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Letter to the Editor

Brain derived neurotrophic factor (*BDNF*) polymorphism Moderates the interactive effect of 5-HTTLPR polymorphism and childhood abuse on diagnoses of major depression in women

To the Editors:

There is growing interest in identifying specific genetic influences that may moderate the impact of environmental stressors (E) on depression risk. The majority of studies have focused on 5-HTTLPR, though findings have been mixed (Karg et al., 2011), suggesting the presence of unmeasured moderating influences. There is evidence that 5-HTTLPR × E effects on depression may be stronger among individuals carrying the BDNF Met allele than among those homozygous for the Val allele (e.g. Kaufman et al., 2006).

This study aimed to replicate and extend previous research by testing a 5-HTTLPR × BDNF Val66Met × E model of risk, oversampling for women with histories of MDD and focusing on histories of childhood abuse as environmental stressors. We predicted that the 5-HTTLPR × childhood abuse interaction would be stronger for women carrying at least one copy of the *BDNF* Met allele than for women homozygous for the Val allele, with the greatest risk for depression observed among women with a history of childhood abuse with at least one copy of the 5-HTTLPR S (or L_G) allele and the *BDNF* Met allele.

A total of 181 women with a history of MDD and 174 who had no lifetime history of any DSM-IV mood disorder and no current Axis I diagnosis were investigated (*M* age = 40.11, S.D. = 6.79, 87.9% Caucasian). Participants' histories of DSM-IV Axis I disorders were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., (1995)). A subset of 20 SCID interviews was coded by a second interviewer and inter-rater reliability for diagnoses of MDD was excellent ($\kappa = 1.00$). The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) was used to assess participants' histories of childhood emotional, physical, and sexual abuse. In this population sample, CTQ exhibited good internal consistency (emotional abuse $\alpha = 0.86$, physical abuse $\alpha = 0.85$, sexual abuse $\alpha = 0.96$). Women were coded as having no history of abuse ($n = 232$), or having a history of any moderate abuse ($n = 123$). The *5-HTTLPR* S alleles, rs25531 SNP and *BDNF* Val66Met were assayed using previously reported methods (Pooley et al., 2003; Wendland et al.,2006). Observed genotype frequencies did not differ from Hardy Weinberg equilibrium ($p = 0.85$; $\chi^2 = 0.28$, $p = 0.60$). Less than 5% of the data were missing and Little's missing completely at random (MCAR) test was non-significant, $\chi^2 = 27.13$ (25), $p = 0.35$, suggesting that the data were missing at random. Therefore, multiple imputation was used to generate 20 datasets and the results presented reflect pooled estimates across these datasets, yielding more reliable parameter estimates than other methods of dealing with missing data (see Schafer and Graham, 2002). We should note, however, that the results were maintained using the original unimputed dataset.

Preliminary analyses indicated that women's history of childhood abuse was not significantly related to their 5-HTTLPR ($\chi^2 = 0.33$, $p = 0.60$, $\phi = 0.03$) or Val66Met ($\chi^2 = 2.54$, $p = 0.13$, $\phi = -0.11$) genotype, suggesting the lack of any significant gene–environment correlations with these two polymorphisms.

Using a hierarchical logistic regression analysis with women's history of MDD (yes, no) serving as the criterion variable, we entered each of the main effects in step 1. We found a significant main effect of childhood abuse (Wald = 42.51, $p < 0.001$, OR = 5.21, CI = 3.22–8.89), but not 5-HTTLPR (Wald = 1.10, $p = 0.31$, OR = 1.31, CI = 0.78–2.25) or *BDNF* Val66Met (Wald = 0.72, $p = 0.42$, OR = 1.21, CI = 0.78–2.04). In the second step, we entered each of the two-way interactions. None of these was significant: 5-HTTLPR × childhood abuse (*Wald* = 0.10, $p = 0.83$, *OR* = 0.86, CI = 0.57–5.84), Val66Met × childhood abuse (Wald = 1.73, $p = 0.23$, OR = 0.27, CI = 0.53–5.12), and 5-HTTLPR × Val66-Met (Wald = 3.16, $p = 0.09$, OR = 0.33, CI = 0.23–2.14). In the third step, we entered the three-way Val66Met × 5-HTTLPR × childhood abuse interaction, which was significant (Wald = 4.47, $p = 0.04$, OR = 14.39, CI = 1.15–172.10).

To examine the form of this interaction, we tested the 5-HTTLPR × childhood abuse interaction separately among carriers of the *BDNF* Met allele ($n = 133$) versus those homozygous for the Val allele ($n = 222$). Among carriers of the *BDNF* Met allele, the 5-HTTLPR × childhood abuse interaction significantly predicted women's history of MDD (Wald = 5.63, $p = 0.02$, OR = 12.38, CI = 1.60–106.98). In contrast, among women homozygous for the Val allele, the 5-HTTLPR × childhood abuse interaction was not significant (Wald = 0.10, $p = 0.83$, OR = 0.86, CI = 0.22–3.37). Focusing next on the impact of childhood abuse among carriers of the *BDNF* Met allele as a function of 5-HTTLPR genotype, we found that the link between women's histories of childhood abuse and MDD was significant among Met carriers with at least one copy of the 5-HTTLPR S′ allele ($n = 99$; Wald = 19.25, $p < 0.001$, OR = 16.28, CI = 4.70–57.93) but not among Met carriers homozygous for the L_A allele ($n = 34$; Wald = 0.22, $p = 0.86$, *OR* = 0.93, CI = 0.26–7.24). We should also note that all of these results were maintained when we limited our sample to Caucasians ($n = 306$) Fig. 1.

These findings suggest that the previous mixed findings observed in studies testing 5-HTTLPR × E models of risk for depression may have been partially due to the failure to account for epistatic influences. In this study, the predicted 5-HTTLPR × childhood abuse interaction was only significant among women carrying at least one copy of the *BDNF* Met allele, but not among those homozygous for the Val allele. Future research is needed to determine whether these findings generalize to predicting prospective onsets of MDD and to

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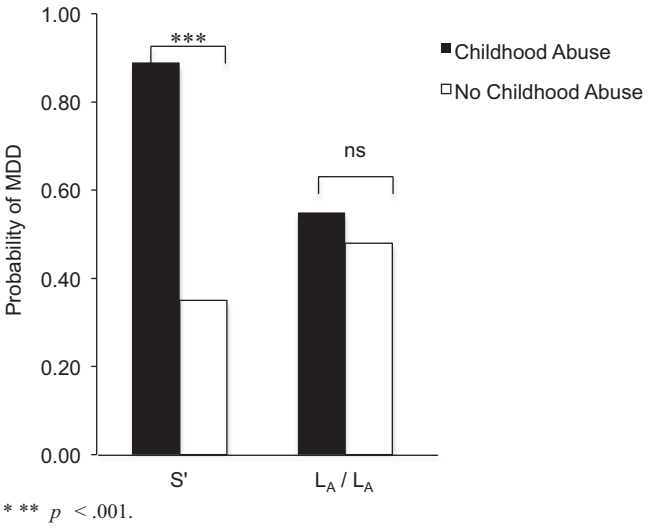

Fig. 1. Supporting a G × G × E model of risk, history of childhood abuse increased the probability of MDD, but only among carriers of both the *BDNF* Met and 5-HTTLPR S′ alleles.

examine specific mechanisms by which early adversity contributes to depression risk among genetically more reactive individuals as these mechanisms might provide useful targets of intervention.

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