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The rs1049353 Polymorphism in the *CNR1* Gene Interacts With Childhood Abuse to Predict Posttraumatic Threat Symptoms

To the Editor: Posttraumatic stress disorder (PTSD) is a heterogeneous condition comprising threat/fear (eg, intrusions, avoidance, hypervigilance) and loss/dysphoria (eg, numbing, dysphoric arousal) symptoms.^{1,2} Contemporary scientific efforts in psychiatry, such as the National Institute of Mental Health Research Domain Criteria project, are encouraging studies of the neurobiological and behavioral underpinnings of transdiagnostic aspects of mental disorders, such as threat and loss symptoms, with the goal of developing novel, mechanism-based classifications of psychopathology, which can be used to develop more targeted treatments.³

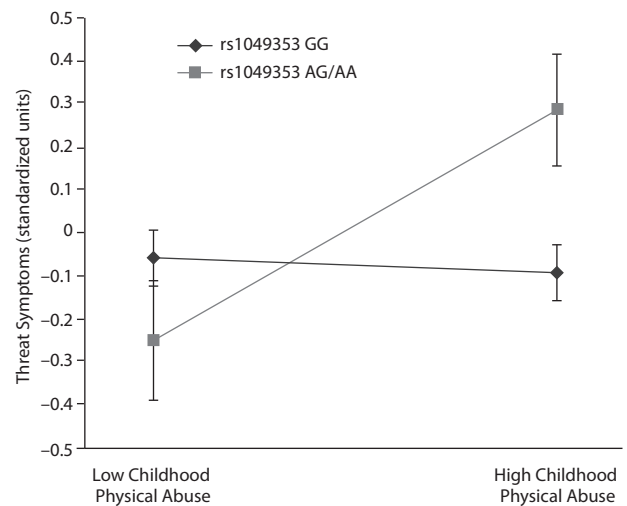
In line with such efforts, we recently found that PTSD is associated with greater cannabinoid type 1 (CB₁) receptor availability⁴ and that greater CB₁ receptor availability in the amygdala was associated with increased threat, but not loss, symptoms in trauma survivors.⁵ Variation in the cannabinoid receptor type 1 (*CNR1*) gene may also contribute to risk for PTSD, with the A allele of rs1049353 associated with increased likelihood of PTSD.⁶ Additionally, rs1049353 has been found to interact with childhood physical abuse (CPA), one type of trauma that might impact the endocannabinoid system, to predict anhedonia.⁷ However, no study has examined associations between rs1049353 genotype—alone or interactively with CPA—and the phenotypic expression of PTSD symptoms.

Using data from the Detroit Neighborhood Health Study^{8,9} (DNHS), an epidemiologic study of predominantly African-American adults from urban Detroit for which data were collected from June 2008 to December 2013, we examined how rs1049353 genotype—alone and interactively with CPA—relates to severity of posttraumatic threat and loss symptoms. We hypothesized that rs1049353 genotype would specifically underlie threat, but not loss, symptoms.⁵ The University of Michigan Institutional Review Board approved the DNHS, and participants provided written informed consent.

Method. A total of 487 adults (mean age = 53.3 [SD = 15.6] years; 57.7% female; 82.7% African-American) provided valid data for rs1049353 and completed the PTSD Checklist¹⁰ and the Conflict Tactics Scale¹¹ measure of CPA. We conducted a multivariate analysis of covariance (MANCOVA) to examine the relation between rs1049353 genotype (AA/AG vs GG) and CPA (alone and in interaction) as predictors of threat (sum of PTSD Checklist intrusion, avoidance, and anxious arousal) and loss (sum of numbing and dysphoric arousal) symptoms. Age, sex, lifetime trauma burden, and the first 2 principal components from a multidimensional scaling analysis of genome-wide data were included as covariates.

Results. CPA predicted threat symptoms ($F_{1,454} = 5.59, P = .018$), but main effects of rs1049353 genotype were nonsignificant (threat: $F_{1,454} = 0.69, P = .41$; loss: $F_{1,454} = 0.51, P = .47$). There was also a significant rs1049353 genotype \times CPA interaction for threat symptoms only ($F_{1,454} = 7.57, P = .006$); minor A allele carriers with high levels of CPA reported greater threat symptoms (Figure 1). In a separate MANCOVA of the 5 PTSD symptom dimensions (reexperiencing, avoidance, anxious arousal, numbing, dysphoric arousal), this interaction also emerged for 2 of 3 dimensions of threat symptoms: avoidance ($F_{1,454} = 6.13, P = .014$) and reexperiencing ($F_{1,454} = 6.13, P = .014$).

Figure 1. Association of *CNR1* SNP rs1049353, Childhood Physical Abuse, and Posttraumatic Threat Symptoms (N = 487)^a



^aError bars represent standard error of the mean. Determination of low vs high level of childhood physical abuse (CPA) was based on summing the items of the Conflict Tactics Scale and dichotomizing based on a median split; GG/low CPA n = 203, GG/high CPA n = 194, AG/AA/low CPA n = 43, AG/AA/high CPA n = 47. Genotype frequencies were as follows: A/A (n = 7 [1.4%]), A/G (n = 83 [17.0%]), G/G (n = 397 [81.6%]); they did not deviate from Hardy-Weinberg equilibrium ($\chi^2_1 = 1.20, P = .27$). Results of a multivariate analysis of covariance revealed a significant rs1049353 genotype \times CPA interaction in predicting threat symptoms only ($F_{1,454} = 7.57, P = .006$). An additional *CNR1* single-nucleotide polymorphism (SNP)—rs806368—which has been implicated in PTSD,⁶ was also examined alone and interactively with CPA in relation to the severity of threat and loss symptoms. Although there was a marginal main effect of rs806368 genotype (minor allele carrier vs not) on severity of threat symptoms ($F_{1,453} = 4.37, P = .037$), it did not withstand the correction for multiple comparisons of 2 SNPs ($P = .025$). rs806368 genotype was also not related to loss symptoms ($F_{1,453} = 2.99, P = .085$), nor was the interaction of this polymorphism and CPA related to threat or loss symptoms (F values < 2.47, P values > .117).

The current findings extend our prior work implicating the endocannabinoid system in PTSD.^{4,5} The rs1049353 single-nucleotide polymorphism (SNP) has been found to interact with CPA to contribute to decreased anhedonia,⁷ and here we demonstrate that rs1049353 genotype interacts with CPA to increase severity of threat/fear, but not loss/dysphoria, symptoms of PTSD. The rs1049353 SNP is exonic, but synonymous, and may cause alterations in *CNR1* protein formation during translation.⁷ Notably, a previous study⁷ observed a protective effect of the minor A allele in rs1049353 and CPA interaction in relation to anhedonia symptoms. One explanation for these results is differing demographic (eg, racial) compositions or trauma exposure characteristics of the samples; another is that the rs1049353 genotype interacts with level of CPA to predict posttraumatic threat symptoms in some CPA survivors and anhedonic symptoms in other samples of CPA survivors. Further research is needed to replicate these results and investigate underlying mechanisms.

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Additional information: Investigators interested in collaborating on a project using data from the Detroit Neighborhood Health Study (DNHS) can obtain information from the DNHS website: <http://dnhs.unc.edu/data-requests/>.

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