatology and not diagnosed depression. Thus, the clinical significance of the findings is unclear. As noted, however, without examining depressive symptomatology as a continuous variable, it would have been difficult to see the particular form of the crossover interaction identified here, involving the protective effects of the s/s genotype in the context of a supportive family environment and a low-stress current environment.

A related concern is that the sample is a nonclinical one. However, as noted, we suggest that there may be certain advantages to exploring G×E interactions in nonclinical samples with measures that cover the full range of the outcome variable in question. Specifically, identifying factors that contribute to risk for clinical disorders in normal samples may enable clinical researchers to more precisely pinpoint what additional cofactors are implicated in diagnosed pathology, including other genetic polymorphisms, intensely stressful life experiences, or other risk factors.

The G×E interaction for early family environment reported here was found in a nonclinical sample in which the "riskiness" of the early environments of participants was relatively modest. There was, for example, no evidence of extreme physical or sexual abuse. No participant with a diagnosed major mental disorder or a PTSD diagnosis was included in the study. The findings, thus, suggest that even moderate family conflict and distress may be tied to an enhanced risk for depressive symptomatology.

Assessment of family environment involves reconstruction by these young adult participants and thus may engage certain biases. Most problematic is the potential for a negative emotional overlay to influence the reconstruction of early environment as well as reports of depressive symptomatology. Such a reporting bias could conceivably affect the main effect of early family environment on depressive symptomatology, although it could not account for the G×E interaction. Several other factors also suggest that a reporting bias does not account for risky family assessments. The instrument on which the risky family assessment is based has demonstrated a dose-response relationship to a broad array of diagnosed mental and physical health outcomes (depression, cancer, CHD) (Felitti et al 1998), and a response bias is highly unlikely to yield such effects. Moreover, in previous investigations, we have formally evaluated statistical models that give psychosocial functioning causal priority to see whether it explains the reconstruction of childhood events (Taylor et al 2004; Lehman et al 2005). In all cases, this alternative model is a weak fit to the data.

Finally, the small sample size is a limitation that may have obscured weak effects, such as a main effect of current stress or genotype on depressive symptomatology, for example. Replication with a larger sample is highly desirable.

Conclusions

A stressful early family environment contributes directly and in interaction with the serotonin transporter polymorphism to depressive symptomatology. Specifically, the s/s genotype is associated with greater depressive symptomatology in offspring from stressful early family environments and with lower depressive symptomatology among offspring from supportive families. The same G×E interaction was found for the effects of current stress and the 5-HTTLPR on depressive symptomatology as well. The pattern was distinctive to depression, as opposed to other measures of psychosocial distress (e.g., anxiety), and it was not significantly affected by psychosocial resources normally found to be protective against psychological distress. We conclude that explorations of genetic contributions to clinical disorders will be facilitated by examining the full range of the predictor and outcome variables in question, if crossover G×E interactions are to be detected. (Bennett et al., 2002; Champoux et al., 2002; Eysenck and Eysenck, 1975; Kendler et al., 1998).

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Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961): An inventory for measuring depression. *Arch Gen Psychiatry* 4:561–571.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al (2003): Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science* 301:386–389.

Eley T, Sugden K, Corsico A, Gregory A, Sham P, McGuffin P, et al (2004): Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Mol Psychiatry* 9:908–915.

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Apitz AM, Edwards V, et al (1998): Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. *Am J Prev Med* 14:245–258.

Gelernter J, Kranzler H, Cubells JF (1997): Serotonin transporter protein (SLC6A4) allele and haplotype frequencies and linkage disequilibria in African- and European-American and Japanese populations and in alcohol-dependent subjects. *Hum Genet* 101:243–246.

Gillespie N, Whitefield J, Williams B, Heath A, Martin N (2005): The relationship between stressful life events, the serotonin (5-HTTLPR) genotype and major depression. *Psychol Med* 35:101–111.

Glatz K, Mossner R, Heils A, Lesch KP (2003): Glucocorticoid-regulated human serotonin transporter (5-HTT) expression is modulated by the 5-HTT gene-promotor-linked polymorphic region. *Neurochemistry* 86: 1072–1078.

Goldberg L (1999): A broad-bandwidth, public-domain, personality inventory measuring the lower-level facets of several five-factor models. *Personality Psychol Europe* 7:7–28.

Grabe H, Lange M, Wolff B, Volzke H, Lucht M, Freyberger H, et al (2005): Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden. *Mol Psychiatry* 10:220–234.

Kaufman J, Yang B-Z, Douglas-Palumberi H, Houshyar S, Lipschitz B, Krystal J, Gelernter J (2004): Social supports and serotonin transporter gene moderate depression in maltreated children. *Proc Natl Acad Sci* 101:17316–17321.

Kendler K, Kuhn J, Vittum J, Prescott C, Riley B (2005): The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression. *Arch Gen Psychiatry* 62: 529–535.

Laland K (1993): The mathematical modeling of human culture and its implications for psychology and the human sciences. *Br J Psychol* 84: 145–169.

Lehman BJ, Taylor SE, Kiefe CI, Seeman TE (2005): Relation of childhood socioeconomic status and family environment to adult metabolic functioning in the CARDIA study. *Psychosom Med* 67:846–854.

Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al (1996): Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 274:1527–1531.

Manuck SB, Flory JD, Ferrell RE, Muldoon MF (2004): Socio-economic status covaries with central nervous system serotonergic responsivity as a function of allelic variation in the serotonin transporter gene-linked polymorphic region. *Psychoneuroendocrinology* 29:651–668.

Markus HR, Kitayama S (1991): Culture and the self: Implications for cognition, emotion, and motivation. *Psychol Rev* 98:224–253.

Pearlin LI, Schooler C (1978): The structure of coping. *Health Soc Behav* 19:2–21.

Rosenberg M (1965): *Society and the adolescent self-image*. Princeton, NJ: Princeton University Press.

Scheier MF, Carver CS (1985): Optimism, coping, and health: assessment and implications of generalized outcome expectancies. *Health Psych* 4:219–247.

Schuster TL, Kessler RC, Aseltine RH (1990): Supportive interactions, negative interactions and depressed mood. *Am J Community Psychol* 18:423–438.

Spielberger CD, Gorsuch RL, Lushene RD (1970): *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Suomi SJ (1999): Attachment in rhesus monkeys. In: Cassidy J, Shaver P, editors. *Handbook of Attachment: Theory, Research, and Clinical Applications*. New York: Guilford Press.

Surtees PG, Wainwright NW, Willis-Owen SA, Luben R, Day NE, Flint J (2006): Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. *Biol Psychiatry* 59:224–229.

Taylor SE, Lerner J, Sherman DK, Sage R, McDowell N (2003): Are self-enhancing cognitions associated with healthy or unhealthy biological profiles? *J Pers Soc Psychol* 85:605–615.

Taylor SE, Lerner JS, Sage RM, Lehman BJ, Seeman TE (2004): Early environment, emotions, responses to stress, and health. *J Pers* 72:1365–1393.

Wilhelm K, Mitchell P, Niven H, Finch A, Wedgwood L, Schimone A, Blair I, et al (2006): Life events, first depression onset and the serotonin transporter gene. *Br J Psychiatry* 188:210–215.