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5-HTTLPR moderates effects of current life events on neuroticism: Differential susceptibility to environmental influences

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ABSTRACT

Research chronicling links between a polymorphism in the serotonin-transporter gene (5-HTTLPR) and neuroticism has yielded inconsistent results. One possible explanation for this inconsistency is that any gene–phenotype association is obscured by a gene-X-environment (GXE) interaction. We studied a healthy non-clinical sample ($N = 118$) to determine whether the 5-HTTLPR interacts with current life events in predicting neuroticism. The differential-susceptibility hypothesis led to the prediction of such an interaction, reflecting the fact that individuals with short alleles would be affected more by *both* negative and positive life events than those homozygous for long alleles. Participants completed questionnaires concerning recent life events and neuroticism. The 5-HTTLPR was genotyped using a standard protocol with DNA extracted from oral fluid. For those homozygous for the short allele, more negative life events proved related to greater neuroticism, whereas more positive life events proved related to less neuroticism. No such association emerged in the case of those homozygous for the long allele. Whereas neuroticism is likely to be an especially stable trait in individuals homozygous for the long allele, this may be less so the case for those carrying short alleles.

Neuroticism is a personality trait generally defined as the proneness to experience negative affect (Costa and McCrae, 1992) and to appraise events as stressful (Hurt et al., 1984). Behavior-genetic studies show it to be approximately 40–50% heritable, just like most other personality traits (Jang et al., 1996; Eaves et al., 1999; Plomin et al., 1994). This result has raised the issue of identifying potential candidate genes associated with neuroticism.

Lesch et al. (1996), focusing on the serotonin transporter, were the first to link neuroticism with the short allele of the serotonin-transporter-linked polymorphic region (5-HTTLPR). Replication of this particular finding has proven difficult, however, just as it has in the case of many other attempts to associate candidate genes with specific behavioral and psychological phenotypes (Burmeister et al., 2008). Whereas three meta-analyses provide support for associations between the short allele of the 5-HTTLPR and neuroticism and/or other anxiety-related personality traits (Sen et al., 2004; Schinka et al., 2004; Munafo et al., 2009), two other meta-analyses focused on the same relationship failed to discern reliable evidence of it (Munafo et al., 2003; Munafo et al., 2005).

Abbreviations: DNA, deoxyribonucleic acid; GXE, gene-X-environment interaction; PTSD, post-traumatic stress disorder; 5-HTTLPR, serotonin transporter gene-linked polymorphic region.

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In the face of similar inconsistent results pertaining to links between candidate genes and antisocial behavior and depression, as well as between specific environmental factors and these psychiatric phenotypes, Caspi and associates (Caspi et al., 2002, 2003) raised the prospect that gene–environment (GXE) interactions could be responsible for the inconsistency in the empirical literature. Because genetic and contextual links to phenotypes might only emerge under, respectively, certain environmental and genetic conditions, failure to consider environmental factors in much of the candidate-gene research focused on neuroticism could explain why gene–phenotype associations have proven inconsistent. Empirical evidence of such GXE interactions showing that specific environmental factors (e.g., stressful life events) predicted specific behavioral outcomes (e.g., depression) to a greater extent in individuals with specific gene variants (e.g., short allele of the 5-HTTLPR (Caspi et al., 2003)) is certainly consistent with this thinking, providing perhaps an explanation for the aforementioned inconsistency in associations between the short 5-HTTPLR allele and neuroticism.

In the current investigation, we apply the same logic as Caspi and associates (Caspi et al., 2002, 2003) but to the issue of relations between life events, the serotonin-transporter gene polymorphism (*5-HTTLPR*) and neuroticism. We reasoned that an interaction between the 5-HTTLPR and life events in the prediction of neuroticism may have complicated replication of the association between the 5-HTTLPR and neuroticism. Whereas a growing number of GXE studies discern significant interactions between the 5-HTTLPR and negative

life events in the prediction of depression or depressive symptoms (Caspi et al., 2003; Wilhelm et al., 2006; Taylor et al., 2006; Eley et al., 2004), we are aware of only one study which investigated such an interaction in the prediction of anxiety-related personality traits (Stein et al., 2008). However, though Stein et al. (2008) found that the 5-HTTLPR moderated the effect of childhood maltreatment on anxiety sensitivity in young adulthood, the same did not prove to be the case with respect to neuroticism.

Most GXE results–including those concerning 5-HTTLPR, life events, and depression–have been interpreted in a diathesis-stress manner with the 5-HTTLPR short allele regarded as a vulnerability factor (or diathesis) that increases the risk of depression in the face of negative life events. But as noted by Taylor et al. (2006) in their study of this particular GXE interaction and by Belsky et al. (2009) in their analysis of many other GXE findings, the short allele may be better conceptualised, at least in some circumstances, as a "plasticity gene" rather than a "vulnerability gene." This is because individuals with the short allele appear in some research to be not only more likely than others to succumb to the negative effects of adverse environments but also more likely than others to benefit from positive supportive ones (Uher and McGuffin, 2008). This proves true even in work in which support is operationalized as merely the absence of negative contextual conditions (e.g., few negative life events). Evidence of this kind is consistent with Taylor et al.'s (2006) reasoning, Way and Gurbaxani's hypothesis of social sensitivity (Way and Gurbaxani, 2008), and Belsky's (1997a,b, 2005, 2007) differential-susceptibility hypothesis which posit that some individuals, including those with the short allele of the 5-HTTLPR, are more affected by both positive and negative environmental conditions than are others—rather than just disproportionately and negatively affected by adversity than others (see also Belsky et al., 2007; Boyce and Ellis, 2005). According to the evolutionary based framework of the differential susceptibility hypothesis this for-better-and-for-worse interaction is reflecting the biological benefits and costs of heightened susceptibility to environmental influences (Belsky, 2005; Belsky and Pluess, 2009; Ellis and Boyce, 2008).

On the basis of the differential-susceptibility reconceptualization of many GXE findings and the view that the short allele of the 5-HTTLPR may be a genetic marker for heightened susceptibility to environmental influences, we predicted that this gene would moderate effects of life events on neuroticism. More specifically, we predicted that individuals with one or two short alleles would be more negatively affected vis-à-vis neuroticism by high levels of negative life events and more positively by high levels of positive life events compared to those homozygous for the long allele.

1. Methods and materials

1.1. Participants

Study participation was advertized to members of the University of California, Los Angeles (UCLA), campus community offering $60 for partaking. Prospective participants with the following conditions were excluded: (1) serious physical or mental health problems, (2) current treatment from a mental health professional, (3) diagnosis of PTSD, and (4) current use of mental health related medication (e.g., selective serotonin reuptake inhibitors). The investigation was approved by the Institutional Review Board of UCLA.

The sample for the current analysis included 118 participants (51 men and 67 women) all of whom were affiliated with UCLA as either employees, students, or both. Participants ranged in age from 15 to 33 years, with a mean age of 21.2 years ($SD = 2.3$). The sample was ethnically diverse with 38.1% of Asian, 34.7% of Caucasian, and 27.1% of other ethnic origin (13.6% Hispanic, 8.5% Middle Eastern, 3.4% African-Americans, 1.7% unknown). Participants reported to a computer laboratory where they completed informed consent forms and questionnaires. 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).

1.2. Measures

Psychological measurement of neuroticism was obtained using the Big Five International Personality Scale (Goldberg, 1999). Depression was measured with the Beck Depression Inventory (Beck et al., 1961). To assess life events, 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 and higher values more positive events.

1.3. 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 (A) an initial 5 min denaturation at 94 °C; (B) 8 cycles with denaturation for 30 s at 94 °C, varied annealing temperatures consisting of 30 s at 66 °C (2 cycles), then 65 °C (3 cycles), then 64 °C (3 cycles), followed by hybridization for 1 min at 72 °C; (C) 35 cycles with an annealing temperature of 63 °C and the same denaturation and hybridization parameters; and (D) 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).

1.4. Data analysis

Exploratory data analysis included examination of variables for missing data, normality, and both univariate and multivariate outliers. Unadjusted associations between the different measures were evaluated using bivariate correlations (Pearson, two-tailed). For the primary multiple regression analyses, variables without normal distribution were transformed (square root). The level of significance for all analyses was set at $\alpha = .05$. All statistical analyses were carried out using the Statistical Package for the Social Sciences, version 16.0 for Windows (SPSS, 2007).

2. Results

Genotype distribution (s/s: 26%, s/l: 49%, l/l: 25%) did not deviate from the Hardy–Weinberg equilibrium ($p > .05$). However, allelic variation of the serotonin-transporter differed by ethnicity, such that Caucasians were underrepresented in the s/s category (9.8%) compared to Asians (40.0%) and other ethnicities (28.1%). Consequently, ethnicity was included as a covariate in subsequent regression models. Simple correlational analyses indicated that genotype

was not associated with life events or neuroticism, thereby ruling out the possibility of gene–environment correlation being misinterpreted as GXE interaction. The life events scale predicted neuroticism scores ($r_{(118)} = -.19$, $p < .05$). Age was not related to neuroticism so it was excluded in subsequent regression analyses, whereas sex was included given its significant association with neuroticism ($r_{(118)} = .19$, $p < .05$).

For the hierarchical regression analyses, variables were entered in the following order to predict neuroticism: (a) sex (1: male; 2: female) and ethnicity (2: Caucasian; 1: all others), (b) 5-HTTLPR (0, 1, 2 for, respectively, l/l, s/l, and s/s) and life events, and (c) the interaction term between the 5-HTTLPR and life events. There were no main effects of sex, ethnicity, 5-HTTLPR, or life events, but a significant two-way interaction between the 5-HTTLPR and life events ($\beta = -.31$, $p < .05$, Effect Size (f^2) = .04) in the prediction of neuroticism scores (adjusted $R^2 = .07$; $F_{(5,117)} = 2.66$, $p < .05$).

Follow-up analyses of simple slopes revealed what Belsky and Pluess (2009) have labeled a "plasticity gradient", with the relation between life events and neuroticism proving strongest (and significant) in the case of individuals homozygous for the short allele ($r_{(31)} = -.38$, $p < .05$), intermediate (and insignificant) for those heterozygous for short and long alleles ($r_{(58)} = -.16$, $p = .24$), and weakest (and insignificant) for those homozygous for the long allele ($r_{(29)} = .04$, $p = .83$). After z-transformation of the standardized regression coefficients (Fisher, 1924), the slope of participants with s/s genotype proved significantly larger than that of l/l genotypes ($p < .05$). These results displayed graphically in Fig. 1 are consistent with differential susceptibility: *Individuals homozygous for the short allele had the highest neuroticism scores when recently exposed to stressful life events and the least when exposed to positive life events.*

Given the significant association between sex and neuroticism and the ethnic differences in allelic variation, we ran additional hierarchical regression models to investigate whether the 2-way interaction between the 5-HTTLPR and life events on neuroticism was further moderated by sex or ethnicity. Testing for gender effects is especially important given recent evidence that associations between 5-HTTLPR and depression (Brummett et al., 2008a) and between serotonergic function and neuroticism (Brummett et al., 2008b) differed as a function of gender. To this end, we entered variables in the following order: (a) sex and ethnicity, (b) 5-HTTLPR and life events, (c) the interaction term between 5-HTTLPR and life events, and (d) a three-way interaction term including 5-HTTLPR, life events and sex or ethnicity. None of the three-way interaction terms proved significant ($p = .17$ for the 3-way interaction term including sex; $p = .75$ for the 3-way interaction term including ethnicity), suggesting that the interaction between the 5-HTTLPR and life events on neuroticism was not moderated by gender[1] or ethnicity[2].

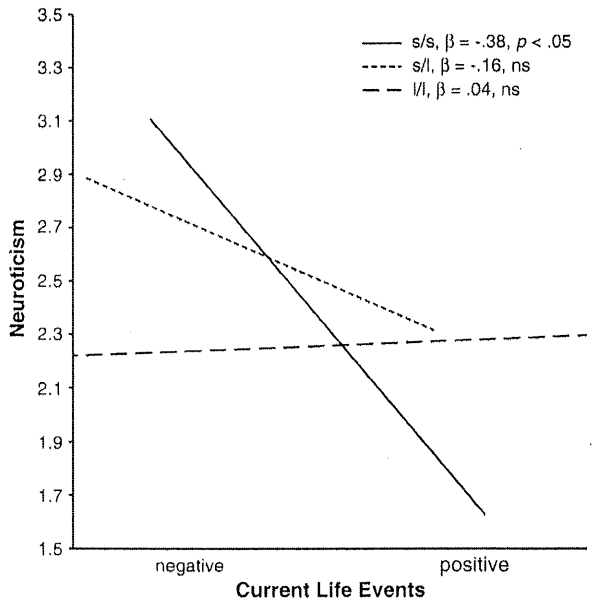

Fig. 1. Linear relations between quality of life events which occurred during the preceding six months and neuroticism scores as a function of 5-HTTLPR.

A second follow-up analysis was carried out in view of the facts that in this sample (a) neuroticism and depression are, unsurprisingly, positively and significantly correlated ($r_{(113)} = .57$, $p < .01$) and (b) Taylor et al. (2006) have previously detected the same significant GXE as reported herein when predicting depression in this sample. Thus, the question not unreasonably arises as to whether the 5-HTTLPR-moderated effect of life events on depression reported herein reflect anything more than what Taylor et al. (2006) already discerned. To address this issue, neuroticism was statistically adjusted for depression and the resultant residualised neuroticism score was related to life events, separately for those with only long 5-HTTLPR alleles and those with at least one short allele. Only in the latter case was the association significant (one or more short alleles: $r_{(87)} = -.27$, $p < .05$; homozygous for the long allele: $r_{(26)} = .06$, *ns*), thereby indicating that the differential effect of life events on neuroticism as a function of genotype originally chronicled in this inquiry is not simply a byproduct of the overlap between depression and neuroticism.

3. Discussion

Like many other studies (Wilhelm et al., 2006; Flory et al., 1999; Willis-Owen et al., 2005; Lang et al., 2004; Middeldorp et al., 2007) we were not able to detect a direct association between the short allele of the 5-HTTLPR and neuroticism. As hypothesized, a significant interaction between the 5-HTTLPR and life events emerged in the prediction of neuroticism. Whereas neuroticism scores of individuals homozygous for the long allele proved unrelated to current life events, individuals with one or more short alleles scored higher or lower on the neuroticism scale depending on recent experiences; recall, though, that this association between life events and neuroticism only proved significant for those homozygous for the short allele.

Importantly, the presence of short alleles was not only associated with increased neuroticism scores in response to negative life events as a diathesis-stress model would suggest. Consistent with the differential-susceptibility hypothesis, individuals with the short alleles–specifically those homozygous for the short allele–were more sensitive to both the respective negative and positive effects of negative and positive life events experienced over the six month period that preceded data collection. That is, such individuals manifested the highest neuroticism scores if they experienced many negative life events but also the lowest scores if exposed to many positive life events. Consequently, these results provide further empirical support for the reconceptualization of the short allele of the 5-HTTLPR as a marker of plasticity rather than just vulnerability to negative effects of adverse environments (Belsky et al., 2009). However, the fact that neuroticism is heritable (Jang et al., 1996; Eaves et al., 1999; Plomin et al., 1994) and has been found to predict exposure to adversity (Kendler et al., 2003) may also suggest an

[1] When the original regression analysis was run separately for males ($n = 51$) and female ($n = 67$), the 2-way interaction between 5-HTTLPR and life events predicting neuroticism was marginally significant in males ($p = .08$) but not in females ($p = .40$) while the total model failed to reach significance in both groups ($p = .32$ and $p = .10$, respectively). However, simple slopes run separately for males and females revealed similar cross-over interactions as found with the whole sample.

[2] When the original regression analysis was run using only the Asian subsample ($n = 45$), the 2-way interaction between 5-HTTLPR and life events predicting neuroticism was marginally significant with $p = .08$ and the slopes revealed the same cross-over interaction as found with the whole sample.

alternative interpretation of the interaction between the 5-HTTLPR and life events: individuals scoring high on neuroticism and carrying short alleles may be more likely to encounter adverse experiences, as a function of neuroticism, and more likely to be negatively affected by such events, as a function of short alleles, compared to individuals with short alleles who score low in neuroticism and are therefore less prone to encounter adversity or any group with long alleles. With either explanation, however, the short allele of the 5-HTTLPR appears to be related to heightened susceptibility to environmental influences.

The question arises as to what mechanisms might account for the heightened susceptibility to both negative and positive environments of individuals carrying one or more copies of the 5-HTTLPR short allele. Belsky (2005) suggested that susceptible individuals may be characterized by a generally more sensitive nervous system. Empirical support for this proposition can be found in research linking the short allele of the 5-HTTLPR with higher amygdala reactivity to fearful stimuli (Munafo et al., 2008), better acquisition of fear conditioning (Lonsdorf et al., 2009; Garpenstrand et al., 2001), and enhanced social learning of fear (Crisan et al., 2009). The fact that the just-cited studies focused exclusively on negative stimuli would seem to leave open to question, however, exactly why individuals with short alleles also appear more responsive to beneficial effects of positive experiences/environments.

It is the common understanding that personality traits tend to be stable in adulthood (Caspi et al., 2005; McCrae and Costa, 1994). However, some empirical work suggests that neuroticism can change over time and that there is considerable interindividual variation in neuroticism trajectories (Roberts et al., 2006; Scollon and Diener, 2006; Mroczek and Spiro, 2003). The current analysis supports the notion that personality traits may be less stable in some individuals compared to others—at least regarding neuroticism. For individuals carrying short alleles of the 5-HTTLPR neuroticism scores reflect, at least in part, the interaction between genetic susceptibility and environment, whereas the environment, at least as measured in this inquiry, seems to exert no apparent influence on the neuroticism scores of individuals homozygous for the long allele. This may pose a general but as of yet un-noted problem when evaluating the stability of neuroticism—and perhaps other personality traits, too. Indeed, the findings presented here lead to the prediction that neuroticism should be less stable in the case of more environmentally malleable individuals who carry short–and especially two short–alleles, yet highly stable in the case of those who carry only long alleles and appear impervious to at least some environmental effects.

According to behavior-genetics studies, neuroticism is generally 40–50% heritable (Jang et al., 1996; Eaves et al., 1999; Plomin et al., 1994). The current findings suggest that heritability of neuroticism might actually be higher in individuals homozygous for the long 5-HTTLPR allele and lower in those with short alleles. For individuals with short alleles of the 5-HTTLPR neuroticism may not just be a genetically predisposed and heritable personality trait, but the result of the interaction between genetically heightened susceptibility to the environment and the experienced environment. This may explain why heritability estimates for neuroticism are generally lower than 50% (Jang et al., 1996; Eaves et al., 1999; Plomin et al., 1994).

The results of the present study should be viewed in the context of several investigatory limitations however: (1) the study design was correlational, thereby limiting the confidence that can be placed in any causal inferences drawn; individuals with high neuroticism, for example, may be more likely to experience negative life events or to interpret major life events negatively; (2) the interaction effect detected was small; (3) the sample was heterogeneous regarding ethnicity and age; (4) life events were based exclusively on self-report; (5) the study did not genotype and differentiate between L_A and L_G alleles (SNP rs25531) (Hu et al., 2006); (6), the small sample size may have obscured small effects, including main effects of life events and/or genotype on neuroticism or of life events on neuroticism in the case of heterozygotes and also moderation effects of gender and ethnicity. Replication with a larger sample would be highly desirable. That said, empirical support for the reported GXE findings emerged recently in a study ($N=206$) by Vinberg et al. (2009) in which 5-HTTLPR interacted with recent life events in the prediction of neuroticism: individuals with short alleles had higher neuroticism scores in response to stressful life events compared to those homozygous for the long allele; and, (7) finally, an outcome measure of human functioning along a continuum ranging from dysfunction to competence and not just from dysfunction to its absence–as in the current study–may have yielded even more substantial evidence of differential susceptibility.

In conclusion, the short allele of the 5-HTTLPR is associated with greater plasticity as evidenced by a higher susceptibility to both negative and positive effects of life events in the prediction of neuroticism. Whereas neuroticism is likely to be an especially stable trait in individuals homozygous for the long allele, this may be less so the case for those carrying a short–and especially two short–alleles, given their apparent distinctive susceptibility to environmental influences.

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