


Cannabinoid Receptor 1 rs1049353 Variant, Childhood Abuse, and the Heterogeneity of PTSD Symptoms: Results From the National Health and Resilience in Veterans Study

Nachshon Korem^{1,2} , Or Duek^{1,2}, Ke Xu^{1,2},
Ilan Harpaz-Rotem^{1,2} , and Robert H. Pietrzak^{1,2}

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Abstract

Background: Accumulating evidence implicates the endocannabinoid system, including variants in the cannabinoid-1 receptor gene (*CNR1*), in the pathophysiology of posttraumatic stress disorder (PTSD). The synonymous G1359A variant (rs1049353) in the *CNR1* gene has been linked to PTSD in individuals exposed to childhood abuse. In this study, the effects of the rs1049353 genotype and childhood abuse on overall PTSD symptoms, as well as PTSD symptom clusters were examined in order to examine how this interaction relates to the phenotypic expression of this disorder.

Method: Data were analyzed from 1,372 Caucasian U.S. veterans who participated in the National Health and Resilience in Veterans Study. Multivariable analyses were conducted to evaluate the association between rs1049353 genotype, childhood abuse, and their interaction in relation to PTSD symptoms.

Results: A significant interaction between rs1049353 genotype and childhood abuse was observed, with A allele carriers with histories of childhood abuse reporting greater severity of PTSD symptoms, most notably anxious arousal, relative to G/G homozygotes. Significant main effects of childhood abuse on overall PTSD symptoms, and re-experiencing, emotional numbing, and dysphoric arousal symptom clusters, as well as of A allele carrier status on anxious arousal symptoms were observed.

Conclusions: Results of this study replicate prior work and suggest that the rs1049353-by-childhood abuse interaction is particularly associated with the manifestation of anxious arousal symptoms of PTSD. Taken together, these findings underscore the importance of considering the phenotypic heterogeneity of PTSD in gene-environment studies of this multifaceted disorder.

Keywords

CNR1 rs1049353, child abuse, PTSD, veterans, genetics

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Introduction

Posttraumatic stress disorder (PTSD) is characterized by heterogeneous symptom clusters. The number and nature of PTSD symptom clusters have evolved from the original model of two symptom clusters (i.e., re-experiencing of trauma and numbing of responsiveness to the external world) and a third nameless cluster of miscellaneous symptoms¹ to the current four-cluster system in the DSM-5.² Yet, there is continued discussion and empirical work centered on the optimal structural representation of PTSD symptoms. While most models agree on the placement of symptoms related to re-

experiencing and avoidance, there is debate concerning the placement of the other symptoms.^{3,4} Elhai et al.,⁵ proposed a model of DSM-IV PTSD symptoms that included

¹U.S. Department of Veterans Affairs National Center for Posttraumatic Stress Disorder, Clinical Neurosciences Division, VA Connecticut Healthcare System, West Haven, CT, USA

²Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Corresponding Author:

Nachshon Korem, Department of Psychiatry, Yale School of Medicine, 300 George St, New Haven, CT 06510, USA.

Email: Nachshon.Korem@Yale.edu



five symptom clusters: re-experiencing, avoidance, emotional numbing, dysphoric arousal (i.e., sleep disturbance, concentration difficulties, anger/irritability), and anxious arousal (i.e., hypervigilance and exaggerated startle response). The key differentiating feature of this model was combining sleep disturbance, irritability/anger, and difficulty concentrating symptoms into a *dysphoric arousal* cluster, as they are more reflective of general distress characterized by restlessness and agitation from the two hyperarousal symptoms of hypervigilance and exaggerated startle response, which are more characteristic of fear-based disorders.⁶ This five-factor model has demonstrated a better fit to DSM-IV PTSD symptom data in a broad range of trauma survivors.^{5,7,8} It is also reflected in contemporary structural models of DSM-5 PTSD symptoms.^{9,10} This model has also yielded stronger associations with external measures of psychopathology than less nuanced phenotypic models.^{7,11} Thus, employment of this more nuanced model of PTSD symptoms can provide greater insight into the phenotypic expression of PTSD, and possibly also genetic and environmental risk factors that underlie the phenotypic heterogeneity of this disorder.

The endocannabinoid system, which plays a key role in learning and extinction of fear memories, has been increasingly implicated in the development of PTSD and related disorders.¹² The *CNRI* is a protein-coding gene located on chromosome 6 band 6q15 that encodes the cannabinoid receptor 1 (CB1) in the central nervous system.¹³ Several *CNRI* gene variants have been linked to anxiety and depression in humans,^{14,15} most notably the G1359A variant rs1049353.¹² Despite lack of knowledge of the specific mechanisms by which synonymous genetic variants such as rs1049353 exert their effects, studies have shown that they can influence mRNA stability,¹⁶ structural folds,¹⁷ and gene function and phenotype,¹⁸ and may thus alter protein function and expression. Indeed, rs1049353 polymorphisms have been implicated in several disorders, including autoimmune disorders¹⁹ and alcohol dependence.²⁰ Higher rates of PTSD have also been observed in carriers of the A allele of rs1049353.²¹ Furthermore, rs1049353 A allele carriers with histories of childhood abuse were found to have elevated severity of threat symptoms (e.g., intrusions, avoidance, anxious arousal) relative to A allele carriers without such histories.²² Yet, not all

studies have replicated this finding.²³ A possible reason for these mixed findings is that extant studies have not considered the phenotypic heterogeneity of PTSD symptoms or possible environmental moderators of this polymorphism. To address this gap, the *CNRI* G1359 A variant (rs1049353) relation to the phenotypic expression of PTSD was evaluated, independently and interactively with childhood abuse.

Using data from the National Health and Resilience in Veterans Study (NHRVS)¹, which surveyed a nationally representative sample of U.S. military veterans, the main and interactive effects of the *CNRI* G1359 A variant (rs1049353) and childhood abuse in relation to overall PTSD symptoms and PTSD symptom clusters were examined. Based on previous studies, the main hypotheses in this study were: (a) that A allele carriers with histories of childhood abuse would report greater severity of PTSD symptoms relative to G/G homozygotes; and (b) that this effect would be most pronounced for PTSD symptoms reflecting threat symptoms (e.g., anxious arousal).^{22,24}

Materials and Methods

Participants

Participants were recruited from a research panel of over 50,000 U.S. households developed and maintained by GfK Knowledge Networks, Inc. (Menlo Park, CA, USA), and representing approximately 98% of U.S. households. Participants in this research panel were recruited into the NHRVS, conducted in 2011, if they answered affirmatively to the question, "Have you ever served on active duty in the U.S. Armed Forces, Military Reserves, or National Guard?" The NHRVS surveyed a nationally representative study of U.S. veterans, which included 1,372 trauma-exposed, Caucasian U.S. military veterans who provided a saliva sample for genotyping (mean age = 62.1 [SD = 14.3] years; 91.2% male; see Table 1 for more details). The over-representation of men in the NHRVS cohort is consistent with the demographic composition of the US veteran population. While non-European American veterans are included in the NHRVS sample, the sample sizes were too small for adequately powered analyses. Post-stratification weights were applied based on the demographic distribution of

Table 1. Demographic data of the study sample.

	Childhood abuse	n	Men (%)	Age (SD)
rs1049353 GG genotype	No	524	484 (93.1)	63.6 (14.6)
	Yes	172	146 (84.9)	59 (12.3)
rs1049353GA/AA genotype	No	518	486 (94.1)	63.3 (13.2)
	Yes	158	136 (89.3)	56.6 (15.5)

veterans (age, sex, education, race/ethnicity, metropolitan area, and Census region) in the GfK Knowledge Networks survey panel and calibrated against U.S. Census data. The NHRVS was approved by the Veterans Affairs (VA) Connecticut Healthcare System and the VA Office of Research & Development.

Assessments

Cumulative Trauma Burden. The Trauma History Screen (THS) was used to assess lifetime exposure to 13 potentially traumatic events,²⁵ including child and adult physical and sexual assault, natural disaster, and unexpected loss of a loved one; an additional event—life-threatening illness or injury—was added in the NHRVS. Events were summed to yield a summary measure of cumulative trauma burden.

PTSD Symptoms. The PTSD Checklist (PCL) was used to assess lifetime PTSD symptoms based on respondents' worst reported traumatic event on the THS. The DSM-IV and Specific Stressor version (PCL-Specific Stressor [PCL-S]) was used ($\alpha = .94$). Veterans were classified as having probable PTSD if their PCL score was ≥ 50 .²⁶ Responses on items comprising each symptom cluster were summed to yield severity measures; Cronbach's alphas suggested acceptable-to-excellent internal consistency for all symptom clusters: re-experiencing ($\alpha = .88$); avoidance ($\alpha = .71$); emotional numbing ($\alpha = .82$); dysphoric arousal ($\alpha = .79$); anxious arousal ($\alpha = .80$).

CNR1 Genotyping. Participants provided saliva for DNA extraction (for rs1049353 genotype). Saliva was collected using Oragene DNA (OG-250) kits. DNA was extracted using prepIT-L2P reagent (DNA Genotek, Ontario, Canada) according to manufacturer's directions. The sample was genotyped with the PsychChip GWAS array. Genotypes were called using GenomeStudio software V2011.1 and genotyping module V1.8.4 (Illumina, San Diego, CA, USA). Ninety samples with missing genotyping rate $>5\%$ were excluded from the analysis. The following criteria were used for including SNPs: minor allele frequency (MAF) $>0.01\%$, missing genotyping rate per SNP $<5\%$ and Hardy-Weinberg equilibrium (HWE) p -value $>10^{-5}$. This resulted in 423,415 autosomal SNPs. Duplicates were detected by estimating the genome-wide identity-by-descent (IBD) sharing for all pairwise samples in PLINK²⁷ using 93,814 independent SNPs with MAF >0.01 . Nine duplicate pairs and 12 additional pairs with a high level of IBD sharing (>0.1) were detected. One subject of the duplicate or related pairs was randomly removed, retaining 2,718 independent samples (2,270 EAs). Principal components (PC) for the GWAS data was computed using EIGENSOFT²⁸ based on a common set SNPs (64,219) with Hapmap3, which

were in low linkage disequilibrium (LD) with one another and have a MAF >0.01 . 95 outlier Caucasian samples from the PC analysis were detected and removed. Outliers were defined as samples whose ancestry was at least three standard deviations from the mean on one of the two largest PCs. 1000 genome variants were then imputed into the Caucasian samples following the best practice guidelines using IMPUTE2.²⁹ Pre-phasing was first performed with SHAPEIT³⁰ to infer haplotypes for the Caucasian samples based on 295,837 autosomal SNPs with MAF >0.01 . Imputation was then carried out on pre-phased haplotypes using IMPUTE2 against reference data from the 1000 Genomes Phase III integrated variant set. After post-imputation QC (SNP missing rate <0.05 , MAF >0.005 , imputation quality score (info) >0.5 , and HWE $>10^{-6}$), 10,377,932 SNPs remained. The CNR1 SNP—rs1049353 was extracted from the imputed data of Caucasian samples for a candidate gene analysis of rs1049353 carrier status. This SNP defines CNR1 variant status and was selected in accordance with previous literature.²² To determine rs1049353 carrier status, hard genotype calls were made on the imputed SNP by applying a posterior genotype probability threshold of 0.9. There was no evidence of deviation from Hardy-Weinberg expectations for the rs1049353 genotype ($p = 0.14$). A dichotomous variable of 0 versus 1 rs1049353 alleles was created (49.9% G/G homozygotes; 50.1% A allele carriers).

Data Analysis

Analyses focused on continuous PCL scores given that the focus of this study was to examine the relationship between rs1049353, childhood abuse, and symptom dimensions of PTSD; to be consistent with prior studies of this GxE interaction; and to maximize statistical power. An analysis of covariance (ANCOVA) was conducted to evaluate the relation between CNR1 rs1049353 carrier status, childhood abuse and their interaction on overall PTSD symptoms. Covariates/fixed factors included age, sex, top 10 PCs from population stratification analysis (to control for ancestry proportions), combat veteran status, number of lifetime traumas other than childhood abuse, and nature of index trauma (i.e., assaultive vs. non-assaultive). To evaluate the relationship between CNR1 rs1049353 allele carrier status, childhood abuse and their interaction on severity of PTSD symptom clusters, a multivariate ANCOVA was conducted with scores on each of the PTSD symptom clusters entered as dependent variables. A statistical significance threshold of $\alpha = 0.01$ (0.05/5 symptom clusters) was employed in this analysis to reduce the likelihood of Type I error. Effect sizes (Cohen's d) and standard errors (SE) are reported. Reported raw frequencies are unweighted; means, percentages, and inferential statistics are post-stratification weighted to reflect

the general population of U.S. veterans. Analyses were conducted using SPSS version 27.

This study conforms to the editorial policy proposed by Hewitt³¹ for gene \times environment studies in the following ways: it is a rigorously conducted, adequately powered, replication of a previously reported result. Specifically, findings replicate those reported in a predominantly African American and female sample by Mota et al.,²² and extend these findings to a nationally representative sample of Caucasian and predominantly male U.S. military veterans. Moreover, statistical tests were corrected for multiple comparisons.

Results

As shown in Table 2, for overall severity of PTSD symptoms, a main effect for childhood abuse (Cohen's

$d = 0.15$), as well as a significant $rs1049353 \times$ childhood abuse interaction was observed. Among veterans with childhood abuse histories, A allele carriers reported significantly greater severity of PTSD symptoms (Mean = 35.1, SE = 0.99) relative to G/G homozygotes (Mean = 31.8, SE = 0.97; Cohen's $d = 0.28$; Figure 1).

Analysis of PTSD symptom clusters revealed a significant main effect of $rs1049353$ A allele carrier status on anxious arousal symptoms (Cohen's $d = 0.31$); significant main effect of childhood abuse on emotional numbing (Cohen's $d = 0.15$), dysphoric arousal (Cohen's $d = 0.15$), and re-experiencing (Cohen's $d = 0.09$) symptoms; and a significant $rs1049353 \times$ childhood abuse interaction on anxious arousal, dysphoric arousal and emotional numbing symptoms. Specifically, among veterans with childhood abuse histories, A allele carriers reported greater severity of anxious arousal (Cohen's

Table 2. Results of multivariable analyses evaluating the relation between the *CNR1* rs1049353 genotype, childhood abuse, and PTSD symptoms.

	PTSD symptoms		Re-experiencing		Avoidance		Emotional numbing		Dysphoric arousal		Anxious arousal	
	F	p	F	p	F	p	F	p	F	p	F	p
rs1049353 A allele carrier	2.93	0.087	0.05	0.82	0.25	0.62	1.76	0.18	3.04	0.082	26.61	2.9×10^{-7}
Childhood abuse	35.51	2.4×10^{-4}	6.95	0.008	0.24	0.63	17.77	2.7×10^{-5}	18.317	2×10^{-5}	2.41	0.12
rs1049353 A allele carrier \times Childhood Abuse	11.92	0.001	4.54	0.033	0.01	0.91	8.16	0.004	11	0.001	36.26	2.3×10^{-12}

Note. Analyses are adjusted for age, sex, first 10 PCs, combat veteran status, number of lifetime traumas other than childhood abuse, and nature of index trauma (i.e., assaultive vs. non-assaultive).

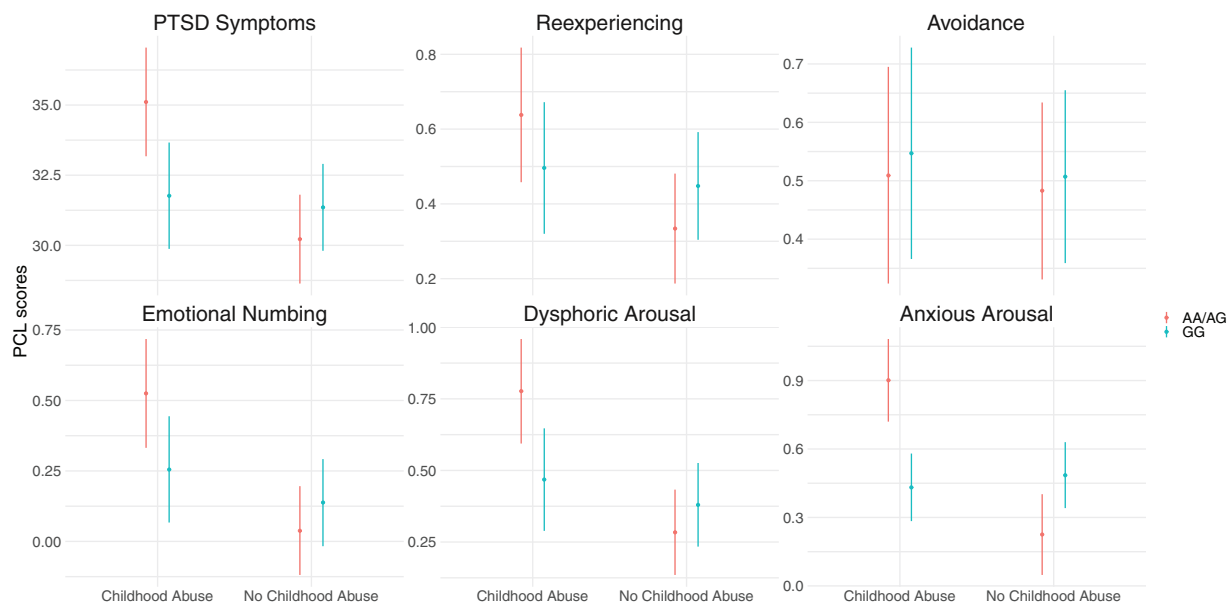


Figure 1. Significant interactions of $rs1049353$ genotype and childhood abuse in predicting overall PTSD symptoms and PTSD symptom clusters. Overall severity of PTSD symptoms is expressed as raw PTSD Checklist scores; PTSD symptom clusters are expressed as standardized scores to facilitate interpretation of magnitudes of group differences. Error bars represent 95% confidence intervals. Childhood abuse was operationalized as report of physical and/or sexual abuse during childhood on the Trauma History Screen.

$d = 0.61$), dysphoric arousal (Cohen's $d = 0.27$), and emotional numbing (Cohen's $d = 0.23$) symptoms relative to G/G homozygotes.

Discussion

This study examined the relation between the *CNR1* rs1049353 genotype, childhood abuse, and PTSD symptoms in a nationally representative sample of Caucasian and predominantly male U.S. military veterans. Results revealed that in veterans with a history of childhood abuse, A allele carriers reported significantly greater severity of PTSD symptoms relative to G/G homozygotes. Furthermore, this association was most pronounced for anxious arousal symptoms (i.e., hypervigilance, exaggerated startle response).

Results of this study extend prior work implicating the role of *CNR1* gene variants in PTSD.^{21,22} For example, Lu et al.²¹ found that rs1049353 A allele carriers had increased risk for PTSD in a sample of 480 Caucasian Americans and 310 Finnish adults. The inability to replicate this finding in a later study²³ may, at least in part, be related to examining PTSD as a homogeneous entity and without consideration of possible environmental moderators. Indeed, Mota et al.²² did not observe a main effect of rs1049353 genotype on severity of threat (sum of intrusion, avoidance, and anxious arousal) or loss (sum of emotional numbing and dysphoric arousal) symptoms, but did find that among A allele carriers, those with childhood abuse histories reported greater severity of threat symptoms relative to those without such histories. Results of the current study extend results of Mota et al.'s²² study, which focused on a predominantly African-American and female sample, to a predominantly European-American and male sample of military veterans. The robustness of the observed GxE association with the phenotypic expression of PTSD symptoms is particularly notable in light of prior work suggesting gender differences in cannabinoid effects.³² Taken together, results of the Mota et al.²² coupled with those of current study suggest that the interaction of the rs1049353 polymorphism with childhood abuse is most strongly associated with threat/arousal symptoms of PTSD in two distinct populations. Results of the current study align with other work suggesting an association between childhood abuse and PTSD,³³ and between A allele carrier status and higher levels of impulsivity,^{34,35} which often co-occurs with hyperarousal,³⁶ and may thus contribute to the pathophysiology of hyperarousal symptoms in trauma survivors. A possible mechanism for the strong effect of this polymorphism on anxious arousal symptoms, is the interconnection between the cannabinoid system and noradrenergic system.³⁷ Genetic variants in the noradrenergic system have been linked to anxious arousal

symptoms³⁸ and may thus contribute to greater severity of anxious arousal symptoms, particularly among individuals with childhood abuse histories. Overall, these findings suggest that the rs1049353 phenotype in veterans with histories of childhood abuse may be most strongly linked to anxious arousal symptoms of PTSD. However, further research in a single cohort that is more representative of the entire population, and that includes relatively equal numbers of both genders and multiple ethno-racial groups is needed to confirm these findings.

The finding that rs1049353 A allele carriers with histories of childhood abuse reported greater severity of hyperarousal symptoms than G/G homozygotes aligns with results of a functional magnetic resonance imaging (fMRI) study of healthy adolescents, which revealed that A allele carriers showed earlier recognition of facial expressions changing from anger or happiness to fear or sadness, and greater amygdala and insula activation in response to angry faces.³⁹ rs1049353 A allele carriers may thus be more vigilant in monitoring changes in emotional expressivity. However, another fMRI study of healthy adults found that A allele carriers evidenced *greater* ventromedial prefrontal cortical activation, a marker of emotional modulation, when viewing negative stimuli following a stress induction.⁴⁰ While further research is needed to evaluate the role of *CNR1* variants in relation to stress-related neural processing and psychiatric phenotypes, particularly in individuals with histories of childhood abuse, results of the current study underscore the importance of employing nuanced models of phenotypic heterogeneity when examining gene x environment associations in trauma survivors. They further implicate the role of this genetic variant in the phenotypic expression of PTSD.

Results of this study have some potential clinical implications. By examining GxE associations with rs1049353 polymorphisms and childhood abuse histories may present with a certain clinical profile characterized most notably by elevated anxious arousal symptoms. Prior work using latent class/profile analyses has identified different subtypes of PTSD, one of which is characterized by marked elevations of 'threat' symptoms of PTSD that include anxious arousal symptoms; and another by elevations of 'dysphoric' symptoms of PTSD.⁴¹⁻⁴³ Thus, results of the current study suggest that rs1049353 with childhood abuse histories may benefit from exposure-based treatments that focus on mitigating anxious arousal and related symptoms of PTSD;⁴² in contrast, behavioral activation may be more effective for individuals presenting with more prominent dysphoric symptoms of PTSD.⁴³ Elucidation of GxE—and also polygenic risk x E—associations with the phenotypic expression of PTSD symptoms may ultimately help inform understanding of distinct clinical profiles and possible subtypes of

PTSD. Such profiles may in turn help guide precision medicine interventions for this multifaceted disorder.

Methodological limitations of this study must be noted. First, although rs1049353 variant was studied previously in several conditions, the molecular pathways by which it may influence either CB1 receptors or other proteins remains speculative and should be further studied. One possible pathway is differential affinity of receptors to cannabinoids.⁴⁴ Second, the candidate gene approach of focusing on a single SNP is not as informative as GWAS or polygenic studies of genetic risk for PTSD. Future studies using larger datasets and these approaches are needed to evaluate the role of childhood abuse in moderating these cumulative measures of genetic risk on the phenotypic expression of PTSD symptoms.

In summary, results of this study suggest that the rs1049353 interacts with history of childhood abuse to predict greater severity of PTSD symptoms, especially anxious arousal, in a nationally representative sample of Caucasian U.S. military veterans. Further research is needed to examine the direct and interactive role of *CNR1* variants and childhood abuse in relation to the broader transdiagnostic spectrum of trauma-related psychopathology; identify biopsychosocial mechanisms linking this and other gene-by-environment associations to the phenotypic expression of PTSD symptoms; and determine the efficacy of treatments targeting the endocannabinoid system in mitigating PTSD symptoms.



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ORCID iDs

Nachshon Korem  <https://orcid.org/0000-0003-1859-2668>
 Ilan Harpaz-Rotem  <https://orcid.org/0000-0002-6066-9406>

Note

1. <https://www.vacsp.research.va.gov/CSPEC/Studies/INVESTD-R/Ntl-Health-Resilience-Veterans-Study.asp>

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