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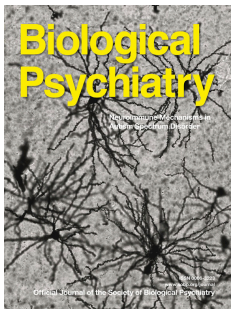

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PII: S0006-3223(20)31947-8

DOI: https://doi.org/10.1016/j.biopsych.2020.09.018

Reference: BPS 14345

To appear in: *Biological Psychiatry*

Received Date: 8 July 2020

Revised Date: 15 September 2020

Accepted Date: 15 September 2020

Please cite this article as: Tamman A.J.F., Wendt F.R., Pathak G.A., Krystal J.H., Montalvo-Ortiz J.L., Southwick S.M., Sippel L.M., Gelernter J., Polimanti R. & Pietrzak R.H., Attachment style moderates polygenic risk for posttraumatic stress in United States military veterans: Results from the National Health and Resilience in Veterans Study, *Biological Psychiatry* (2020), doi: https://doi.org/10.1016/j.biopsych.2020.09.018.

Attachment style moderates polygenic risk for posttraumatic stress in United States military veterans: Results from the National Health and Resilience in Veterans Study

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Key words:

Polygenic risk; attachment style; posttraumatic stress disorder; gene enrichment

Running title:

Attachment style moderates polygenic risk for PTSD symptoms

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ABSTRACT

Background: Polygenic risk scores (PRS) derived from genome-wide association studies (GWAS) of posttraumatic stress disorder (PTSD) may inform risk for this disorder. To date, however, no known study has examined whether social environmental factors such as attachment style may moderate the relation between PRS and PTSD.

Methods: We evaluated main and interactive effects of PRS and attachment style on PTSD symptoms in a nationally representative sample of trauma-exposed, European-American U.S. military veterans (*N*=2,030). PRS were derived from a GWAS of PTSD re-experiencing symptoms (*N*=146,660) in the Million Veteran Program cohort. Using one-sample Mendelian randomization (MR) with data from the UK Biobank (*N*=115,099), we evaluated the effects of re-experiencing PRS and attachment style on PTSD symptoms.

Results: Higher re-experiencing PRS and secure attachment style were independently associated with PTSD symptoms. A significant PRS-by-attachment-style interaction was also observed (β=-0.11, p=0.006) with a positive association between re-experiencing PRS and PTSD symptoms observed only among veterans with an insecure attachment style. One-sample MR analyses suggested that the association between PTSD symptoms and attachment style is bidirectional. PRS enrichment analyses revealed a significant interaction between attachment style and a variant mapping to the *IGSF11* gene (rs151177743; $p=2.1\times10^{-7}$), which is implicated in regulating excitatory synaptic transmission and plasticity.

Conclusions: Attachment style may moderate polygenic risk for PTSD symptoms, and a novel locus implicated in synaptic transmission and plasticity may serve as a possible biological mediator of this association. These findings may help inform interpersonally-oriented treatments for PTSD for individuals with high polygenic risk for this disorder.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a chronic and disabling psychiatric disorder that can develop in response to trauma exposure (1). However, a relatively small proportion of individuals who are exposed to trauma develop PTSD (2). Consequently, an extensive literature has reported factors that differentiate those who do and do not develop PTSD after trauma exposure. Given high heritability estimates for PTSD (24-72%), increasing research has examined genetic factors associated with the disorder (3).

In recent years, genetic studies of PTSD have transitioned away from hypothesis-driven candidate gene studies in favor of more agnostic, genome-wide association studies (GWAS). GWAS identify polymorphic variants that differ in frequency between PTSD-affected and unaffected individuals across the entire genome (4-7). Using GWAS summary statistics, polygenic risk scores (PRS) can be derived by weighing an individual's risk alleles per-SNP by the GWAS effect size estimate. The resulting PRS represents an aggregated score of multiple risk SNPs, with higher PRS indicating greater genetic predisposition to PTSD (8). PRS may be more informative and intuitively decipherable than examining multiple individual genes, and may reduce multiple testing burden and consequent false positives (8).

Although genetic factors such as PRS are important for predicting PTSD, genetic risk cannot be understood without considering the environmental context within which it occurs (9-11). To date, most gene-by-environment interaction studies have employed candidate gene approaches, evaluating whether the association between SNPs selected based on known biology and association with PTSD is mediated or moderated by environmental factors such as childhood abuse (12-16). With novel methods such as PRS-based analyses and GWAS, these candidate gene-by-environment analyses have been superseded by PRS-by-

environment analyses. Although some studies have looked at PRS-by-environment predictors of major depressive, social anxiety, bipolar, substance use, and attention-deficit hyperactivity disorders (17-25), to date, no known study has examined PRS-by-environment predictors of PTSD.

In the present study, we focused on the role of attachment style, which was conceptualized broadly as the framework that an individual uses to navigate their interpersonal relationships, as a potential socio-environmental moderator of the association between re-experiencing PRS and PTSD symptoms. Attachment style represents an individual's expectations of the availability and responsiveness of important others in multiple contexts. It is thought that attachment systems are activated during times of stress (26), potentially representing a protective factor for PTSD. Securely attached adults perceive their interpersonal relationships as positive and trusting, feel worthy of love, and have confidence that they can have caring relationships (27). Insecure attachment styles are typically conceptualized by evasion of intimacy (*i.e.*, insecure-avoidance attachment style) or high anxiety about reciprocation of intimacy (*i.e.*, insecure-ambivalent attachment style). Attachment style is robustly associated with PTSD symptoms, diagnosis, and treatment outcomes in both longitudinal and cross-sectional studies (28-35), thus suggesting causal evidence for the influence of attachment style on PTSD risk. Having an insecure attachment style is associated with maladaptive appraisals and emotion regulation strategies during times of stress, which may in turn increase risk for PTSD (36-40).

To date, a small number of candidate gene studies have found that insecure attachment style interacts with polymorphisms in *FKBP5* and *OXTR* genes to predict heightened cortisol reactivity and PTSD symptoms, suggesting that secure attachment style may buffer against

genetic risk amongst trauma-exposed individuals (41-43). However, no known study has examined whether attachment style may buffer against polygenic risk for PTSD symptoms using GWAS-derived PRS measures. This is a particularly important area for investigation, as attachment style represents a potentially modifiable moderator of the association between PRS, trauma load, and PTSD (44). Evidence that attachment style is a moderator of polygenic risk for PTSD may help inform the etiology of PTSD, as well as prevention and treatment efforts for this disabling disorder.

Gene enrichment analyses have been used to improve biological interpretation of genetic findings such as PRS by testing for the overrepresentation of gene categories rather than individual genes (45). If genes under examination underlie the same biological function or pathway, then considering the pathway as the unit of analysis increases the power to detect a relationship between the genes and the disorder. This approach uses categories defined by databases such as the Gene Ontology (GO) database to identify underlying biological pathways and molecular mechanisms implicated in the relationship between genetic susceptibility and a given disorder (*e.g.* 46-48). Bioinformatics approaches such as gene enrichment and gene pathway analyses are crucial to advancing understanding of the complex etiology of mental disorders, including PTSD (49). In the current study, we employed such analyses to identify potential biological mediators of the association between PRS, attachment style, and PTSD symptoms.

The aim of the current study was to examine whether attachment style moderates polygenic risk for PTSD symptoms in a nationally representative sample of U.S. military veterans. PRS were derived from a large, contemporary GWAS of PTSD symptoms in 146,660 European American (EA) U.S. military veterans in the U.S. Million Veteran Program (MVP), that

focused on re-experiencing symptoms (50). We utilized re-experiencing PRS because: (a) re-experiencing symptoms are among the more characteristic symptoms of PTSD and related disorders (50-53); (b) re-experiencing symptoms often trigger other PTSD symptoms and thus represent a key driver of the disorder (54-55); (c) these scores were derived from the genome-wide association statistics of the largest publicly available GWAS of PTSD symptoms in veterans to date (dbGaP Study Accession: phs001672.v4.p1); and (d) genetic correlations are high (>0.90; 95%CI 0.91-0.95) among pairs of PTSD symptom clusters and overall severity of symptoms, including between re-experiencing and avoidance (56).

Based on prior work (41-43), we hypothesized that veterans with higher re-experiencing PRS and an insecure attachment style would have greater severity of PTSD symptoms. We further hypothesized that attachment style would moderate the association between re-experiencing PRS and PTSD symptoms, such that veterans with higher re-experiencing PRS and insecure attachment style would have greater severity of PTSD symptoms than those with a secure attachment style. We additionally conducted a one-sample Mendelian randomization study to evaluate the directionality of association between attachment style and PTSD symptoms, and examined PRS enrichment to identify possible biological mediators of the link between PRS and attachment style, and PTSD symptoms.

METHODS AND MATERIALS

***Participants*.** The sample consisted of 2,030 EA veterans who participated in the National Health and Resilience in Veterans Study (NHRVS), which surveyed a nationally representative sample of U.S. military veterans. The sample was ascertained from a nationally representative survey research panel of more than 50,000 U.S. households

maintained by GfK Knowledge Networks (now Ipsos). All participants were EA trauma-exposed men whose data were meta-analyzed from two independent cohorts of the NHRVS that were collected in 2011 (n=1,509) and 2013 (n=521). To permit generalizability of study results to the entire population of U.S. veterans, post-stratification weights were applied to inferential analyses; these weights were computed based on the demographic distribution of U.S. veterans from concurrent U.S. Census Bureau Current Population Survey data. The Human Subjects Subcommittee of the VA Connecticut Healthcare System approved the study.

Genotyping

Participants provided saliva for DNA extraction. Saliva was collected using Oragene DNA (OG-250) kits. Details regarding DNA extraction and genotyping (57-60) are available in supplemental methods.

Polygenic Risk Scoring. We calculated PRS in the NHRVS samples using PRSice 1.25 software (61). We used summary statistics generated from the recent GWAS of PTSD re-experiencing symptoms conducted in the MVP cohort (50). To avoid biases due to population structure (62), this analysis was performed using MVP EA participants. Additionally, we verified that no overlap is present between NHRVS and MVP. We considered multiple genome-wide association p-value thresholds (PT=5×10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 0.001, 0.05, 0.3, 0.5, 1) for SNP inclusion. Details are reported in Supplemental methods. We examined correlations between various PRSs and PTSD symptom severity scores and selected the PRS defined at PT=0.3 for it had the largest magnitude association with PCL scores (r^2=0.09, p=9.3×10^{-5}). Selection of this PRS survived multiple testing after Bonferroni correction for the number of PRSs examined (0.05/10=0.005).

Assessments

Attachment Style. Attachment style was assessed using the three-item Adult Attachment Style Questionnaire (ASQ; 27; 63). Details regarding the items are available in supplemental methods. As less than 5% of individuals reported having an insecure-ambivalent attachment style, avoidant and ambivalent attachment styles were recoded into a single insecure attachment style category.

PTSD Symptoms. Lifetime and past-month PTSD symptoms were assessed with the PTSD Checklist (PCL; 64). The 17-item *Diagnostic and Statistical Manual of Mental Disorders IV* (*DSM-IV*) version of the PCL was administered in the 2011 sample (Cronbach's a=0.94) and the 20-item *DSM-5* version (65) was administered in the 2013 sample (Cronbach's a=0.95). The PCL contains items about PTSD symptoms related to an individual's worst traumatic event, which was assessed using the Trauma History Screen (66). On a 5-point scale ranging from *not at all* to *extremely*, participants rated the extent to which they were bothered by each of symptoms in their lifetime. The PCL is a commonly used and well-validated measure of PTSD, with good temporal stability, internal consistency, test-retest reliability, and convergent validity (67). A crosswalk algorithm developed by Moshier et al. (68) was used to convert DSM-IV PCL scores to DSM-5 PCL scores. Probable PTSD was operationalized as a score $\geq$ 13, which is the DSM-5 equivalent of a score of $\geq$ 30 that has been recommended in studies of non-treatment-seeking, population-based samples (69). See supplemental methods for description of how symptom cluster comparability was achieved (70).

Data Analysis

PRS and PRS-by-attachment style analyses. A Spearman correlation analysis revealed that re-experiencing PRS and attachment style were not associated (r= -0.04, p=0.10), thus ruling out the potentially confounding presence of a gene-environment correlation (rGE). We then conducted two sets of multiple regression analyses to evaluate associations between re-experiencing PRS, attachment style, and their interaction in relation to lifetime and past-month PTSD symptoms. These analyses were adjusted for age, the top 10 ancestry principal components (PCs), combat veteran status, cumulative trauma burden, nature of index trauma (assaultive *vs.* non-assaultive), and time since index trauma. We then conducted secondary multiple regression analyses to examine how re-experiencing PRS, attachment style, and their interaction related to lifetime and past-month PTSD symptom clusters. To correct for multiple comparisons, we adjusted the false discovery rate using the Benjamini-Hochberg procedure for the two primary analyses and the eight secondary analyses, respectively (71).

One-Sample Mendelian Randomization. Mendelian randomization (MR) infers putative causal relationships between two traits using genetic variants (e.g., SNPs) as non-modifiable instrumental variables (72). We considered the per-SNP association statistics from large-scale GWASs of a) re-experiencing (50) as a proxy for per-SNP associations with PCL/PTSD; and b) "*been in a confiding relationship as an adult*" (UK Biobank Field ID 20522, N=115,099) as a proxy phenotype for per-SNP associations with attachment style. To evaluate the stability of inverse-variance weighted (IVW) effect estimates, we considered multiple genetic instruments defined on the basis of the following significance thresholds: PT=0.3, 0.05, 1 x 10^{-5}, 5x10^{-8}. IVW estimates were generated with the MendelianRandomization R package (73) testing four hypotheses: i) attachment style → PTSD, ii) PTSD → attachment style, iii)

attachment style → lifetime PCL total score, and iv) lifetime PCL total score → attachment style. We adjusted the IVW estimates using the within-sample correlation between exposure and outcome in the NHRVS data (*i.e.*, setting the psi flag in the mr_ivw feature equal to the observed correlation between the variables tested (see Supplement methods). To test for effect size outliers biasing the genetic instruments, we evaluated the Cochran's *Q* statistic and its associated *p*-value for the hypothesis that the genetic instruments in question show no evidence of effect size heterogeneity.

PRS Enrichment. The re-experiencing PRS variants were categorized for variants surviving multiple testing threshold ($p=3.19\times10^{-7}$) and nominally significant variants ($p\leq0.05$) for the effect of PRS x attachment style and PTSD symptoms (Supplementary Figure S1). Nominally significant variants that displayed concordant direction of effect between PRS x attachment style and PTSD symptoms were selected for gene ontology enrichment. The variants were mapped to genes using Ensembl's Variant Effect Predictor (GRCh37), followed by testing for gene ontology using ShinyGO (74) and functional profiling using g:Profiler (75) with FDR *p*-value (p_{FDR})<0.05. The variants were annotated using DeepSEA (76), a functionally annotating algorithm for SNPs based on their weights in the regulatory sequence code obtained from chromatin profiling, and known phenotypic association using SNPnexus (77).

RESULTS

Table 1 shows descriptive statistics of the NHRVS samples.

Re-Experiencing PRS, Attachment Style, and PTSD Symptoms

Table 2 shows results of multiple regression analyses of the association between re-experiencing PRS, attachment style, and their interaction in predicting PTSD symptoms.

Overall, the models were significant for lifetime (F(18,1530)=49.04, p=4.76×10^{-137}) and past-month (F(18,1400)=41.87, p= 4.14×10^{-117}) PTSD symptoms. This multiple regression accounted for 35.8% and 34.2% of the variance in lifetime and past-month symptoms respectively (R^2). Higher PRS and insecure attachment style were independently associated with greater severity of both lifetime and past-month PTSD symptoms. The interaction of re-experiencing PRS and attachment style also significantly predicted severity of lifetime and past-month PTSD symptoms. In particular, the interaction revealed a positive association between PRS and severity of PTSD symptoms for insecurely attached, but not securely attached veterans. As shown in Figures 1 and 2, there was a linear R^2 value of 0.13 and 0.18 between polygenic risk score and lifetime and past-month severity of PTSD symptoms, respectively, for insecurely attached veterans; in contrast, these R^2 values were 0.01 and 0.02, respectively, for securely attached veterans.

Re-Experiencing PRS, Attachment Style, and PTSD Symptom Clusters

Table 2 shows results of secondary multiple regression models examining the effects of re-experiencing PRS, attachment style, and their interaction in predicting PTSD symptom clusters. Overall, the models were significant for lifetime re-experiencing (F(18,1533)=38.61, p=9.67×10^{-111}, R^2=0.30); avoidance (F(18,1533)=26.27, p=9.51×10^{-77}, R^2=0.23); numbing (F(18,1533)=39.78, p=8.51×10^{-114}, R^2 =0.31); and hyperarousal (F(18,1533)=38.30, p=6.56×10^{-110} , R^2 =0.30. The models were also significant for past-month re-experiencing (F(18,928)=10.60, p=9.22×10^{-28}, R^2 =0.15); avoidance (F(18,929)=7.93, p=9.22×10^{-20}), R^2 =0.12; numbing (F(18,927)=9.77, p=2.89×10^{-25}, R^2 =0.14 and hyperarousal (F(18,926)=11.15, p=2.24×10^{-29}, R^2 =0.16). Statistically significant interactions between re-experiencing PRS and attachment style were observed for lifetime re-experiencing, numbing, and hyperarousal symptoms; and past-month re-experiencing, avoidance, and numbing

symptoms, with veterans with higher PRS and an insecure attachment style scoring higher on these measures than those with a secure attachment style.

Bidirectional Effects Between Attachment Style, and Diagnosis and Severity of PTSD Symptoms

One-sample MR was used to test for a causal relationship between attachment style, PTSD case/control diagnosis, and lifetime severity of PTSD symptoms using genetic variants associated with exposure phenotypes "*been in a confiding relationship as an adult"* (UK Biobank Field ID 20522) as a proxy for the per-SNP associations with attachment style, and re-experiencing as a proxy for the per-SNP associations with PTSD diagnosis and lifetime PCL total scores. After multiple-testing correction for the number of trait pairs tested, all causal estimates were devoid of heterogeneity in their genetic instruments (false discovery rate $q< 0.05$). We detected stable and bidirectional IVW estimates for i) PTSD diagnosis ↔attachment style (PTSD→attachment style mean IVW $\beta = 0.252\pm0.195$ and attachment style→PTSD mean IVW $\beta=0.426\pm0.153$) and ii) lifetime PCL total score↔attachment style (PCL→attachment style mean IVW $\beta=0.124\pm0.063$ and attachment style→PCL mean IVW $\beta=0.296\pm0.025$; Table 3). The GWAS for "*been in a confiding adult relationship as an adult*" did not detect genome-wide significant SNPs, so we were unable to assess i) attachment style→PTSD diagnosis and ii) attachment style→PCL at this level of genetic instrument inclusion (Table 3).

Functional Annotation and Enrichment of PRS Variants

Of the PRS variants, one (rs151177743 on chromosome 3, $p=2.07\times10^{-7}$) survived multiple-testing correction for the PRS-by-attachment style interaction → PTSD symptoms. This variant was associated with PTSD symptoms ($\beta=0.68$, $p=8.16\times10^{-4}$) in veterans with a secure

attachment style, but not in veterans with an insecure attachment style (β=-0.17, p=0.47), highlighting a unique role of attachment style in moderating polygenic risk for PTSD. This variant was not significantly associated with PTSD symptoms (β=0.02, p=0.90) in the full cohort. A total of 731 SNPs among 1,628 nominally significant variants had concordant effect directions between phenotype-PTSD and the PRS-by-attachment style interaction. Sixty-four SNPs of the PRS variants had > 0.7 probability for eQTL (Supplementary Table S1). 175 SNPs have been previously associated with psychiatric disorders either directly or via proxy-SNPs (Supplementary Table S2). Functional profiling identified Reactome's O-glycosylation of thrombospondin type 1 repeat (TSR) domain-containing proteins (p_{FDR} =0.023) and miRNA, hsa-miR-6873-3p (p_{FDR} = 0.049; Supplementary Figure S1). The categories enriched for GO: molecular function were amino acid: sodium symporter activity (p_{FDR} =0.011), sodium ion transmembrane transporter activity (p_{FDR} =0.021) Amino acid: cation symporter activity (p_{FDR} =0.020) and inorganic cation transmembrane transporter activity (p_{FDR} =0.046) among others (Supplementary Table S3). The genes overlapping these SNPs were enriched for synapse organization (p_{FDR} =0.031), cell morphogenesis involved in neuron differentiation (p_{FDR} =0.046), among others for GO: Biological Process (Supplementary Table S4).

DISCUSSION

Using data from a nationally representative sample of EA U.S. veterans, we found that higher re-experiencing PRS were associated with greater severity of PTSD symptoms, consistent with prior findings that PTSD PRS is associated with the onset and severity of PTSD (8). Our findings extend this work to suggest that the association between higher PRS and greater severity of PTSD symptoms was observed only in veterans with an insecure attachment style.

The PRS-by-attachment style interaction was specifically associated with greater severity of lifetime and past-month re-experiencing and numbing symptoms, lifetime hyperarousal symptoms, and past-month avoidance symptoms.

Our observations regarding the moderating role of attachment style on PTSD risk were supported by one-sample MR analyses of instrumental variables associated with large-scale studies of two proxy phenotypes for attachment style and PTSD in the UK Biobank cohort. Specifically, we found evidence of bidirectional effects between attachment style, and diagnosis and severity of PTSD, with concordant effect directions and magnitudes. These findings support shared biology (*i.e.*, pathways, mechanisms, gene-sets) between attachment style and PTSD. These biological underpinnings may elucidate mechanistic targets, which may help explain protective effects of secure attachment on PTSD symptoms (28-43).

Among the variants included in the significant PRS (PT = 0.3), rs151177743 showed an interaction with attachment style that survived multiple-testing correction and distinct relationships with severity of PTSD symptoms in securely (rs151177743 TA allele was linked to greater severity of PTSD symptoms) versus insecurely attached veterans (rs151177743 TA allele was unrelated to PTSD symptoms). Importantly, although rs151177743 was associated with a paradoxical increase in severity of PTSD symptoms in securely attached veterans only, PTSD is a complex phenotype characterized by the additive effects of numerous loci across the genome and a single SNP-by-attachment style interaction in the opposite direction of epidemiological effects should not be interpreted as conflicting evidence for attachment-style-PTSD protective effects. Another consideration is that, due to the limited sample size, analyses of the insecurely attached subsample (N=497) had lower statistical power than those of the securely attached subsample (N=1,526).

The variant rs151177743 maps to *IGSF11*, a gene encoding for a homophilic adhesion molecule preferentially expressed in the brain that it is involved in regulating excitatory synaptic transmission and plasticity (78). Variants mapped to *IGSF11* have been previously associated with pleiotropic effects linking schizophrenia and cognitive ability (79). Consistent with *IGSF11* involvement in synaptic adhesion, the PRS enrichment analysis identified several cell adhesion and synaptic processes. Synaptic cell adhesion molecules are critical in maintaining synaptic plasticity. Certain synaptic cell adhesion molecules such as SyCAM1 have been associated with long-term depression (80-81). These synaptic processes may be implicated in PTSD via their mediation of fear conditioning and extinction learning, which have been found to be abnormal in trauma-exposed individuals with PTSD relative to controls (81-83). Evidence from animal models of behavioral abnormalities observed in PTSD, such as over-generalization of fear associations and impaired fear extinction, suggest that abnormal synaptic plasticity may be one mechanism underlying the development of PTSD (82-84). While we did not directly examine synaptic plasticity in this study, one possibility is that secure attachment style may counteract the effects of genetically-mediated aberrant synaptic plasticity in those with high re-experiencing PRS. Securely attached veterans may better engage adaptive affect-regulation strategies such as accessing social support, thus mitigating polygenic risk for PTSD after trauma exposure (39-40). Conversely, individuals with an insecure attachment style, particularly insecure-avoidant attachment style, may be less inclined to seek treatment for PTSD due to denial of distress and/or general reluctance to seek help (85). Further research is needed to directly examine potential shared biological underpinnings that underlie the moderating effect of attachment style (*e.g.* 41).

While the association between attachment style and PTSD is likely bidirectional (30), our

findings have some clinical implications. For example, identification of individuals with high polygenic risk and an insecure attachment style may help inform risk stratification models for PTSD (86). This information may also help to identify at-risk veterans who may benefit from early intervention following trauma (86). Results of this study also suggest that modification of attachment style (87-88) through psychotherapies directed at interpersonal relationships (44; 87-93) may potentially help to mitigate polygenic risk for PTSD. Such therapies focus on the reparative therapist-patient relationship and other key relationships, to develop more adaptive and flexible templates of interpersonal relationships, bolster social support, and improve social skills such as mentalizing abilities (44; 90-93). The present study also highlights two factors—polygenic risk and attachment style—that could be considered in precision medicine treatment efforts for PTSD (94-95). For instance, individuals with elevated PRS and an insecure attachment style may benefit from a specific focus on strategies to reinforce interpersonal relationships and support (44; 87-93).

This study has some methodological limitations. First, although we verified lack of effect size heterogeneity among the genetic instruments, proxy phenotype selection also may bias these effect sizes. Second, our sample may not be representative of other non-veteran populations that experience PTSD, or of non-EA veterans; results should be replicated in the general population and more diverse samples of veterans. Importantly, these studies will require equally powered GWAS of PTSD in non-European American populations to appropriately weight the per-SNP contributions to a polygenic risk score. Third, given that attachment style is a developmental variable that is thought to develop as early as infancy, future work should examine the relationship between childhood attachment style and PTSD (96). Fourth, additional research using more comprehensive measures of attachment style is needed for a more nuanced operationalization of this complex socio-environmental construct (27; 97).

Fifth, the cross-sectional design of the study did not allow us to draw causal conclusions of the relationship between attachment style and PTSD symptoms. For instance, more severe PTSD symptoms may erode interpersonal relationships more than less severe PTSD symptoms; there may be a bidirectional relationship between PTSD, trauma and attachment style; or this association may be mediated by other variables, such as personality, coping strategies, and social support (98-103). Future work with larger sample sizes should employ multivariable MR (104-105) to disentangle the components of attachment style and their effects on PTSD. Additionally, due to the broad spectrum of life events and dispositional factors resulting in secure versus insecure attachment styles, large-scale, gene-by-environment genome-wide interaction studies are needed to elucidate specific environmental profiles (*e.g.*, specific types of social support, relationship violence, risk-taking behaviors, and/or access to care during adolescence) that may moderate/exacerbate polygenic risk for PTSD (106-107).

Notwithstanding these limitations, results of this study suggest that PRS scores for PTSD re-experiencing symptoms derived from the MVP cohort—the largest and best-powered studied to date for PTSD—interact with attachment style to predict severity of PTSD symptoms, with these effects most pronounced for re-experiencing/intrusive symptoms. They further implicate a variant in the *IGSF11* gene (rs151177743), which is associated with the regulation of excitatory synaptic transmission and plasticity, as a possible biological mediator of the relation between PRS x attachment style and PTSD symptoms. Further research is needed to elucidate biopsychosocial mechanisms linking re-experiencing PRS, attachment style, and PTSD symptoms; distinguish effects of insecure attachment style subtypes in moderating the effect of re-experiencing PRS and PTSD symptoms; and evaluate the efficacy

of attachment style- and social support-focused interventions in mitigating PTSD symptoms in veterans with high polygenic risk.

Acknowledgements

The National Health and Resilience in Veterans Study is funded by the U.S. Department of Veterans Affairs National Center for Posttraumatic Stress Disorder. The authors thank the veterans who participated in this study.

Disclosures

AJFT, FRW, GAP, RP, LMS, JLMO, and SMS reported no biomedical financial interests or potential conflicts of interest. RHP is a scientific consultant to Cogstate, Ltd., for work that bears no relationship to the current study. JG is named as an inventor on PCT patent application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018. JHK has served as a scientific consultant to the following companies (the Individual Consultant Agreements listed are less than $5000 per year): AMGEN; AstraZeneca Pharmaceuticals; Bigen, Idec, MA; Biomedisyn Corporation; Forum Pharmaceuticals; Janssen Research & Development; Otsuka America Pharmaceutical, Inc.; Sunovion Pharmaceuticals, Inc.; Takeda Industries; Taisho Pharmaceutical Co., Ltd. He is on the Scientific Advisory Board for the following companies: Biohaven Pharmaceuticals; Blackthorn Therapeutics,Inc.; Lohocla Research Corporation; Luc Therapeutics, Inc.; Pfizer Pharmaceuticals; TRImaran Pharma. He holds stock in Biohaven Pharmaceuticals Medical Sciences and stock options in Blackthorn Therapeutics, Inc. and Luc Therapeutics, Inc. He is editor of Biological Psychiatry (Income greater than $10,000).

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Table and Figure Legends

Table 1. Sociodemographic, military, trauma, and clinical **c**haracteristics of NHRVS sample.

**Note.* Within the insecurely attached group, 23.0% (*n*=885) reported having an avoidant attachment style; and 3.8% (*n*=132) reported having an ambivalent attachment style.

***Note.* Probable PTSD was operationalized as a score $\geq$ 13, which is the DSM-5 equivalent of a score of $\geq$ 30 that has been recommended in studies of non-treatment-seeking, population-based samples (68).

Table 2. Results of linear regression analyses evaluating relation between re-experiencing polygenic risk scores, attachment style, and severity of lifetime and past-month PTSD symptoms and symptom clusters.

**Note*. Tests that were significant after false discovery rate correction for multiple tests are signified by an asterisk(*).

β values represent standardized beta coefficients, with insecure attachment as the reference group.

Table 3. Summary of one-sample Mendelian randomization results testing the genetic mediation between attachment style and posttraumatic stress disorder (PTSD case/control diagnosis and PCL quantitative phenotype). Though one-sample MR was performed using NHRVS data, genetic instruments were selected based on their

association with large-scale genetic studies of *re-experiencing* (proxy for PTSD/PCL) and "*been in a confiding adult relationship as an adult* (UK Biobank Field ID 20522; proxy for attachment style).

Figure 1. Weighted predicted unstandardized lifetime PCL scores as a function of *z*-scored PRS moderated by attachment style.

Model adjusted for age, sex, ancestral proportion scores, combat veteran status, cumulative trauma burden, time since index trauma, and nature of index trauma (assaultive vs. non-assaultive).

Lines represent regression lines for secure and insecure attachment, with 95% confidence intervals.

Figure 2. Weighted predicted unstandardized past-month PCL scores as a function of *z*-scored PRS moderated by attachment style.

Model adjusted for age, sex, ancestral proportion scores, combat veteran status, cumulative trauma burden, time since index trauma, and nature of index trauma (assaultive vs. non-assaultive).

Lines represent regression lines for secure and insecure attachment, with 95% confidence intervals.

Tables

Table 1.

	N=2,030
	Weighted *M* (*SD*) or unweighted *n* (weighted %)
Sociodemographic Characteristics	
Age	63.9 (14.1)
Some college or higher	1,724 (65.5%)
Married/living with partner	1,606 (76.4%)
Currently employed	748 (36.3%)
Household income ≥ 60,000 a year	1,072 (43.4%)
Military Characteristics	
Combat status	751 (34.8%)
Years in military	6.9 (7.3)
Trauma and Clinical Characteristics	
Number of lifetime traumatic events	3.4 (2.6)
Index traumatic event	
Sudden death of close family member or friend	564 (33.8%)
Life-threatening illness or injury	314 (17.1%)
Military-related trauma	159 (8.9%)
Child physical or sexual abuse	62 (3.2%)
Lifetime PCL Score*	10.6 (12.7)
Positive screen for lifetime PTSD	549 (30.0%)
Past-Month PCL Score	6.7 (10.9)

Positive screen for past-month PTSD	249 (16.0%)
Attachment Style**	
Secure	1,526 (73.1%)
Insecure	497 (26.9%)
Polygenic Risk Score	-0.00186 (10.91148)

Table 2.

	Lifetime PTSD Symptoms			Past-Month PTSD Symptoms		
	β	*t*	*p*	*β*	*t*	*p*
PRS	0.13	3.37	7.68×10^{-4}*	0.16	3.89	1.06×10^{-4}
Attachment Style	-0.30	13.88	2.45×10^{-41}*	-0.32	13.99	1.04×10^{-41}*
PRS x Attachment Style	-0.11	2.77	0.006*	-0.10	2.42	0.02*

	Re-experiencing			Avoidance			Emotional Numbing			Hyperarousal		
Lifetime	*β*	*t*	*p*	*β*	*t*	*p*	*β*	*t*	*p*	*β*	*t*	*p*
PRS	0.15	3.68	2.45×10^{-4}*	0.04	0.91	0.36	0.13	3.35	8.23×10^{-4}*	0.14	3.43	6.22×10^{-4}*
Attachment Style	-0.21	9.23	9.06×10^{-20}*	-0.23	9.51	6.79×10^{-21}*	-0.34	15.26	4.61×10^{-49}*	-0.26	11.58	8.37×10^{-30}*
PRS x Attachment Style	-0.16	3.90	9.90×10^{-5}*	-0.02	0.38	0.71	-0.10	2.55	0.01*	-0.10	2.53	0.01*
Past month	*β*	*t*	*p*	*β*	*t*	*p*	*β*	*t*	*p*	*β*	*t*	*p*
PRS	0.08	1.28	0.20	0.12	1.91	0.06	0.15	2.33	0.02*	0.05	0.83	0.41
Attachment Style	-0.20	6.17	1.03×10^{-9}*	-0.15	4.62	4×10^{-6}*	-0.27	8.39	1.86×10^{-16}*	-0.25	7.63	5.95×10^{-14}*
PRS x Attachment Style	-0.13	2.12	0.03*	-0.16	2.54	0.01*	-0.13	2.11	0.03*	-0.05	0.74	0.46

Table 3.

Exposure	Outcome	GWS P-value Threshold Applied	IVW Estimate	Lower 95% CI	Upper 95% CI	Cochran's Q p-value
PTSD Diagnosis	Attachment Style	0.3	0.13	0.12	0.13	0.05
		0.05	0.14	0.13	0.15	0.83
		$1x10^{-5}$	0.20	-0.01	0.41	0.47
		$1x10^{-8}$	0.54	-0.04	1.12	0.56
PTSD Symptoms (PCL)	Attachment Style	0.3	0.04	0.04	0.04	0.03
		0.05	0.13	0.12	0.13	1
		$1x10^{-5}$	0.17	0.11	0.24	1
		$1x10^{-8}$	0.17	-0.02	0.35	1
Attachment Style	PTSD Diagnosis	0.3	0.33	0.31	0.34	1
		0.05	0.34	0.31	0.37	1
		$1x10^{-5}$	0.60	0.20	1.01	0.54
		$1x10^{-8}$	-	-	-	-
Attachment Style	PTSD Symptoms (PCL)	0.3	0.27	0.27	0.28	1
		0.05	0.29	0.27	0.31	1
		$1x10^{-5}$	0.32	-0.17	0.81	0.21
		$1x10^{-8}$	-	-	-	-