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The rs1049353 polymorphism in the *CNR1* gene interacts with childhood abuse to predict posttraumatic threat symptoms

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To the Editor

Posttraumatic stress disorder (PTSD) is a heterogeneous condition comprised of threat/fear (e.g., intrusions, avoidance, hypervigilance) and loss/dysphoria (e.g., numbing, dysphoric arousal) symptoms.^{1,2} Contemporary scientific efforts in psychiatry, such as the National Institute of Mental Health Research Domain Criteria (RDoC) project, are encouraging

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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 availability,⁴ 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 minor (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 (DNHS), an epidemiologic study of predominantly African-American adults from urban Detroit,^{8,9} 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 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 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 intrusion, avoidance, and anxious arousal) and loss (sum of numbing and dysphoric arousal) symptoms. Age, sex, lifetime trauma burden, and the first two 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 non-significant (threat: $F[1,454]=0.69, p=0.41$; loss: $F[1,454]=0.51, p=0.47$). 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 five PTSD symptom dimensions (re-experiencing, avoidance, anxious arousal, numbing, dysphoric arousal), this interaction also emerged for two of three dimensions of threat symptoms: avoidance ($F[1,454]=6.13, p=0.014$) and re-experiencing ($F[1,454]=6.13, p=0.014$).

Discussion

The current findings extend our prior work implicating the endocannabinoid system in PTSD.^{4,5} The rs1049353 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 (e.g., racial) compositions or trauma exposure characteristics of the samples, or 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. Future research is needed to replicate these results and investigate underlying mechanisms.

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Figure 1.

Association of *CNR1* SNP rs1049353, childhood physical abuse, and posttraumatic threat symptoms ($N=487$)

Note. Error bars represent standard error (SE) of the mean. Low and high Childhood Physical Abuse (CPA) was based on summing the items to 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 MANCOVA revealed a significant rs1049353 genotype $\times$ CPA interaction in predicting threat symptoms only ($F[1,454]=7.57$, $p=.006$).

An additional *CNR1* 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 on severity of threat symptoms ($F[1,453]=4.37$, $p=.037$), it did not withstand the correction for multiple comparisons of two 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 ($F's < 2.47$, $p's > .11$).