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ATTACHMENT STYLE MODERATES POLYGENIC RISK FOR PTSD IN U.S. MILITARY VETERANS: RESULTS FROM THE NATIONAL HEALTH AND RESILIENCE IN VETERANS STUDY

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ABSTRACT

ATTACHMENT STYLE MODERATES POLYGENIC RISK FOR PTSD IN U.S. MILITARY VETERANS: RESULTS FROM THE NATIONAL HEALTH AND RESILIENCE IN VETERANS STUDY

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Polygenic risk scores (PRS) derived from genome-wide association studies (GWAS) of posttraumatic stress disorder (PTSD) may inform risk models of PTSD. To date, however, no known study has examined moderators such as attachment style that may impact the relation between PRS and PTSD. Main and interactive effects of PRS and attachment style on PTSD symptoms were evaluated 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. Higher re-experiencing PRS and secure attachment style were independently associated with more severe PTSD symptoms. A significant PRS-by-attachment style interaction was also observed, with a positive association between re-experiencing PRS and PTSD symptoms observed only in the context of insecure attachment style. PRS enrichment analyses conducted to identify biological pathways of PRS revealed a significant interaction between attachment style and a variant mapping to the *IGSF11* gene. This gene is implicated in the regulation of excitatory synaptic transmission and plasticity. These findings suggest that attachment style may moderate polygenic risk for PTSD, with potential implications for preventative treatment for those at highest risk.

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Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that may develop as a consequence of exposure to trauma. A burgeoning body of research has attempted to identify factors that distinguish individuals who do and do not develop PTSD following trauma exposure. In particular, recent literature has examined gene-environment interactions, with a focus on candidate genes involved in neurobiological stress systems that predict or confer risk for PTSD. However, candidate gene studies are riddled with false positives, small effect sizes, and failures to replicate findings (*e.g.* Border et al., 2019). Consequently, recent approaches have aggregated multiple genetic risk indicators derived from genome-wide association studies (GWAS) to obtain a single score of genetic risk for PTSD, or a 'polygenic risk score' (PRS). Building on prior work examining interactions between attachment style and candidate genes predicting risk for PTSD, the present study aimed to examine the main and interactive effects of adult attachment style and PRS on lifetime and past-month PTSD Checklist (PCL) scores in a large, nationally representative sample of U.S. veterans. This research may help to inform prevention and treatment efforts in veterans and other populations at high risk for PTSD following trauma exposure. This is particularly important given findings that attachment is a robust predictor of PTSD symptoms, diagnosis, and treatment outcomes (*e.g.* Lahav, Kanat-Maymon & Solomon, 2015; MacDonald et al., 2008).

Posttraumatic Stress Disorder

Exposure to trauma, or "actual or threatened death, serious injury, or sexual violence" is prevalent, with 70% of the global population exposed to at least one potentially traumatic event in their lifetime (Benjet et al., 2015; *Diagnostic and Statistical Manual of Mental Disorders, 5th Ed, DSM-5,* American Psychiatric

Association, 2013, p. 463). One possible mental health consequence of trauma is the development of posttraumatic stress disorder (PTSD). It is estimated that 7-10% of individuals develop PTSD in response to trauma (de Vries & Olff, 2009; Smith, Goldstein & Grant, 2016).

PTSD is an often-disabling disorder that is costly to individuals, their immediate surroundings, and society, making the identification and treatment of PTSD an important public health issue. Thus, it is critical to examine risk and protective factors for PTSD in veterans given the high prevalence of PTSD in this population. For instance, 31% of Vietnam veterans have been diagnosed with PTSD (Kulka et al., 1990). Personal burdens of PTSD include emotional costs to the survivor, poorer psychological adjustment and quality of life, more medical issues, higher rate of suicide, and financial challenges (Geiling, Rosen, & Edwards; Galovski & Lyons, 2004; Hoffman et al., 2011; Hoge, Terhakopian, Castro, Messer, & Engel, 2007; Jakupcak, Luterek, Hunt, Conybeare, & McFall, 2008; Milliken, Auchterlonie, & Hoge, 2007; Seal, Bertenthal, Miner, Sen, & Marmar, 2007; Thomas, et al., 2010). Psychological sequalae are not limited to the trauma survivor, with a growing body of research documenting higher divorce rates, family conflict, familial distress, and secondary traumatization among family members of veterans with PTSD (Galovski & Lyons, 2004).

PTSD also represents a high burden to society. The disorder has costlier medical care compared to generalized anxiety disorder (GAD) or panic disorder (PD; Marciniak et al., 2005). Furthermore, PTSD is associated with several secondary and tertiary mental and physical health comorbidities, such as obesity, depression, substance abuse, smoking, and family issues (Geiling et al., 2012). Treatment of these comorbidities is also costly. Marshall, Jorm, Grayson, & O'Toole (2000) found that

PTSD diagnoses were accompanied by 60% higher medical care costs than average, which was partly attributable to physical and mental health comorbidities in those with PTSD. One study examining a sample of U.S. Iraq war veterans found that the total societal cost per veteran with PTSD was $16,000 over two years (Kilmer, Eibner, Ringel, & Pacula, et al., 2011; Thomas et al., 2010). Holding constant increases of inflation and prevalence, the societal cost over two years is estimated to reach $50,000, even excluding other health problems (Geiling et al., 2012).

PTSD is the only psychiatric disorder in the *DSM-5* for which the etiology is partially specified; that is, trauma exposure is a necessary precipitant of PTSD (American Psychiatric Association, 2013). As well as necessitating trauma exposure, the *DSM-5* defines PTSD as being comprised of four symptom clusters. The first cluster is intrusion symptoms, or repetitive, involuntary memories of the trauma. The second cluster is avoidance symptoms, which are characterized by avoidance of thoughts and reminders of the trauma. The third cluster is negative alterations in cognitions and mood, for example over-magnified negative beliefs about the world and other people. The fourth cluster is alterations in arousal and reactivity, such as exaggerated startle response and hypervigilance. The cluster 'negative alterations in cognitions and mood' was newly added in the *DSM-5,* increasing the defined PTSD symptom clusters from three to four (American Psychiatric Association, 2013). Although PTSD is caused by trauma, not all individuals who are exposed to trauma develop PTSD. Extant literature has thus investigated factors that differentiate those who do and do not develop PTSD after trauma exposure.

Predictors of PTSD

Several factors are associated with increased risk for the development of PTSD. These factors can be categorized as pre-trauma (*i.e.*, prior to trauma), peri-

trauma (*i.e.*, present during the time of trauma exposure), and post-trauma (*i.e.*, more than three months after trauma; Brewin, Andrews, & Valentine, 2000; Ozer, Best, Lipsey, & Weiss, 2003). Certain factors may increase risk at many time-points, for instance social support being both a pre- and post-trauma risk factor (Johnson & Thompson, 2008; Kaniasty & Norris, 2008). Interestingly, despite positive associations between trauma severity and PTSD, peri-trauma features of the traumatic event account for little variance in PTSD symptoms (Foy, Madvig, Pynoos & Camilleri, 1996).

Sociodemographic risk factors

There is some evidence that pre-trauma sociodemographic factors such as history of prior trauma, female gender, ethnic minority status, lower education, and history of childhood maltreatment predict risk of PTSD, though it is noted that these factors may also increase likelihood of trauma (Breslau et al., 1999; Breslau et al., 1998; Brewin, Andrews, and Valentine, 2000; Bromet, Sonnega, & Kessler, 1998). However a meta-analysis performed by Greene, Neria, and Gross (2016) found inconsistent evidence for the effects of sociodemographic variables. For example, half of the studies reviewed found no gender differences, whereas the other half found that female gender was associated with increased risk. Similarly, some studies found increased risk associated with younger age, lower education, being unmarried, being an immigrant, being an ethnic minority, and being unemployed were associated with increased risk for PTSD, whereas other studies found no influence of these variables.

Cognitive risk factors

In addition, there is research to suggest that certain cognitive factors such as increased attentional bias to threatening information are associated with increased risk of PTSD (Lazarov et al., 2019). For example, a recent meta-analysis by Lazarov and

colleagues' found that sustained attention to threat (*i.e.* attention maintenance) is associated with risk for PTSD (Lazarov et al., 2019). In addition, Herzog, D'Andrea, and DePierro (2019) found that attention bias to threat was associated with some PTSD symptom clusters, but not others using a dot-probe reaction time paradigm. Specifically, 'classic' PTSD symptoms such as re-experiencing, hyperarousal were associated with increased bias to threatening stimuli (shorter reaction times), whereas dissociative symptoms such as derealization and depersonalization were associated with bias away from threat. Other cognitive factors such as verbal learning, speed of information processing attention, working memory, negative attributional style, rumination, anxiety sensitivity, and looming cognitive style are also associated with increased risk for PTSD (Elwood, Hahn, Olatunji, & Williams, 2009; Fani et al., 2012; Scott et al., 2015). However, it is uncertain whether each of these represents pre-trauma factors that increase vulnerability to PTSD, or if cognitive alterations develop post-trauma as consequence of the trauma or of living with PTSD symptoms.

Neurobiological risk factors

Cognitive risk factors for PTSD, like attention bias to threat, may be underpinned by neural structural and functional differences (Fox, Zougkou, Ridgewell, & Garner, 2011). Some evidence for smaller amygdala volumes has been found in individuals with PTSD (Morey et al., 2012; Weniger, Lange, Sachsse, & Irle, 2009). Amygdala hyperresponsivity also correlates with attentional bias to threat in PTSD (Cisler and Koster, 2011; El Khoury-Malhame et al., 2011). Alongside amygdala hyperresponsivity, there is evidence that individuals with PTSD have decreased medial prefrontal activity (MPFC) in the context of conscious fear processing. This decreased activity is believed to result in impaired inhibition over amygdala fear processing networks, resulting in amygdala hyperreactivity (Bryant et

al., 2008; Shin et al., 2005; Williams et al., 2006b). The amygdala hyperresponsivity to threat has been found to mediate hyperarousal symptoms, and may explain the vividness and intensity of trauma memories (Rauch, Shin & Wright, 2003).

More recently, research has examined neural signatures of PTSD using a bottom-up approach, whereby individuals are grouped according to similarity of neural patterns, designating subgroups with shared characteristics (Shin et al. 2020). For example, Maron-Katz et al. (2020) identified neurophysiological subtypes of PTSD in veterans by grouping them into two clusters according to resting-state abnormalities. They found that each group had distinct clinical and cognitive PTSD phenotypes. One group (Cluster 1) had abnormally high visual-sensorimotor functional activity and decreased connectivity between these two networks and the frontoparietal network, whereas the other group (Cluster 2) had abnormally low connectivity between the visual and sensorimotor networks. This latter group had statistically significantly greater re-experiencing symptoms and marginally slower information processing speed, compared to Cluster 1.

There is some support for certain neural alterations being pre-trauma precursors for vulnerability. In evidence, volumetric reductions in hippocampal volume and hyperactive amygdala responsivity to threat predict PTSD occurrence longitudinally (Admon et al., 2009; Bremner et al., 2003; Gilbertson et al., 2002; Vermetten et al., 2006; Vythilinham et al., 2002). It has been theorized that hippocampal structural differences may be implicated in declarative memory impairments observed in PTSD, and difficulty recognizing safe environments (Pittman et al., 2012). However there is also evidence that some neural structural and functional alterations are incurred post-trauma due to traumatic stress or PTSD symptoms (Weiss, 2007).

As well as neural structural and functional differences, alterations in neurobiological stress systems are associated with PTSD. For example, alterations in the hypothalamic-pituitary-adrenal (HPA) axis have been found in those with PTSD (Yehuda, 2002). The HPA axis has a key restorative function in regulating the stress response. Glucocorticoids, in particular cortisol, are released from the adrenal glands during the stress response to stimulate memory formation, arousal, and focused attention (Averill et al. 2018). Cortisol is also responsible for deactivating the stress response and restoring stress-related reactions to baseline, stimulating negative feedback inhibition of the HPA axis once the stressor is no longer present (Mehta & Binder, 2010; Yehuda & LeDoux, 2007). There is some evidence that PTSD is associated with dysregulation of the HPA axis, though the direction of the dysregulation is inconsistent and is likely to depend on a number of factors, such as sex, age, time since the focal trauma, and time of day of cortisol assessment (Lehrner, Daskalakis, & Yehuda, 2015; Morris, Hellman, Abelson, & Rao, 2016; Nicolson & Ponnamperuma, 2019; Pan, Wang, Wu, Wen, & Liu, 2018; Speer et al., 2019). Pan and colleagues' (2018) systematic review and meta-analysis found that individuals with PTSD had lower salivary cortisol when measurements were taken in the morning.

There is some evidence that HPA dysregulation is a pre-trauma risk factor, based on longitudinal findings that low cortisol levels predict later PTSD development (Inslicht et al., 2011; Van Zuiden et al., 2010). Also supporting a causal role for cortisol in the development of PTSD, a single administration of hydrocortisone (a class of corticosteroid medications) following trauma in a double-blind randomized controlled trial was associated with lower risk of developing PTSD at 3 month follow-up, compared to those who were not administered hydrocortisone

(Zohar et al., 2011). However, it is also hypothesized that peri- and post-traumatic cortisol regulation may have a role in PTSD symptom development. One proposed mechanism for the role of cortisol dysregulation in the development of PTSD is that low peri-traumatic and post-traumatic cortisol levels may result in slowed deactivation of the stress response due to impaired negative feedback on the HPA axis that continues once the threat is no longer present, even decades after the trauma (Mason et al., 1988; Yehuda et al., 1995; Yehuda, 2002; Yehuda et al., 2000).

Genetic risk factors

PTSD is estimated to have high heritability (24-72%), with other variance attributable to non-shared environmental factors (Stein, Jang, Taylor, Vernon, & Livesley 2002; Sartor Grant Lynskey McCutcheon Waldron Statham et al., 2012; Sartor et al., 2011; True et al., 1993; Wolf, Miller, Sullivan, Amstadter, Mitchell, Goldberg, & Magruder 2018; Wolf, Mitchell, Koenen, Miller 2014). Thus, a growing body of research has examined genetic factors associated with PTSD. To date, the majority of studies in this area have employed a candidate gene approach to examine PTSD. This is a hypothesis-driven approach, in which a specific gene is selected for examination on the basis of its involvement in neurobiological processes that are altered in PTSD (Halldorsdottir & Binder, 2017). Many genetic markers of interest have been investigated and supported, including genes related to the hypothalamic-pituitary-adrenal (HPA) axis functioning such as *FK-506* binding protein (*FKBP5*), due it its role in the stress response (Sheerin et al., 2017). Other genes that have been investigated include catechol-O-methyltransferase (*COMT*), cholinergic receptor nicotinic alpha3/alpha-5 (*CHRNA3/CHRNA5*), Apolipoprotein E gene polymorphism, corticotropin-releasing hormone receptor 1 (*CRHR1*) (Boscarino et al., 2011; Starr et al., 2014; Hallorsdottir & Binder, 2017; Mota et al., 2017) and the rs53576 single

nucleotide polymorphism (SNP) of the oxytocin receptor gene (*OXTR*) (Cao et al., 2019; Kraaijenvanger et al., 2019).

A notable limitation of candidate gene studies is that they are often restricted by low statistical power, small effect sizes of individual single nucleotide polymorphisms (SNPs), and failures to replicate findings (Hallorsdortir & Binder, 2017; van Winkel, 2015). Further, because multiple genes have been identified in association with PTSD, many gene variants likely operate in tandem to inform risk for PTSD (Kraft & Aschard, 2015). For example, one of the largest published PTSD GWAS to date, consisting of 20,000 participants (25% of whom had PTSD) could not replicate previously identified candidate gene hits. This failed replication was despite having 80% power to detect a causative allele with genotype relative risk of 1.19-1.35 (Duncan et al., 2017).

Instead, examining the cumulative effects of genes has stronger predictive power and effect sizes than looking at individual SNPs (Bulik-Sullivan et al., 2015; Hallorsdortir & Binder, 2017; Maier et al., 2018). For instance, Boscarino and colleagues (2011) found that combining SNPs of *FKBP5*, *COMT* and *CHRNA5* to provide a multi-marker cumulative estimate of PTSD risk predicted a nine-fold increased risk for lifetime PTSD in individuals with six or more risk alleles, providing stronger predictive power than alleles in isolation (Zannas, Binder and Mehta 2016). Thus, individual genes may contribute minimally to risk for PTSD, whereas the combined effect of multiple risk genes may more strongly predict PTSD risk.

Genome-wide Association Studies

In recent years, genetic studies of PTSD have begun to transition away from hypothesis-driven candidate gene studies in favor of more agnostic, genome-wide association studies (GWAS). GWAS involve identifying genetic markers across the

entire genome that differ between individual PTSD patients and non-PTSD controls (Sheerin, Lind, Bluntress, Nugent, Amstadter 2017). Recently, GWAS efforts have been consortium-based, and aggregate very large samples from multiple study teams in the range of tens of thousands (*e.g.* Duncan et al., 2018; Logue et al., 2015). A GWAS provides coefficients of risk for each gene. These coefficients can be used to generate weights for each SNP allele to obtain an overall risk score for each individual in an independent sample. The resulting PRS represents an aggregated score of multiple risk SNPs, with a higher PRS indicating greater genetic predisposition to PTSD (Hallorsdortir & Binder, 2017; Misganaw et al., 2019). A PRS may be more informative and intuitively decipherable than looking at multiple individual genes, and may reduce risk of bias from multiple testing and the consequent false positives (van Winkel, 2015). Information about genetic profiles of risk for PTSD symptom severity and diagnosis is of significant importance for identifying biomarkers for disease prognosis (Misganaw et al., 2019).

In the present study, polygenic risk scores were derived from the largest GWAS of PTSD to date, which consisted of 146,660 EA veterans in the US Million Veteran Program (MVP; Gelernter et al., 2019). In Gelernter and colleagues' study, genome-wide risk factors relevant to the development of PTSD re-experiencing symptoms were identified. The authors GWAS supported eight distinct regions. These regions included *KANSL1, HSD17B11, TCF4, KCNIP4, CAMKV, LINC01360, MAD1L1, SRPK2*, and, within a high linkage disequilibrium region, *CRHR1*. Some of these genes have been implicated in schizophrenia, bipolar disorder, and pleiotropic effects on psychiatric traits (*TCF4* and *MAD1L1*; Lee, Ripke, Neale, Faraone, & Purcell, 2013; Ruderfer et al., 2014). Markers previously implicated in corticosteroid and steroid regulation, specifically *HSD17B11* and *CRHR1*, are of

particular interest in PTSD. *HSD17B11* produces a protein that has a role in steroid hormone metabolism and synthesis, and *CRHR1* regulates the HPA axis by binding to corticotropin releasing hormone, which modulates cortisol release. The *CRHR1* gene has been associated with increased risk for psychiatric disorders and traits, including panic disorder, PTSD, PTSD-related phenotypes, such as neuroticism (Amstadter et al., 2011; Boscarino, Erlich, Hoffman, & Zhang, 2012; Smith, Goldstein, & Grant, 2016; Weber et al., 2016, White et al., 2013). Polymorphisms of this gene also interact with childhood maltreatment history to predict blunted cortisol reactivity to stress in adolescents (Sumner, McLaughlin, Walsh, Sheridan, & Koenen, 2014).

Gelernter and colleagues' (2019) provide a clear rationale for using the symptom cluster of re-experiencing as their PTSD phenotype of interest in the GWAS. This is because re-experiencing symptoms, which can include flashbacks, nightmares, and intrusive images, are the core symptom of PTSD. Whereas hyperarousal and avoidance can occur in several anxiety-related disorders, re-experiencing symptoms are largely unique to PTSD (Ehlers, Hackmann, & Michael, 2004). For example, hyperreactivity to stress may be a transdiagnostic feature across psychiatric disorders (Bryant, O'Donnell, Creamer, McFarlane, & Silove, 2011). In addition, it is theorized that re-experiencing symptoms trigger other PTSD symptoms. For example, McNally et al. (2015) performed a network analysis of PTSD symptoms, whereby interrelations between symptoms are examined. They found that being presented with a reminder of traumatic event was in turn associated with increased psychological and physiological reactions, which was in turn associated with increased avoidance symptoms. Furthermore, Sullivan, Smith, Lewis, and Jones (2016) found that intrusive thoughts had the strongest impact on other PTSD symptoms, using relative importance network analysis. Thus, it may be expected that

using re-experiencing PRS as a predictor variable may provide the strongest associations to PTSD symptoms, because these symptoms are largely unique to PTSD, and are hypothesized to drive other PTSD symptoms. For this reason, re-experiencing PRS was the predictor variable of interest in the present study.

Gene-Environment Interactions. Although genetic factors such as polygenic risk scores are of clear importance for PTSD, genetic risk cannot be understood without considering the environmental setting within which it occurs (Woody & Gibb, 2015). To date, most gene-environment interaction studies have employed candidate gene designs, testing whether the association between SNPs of the gene with PTSD is mediated or moderated by environmental factors such as childhood abuse (*e.g.* Binder et al., 2008; Watkins et al., 2016; Xie et al., 2010). For instance, a number of studies have examined how *FKBP5* interacts with environmental factors such as traumatic life events *(e.g.,* childhood maltreatment) to predict PTSD (see Hawn et al., 2019 for a comprehensive review). With novel genetic methods such as PRS and GWAS, there is a need to extend candidate gene x environment analyses to PRS x environment analyses. Though some studies have looked at PRS x environment effects for psychiatric variables such as depression, externalizing symptoms, social anxiety, and childhood impulsivity, to date, no known study has examined PTSD in this manner (Elam et al., 2017; Mullins et al., 2016; Musliner et al., 2015; Nelemans et al., 2019; Peyrot et al., 2014; Power et al., 2013; Thomas, 2010). Further, prior studies have not examined PRS x environment effects in large, nationally representative, population-based samples of veterans, limiting generalizability to this high-PTSD-risk population (Haskell et al., 2010; Kang, Natelson, Mahan, Lee & Murphy, 2003; Tanielian & Jaycox, 2008, Sadeh et al., 2015). Such research is essential to inform prevention and treatment efforts in

veterans and other individuals who are most at risk for PTSD, beyond the small effect sizes of individual SNPs (Stevelink et al., 2019).

Attachment Style

Social-affiliative processes are of principal importance to managing stress (Feldman, Monakhov, Pratt, & Ebstein, 2016). There is evidence that social support ameliorates stress responses at experiential, cognitive, and neural levels; for example, activating internalized representations of attachment figures is associated with reduced noradrenergic activation following stressor, reduced pain-related neural activation, and reduced attention bias to threat (Bryant, 2016; Eisenberger, Jarcho, Lieberman, & Naliboff, 2006; Master et al., 2009; Mikulincer et al., 2002). There is research to indicate that strong affiliative connections can mitigate the damaging effects of traumatic stress (James, Van Kampen, Miller, & Engdahl, 2013; Matsakis, 2004; Ruhlmann, Gallus, Beck, Goff, & Durtschi, 2019). One affiliative factor of particular relevance to PTSD is attachment style, an individual's template of beliefs and expectations of the availability and responsiveness of important others, particularly during times of stress (Marshall & Frazier, 2019).

Childhood Attachment. Bowlby's (1973) seminal theory of attachment conceptualized interactions and relationships between children and their caregivers, with these early interactions purported to shape this internalized template of beliefs or *internal working model.* Ainsworth (1979) categorized attachment styles using the *Strange Situation* experimental paradigm, a measure of attachment to primary caregivers, whereby infants are exposed to seven episodes, including separations from and reunions with parents, and interactions with strangers. Most infants (approximately 60-65%) have *secure attachment style*, using their primary caregiver as a secure base, showing separation distress, and being easily comforted upon

reunion. Approximately 20% of infants have *insecure-ambivalent* attachment style; these infants are clingy and distressed upon departure, and alternate between comfort-seeking and resisting caregiver upon reunion. Infants with *insecure-avoidant* attachment style (approximately 10-15% of infants) are indifferent to both separation and reunion, and may ignore the caregiver upon reunion (Ainsworth, 1979; Ainsworth, Blehar, Waters, & Wall, 1978).

Adult Attachment. Bowlby (1977) indicated that although attachment is most frequently and clearly observable in infants and children with caregivers others assume the role of our attachment figure as we age. Sroufe (2005) has indicated that attachment style forms foundations that impact later interpretations of situations and responses, such as relationship representations and affect regulation. This theory is partially supported by a 30-year longitudinal study that found that attachment style in infancy predicted emotion regulation and representations of the self and others in relationships in adulthood (Sroufe, 2005). Sroufe (2005) highlights that this process can be dynamic and bi-directional, with a reciprocal interplay between "experience and the representation of experience over time" (Sroufe, 2005, p. 365). For example, early attachment style predicts self- and caregiver-representations, which in turn predicts peer relations. Peer relations may also then impact self- and caregiver-representations. Despite these complexities, attachment theory traditionally postulates that attachment is relatively stable, with some studies finding attachment style stability between childhood and adulthood in approximately 72% of individuals (Main, Kaplan & Cassidy, 1985; Sroufe, Egeland & Kreutzer, 1990; Travis et al., 2001; Waters, Weinfield, & Hamilton, 2000).

Although there have been varied characterizations of insecure adult attachment styles, they typically are conceptualized by evasion of intimacy (insecure-

avoidant attachment style) or high anxiety about reciprocation of intimacy (insecure-ambivalent attachment style; Hazan & Shaver, 1987). Adults with secure attachment style see their relationships as positive and trusting, and feel worthy of love and confident that they can have caring relationships (Hazan & Shaver, 1987). Adult attachment style subtypes have similar, though not identical, prevalence to infant attachment styles. Typically 60-65% of adults are classified as secure, 20-25% as insecure-avoidant, and 8-11% as insecure-ambivalent, and (*e.g.* Ainsworth et al., 1978; Doherty et al., 1994; Mickelson et al., 1997).

Theoretical relationships between attachment and PTSD. Adult insecure attachment and PTSD share features of interpersonal difficulties, making the examination of attachment in the development and maintenance of PTSD an important area of research. Several PTSD symptoms are interpersonal in nature (American Psychiatric Association, 2013), including avoiding others who remind the individual of the trauma, feeling isolated and detached from others, distrusting others, having restricted affect or numbness, and being irritable and angry (Mills & Tunbull, 2004). The association between PTSD and interpersonal deficits is further highlighted by the United States Department of Veteran Affairs clinical practice guidelines. These guidelines recommend that clinicians assess and monitor social functional impairment, among other functional impairments, during treatment. Insecure attachment may exacerbate risk for PTSD during the acute post-trauma period by increasing isolation, depriving an individual of social support, and possibly exacerbating PTSD symptoms (Kaniasty & Norris, 2008). Consequently, there is interest in how attachment style may be a precipitating or exacerbating factor for PTSD (Barazzone, Santos, McGowan, & Donaghay-Spire, 2018).

Empirical relationships between attachment and PTSD. Attachment style robustly predicts PTSD symptoms, diagnoses, and treatment outcomes in both longitudinal and cross-sectional studies (Besser, Neria, & Haynes, 2009; Costa-Martins et al., 2016; Johnson & Williams-Keele, 1998; Lahav, Kanat-Maymon & Solomon, 2015; McDonald et al., 2008; Muller et al., 2008; Muller & Rosenkranz, 2009; Ogle, Rubin, & Siegler, 2016). For example, Isaacs and colleagues found that, relative to U.S. veterans with an insecure adult attachment style, those with a secure adult attachment style were three times more likely to be resilient to traumatic stress (Isaacs et al., 2017). MacDonald et al. (2008) found that insecure attachment style in infancy predicted PTSD at school age following a trauma. Furthermore, increased attachment security has been associated with fewer PTSD symptoms at one and three months post-trauma in individuals recruited from a hospital emergency room (Benoit, Bouthillier, Moss, Rousseau & Brunet, 2007). Further, Lahav and colleagues (2015) examined adult attachment style in wives of prisoners-of-war with and without PTSD following the Yom Kippur War. They found that insecure-ambivalent attachment style 30 years following the Yom Kippur War (Time 1) predicted posttraumatic stress symptoms (PTSS) an additional 8 years later (Time 2) but not the reverse, suggesting that insecure-ambivalent attachment style may be a risk factor for PTSS, rather than the consequence of trauma. Attachment style also has an important role in treatment outcomes, with secure attachment style predicting better PTSD treatment response in veterans compared to insecure attachment style (Forbes, Parslow, Fletcher, Susan, McHugh & Creamer, 2010). Therefore, there is empirical support for a relation between PTSD and attachment style.

Possible mechanisms by which attachment influences risk for PTSD. Although there is evidence for a relation between attachment style and PTSD, there is

a need to understand the mechanisms that may mediate this relationship. To date, the four explanations below have received the most attention in the literature.

'*Classic' attachment theory.* Bowlby's (1969; 1973) attachment theory posits that proximity-seeking to attachment figures is a biological, evolved mechanism in place to enhance likelihood of survival. Attachment systems are particularly activated in times of stress, such as in context of trauma (Bowlby, 1973). Bowlby (1973) indicated that the caregivers provide a *safe base* that increases their child's security in exploring the environment, but that they can return to in times of stress. Repeated experiences with their caregiver provide children a prototype from which they can predict caregiver availability and responsiveness. Experience with available, sensitive and responsive caregivers gives rise to positive representations of the self and others. Later in life, this often develops into positive expectations about others' availability and views of self as worthy of love and competent. Consequently, such individuals use proximity seeking to help regulate their affect (Bowlby, 1973). In contrast, when caregivers are unpredictable, insensitive to a child's needs, unresponsive to proximity seeking, and cannot be relied upon to be a safe base, a child may respond to stressful situations with fear, anxiety, or avoidance. Consequently, the child develops negative expectations about others' availability and responsiveness, as well as their own value and competency, which often persist into adulthood. Because of these negative expectations, such individuals do not learn to seek proximity to others to alleviate distress, instead using maladaptive emotion regulation strategies such as disengagement and dissociation (Bowlby, 1973). Use of maladaptive coping strategies may lead to failure to effectively regulate ones' emotions, leading to psychiatric symptoms such as PTSD.

Emotion regulation. Mikulincer and colleagues have further developed Bowlby's theory of attachment and responses to trauma. They similarly propose that differing emotion regulation strategies may account for increased risk for PTSD in those with an insecure attachment style. The authors build upon Bowlby's theory by specifying types of strategies associated with each attachment style subtype. The authors suggest that individuals with anxious hyper-activating attachment strategies are overly dependent on partners, and perceive themselves as helpless in regulating their emotions. Those with avoidant deactivating strategies down-regulate their attachment systems. They evade dependence on partners, deny threats, fail to acknowledge distress, and keep emotional distance (Mikulincer & Shaver, 2003, 2007a, Shaver & Mikulincer, 2002, Mikulincer, Shaver, & Solomon 2015). Bowlby described insecure-avoidant individuals as having "compulsive self-reliance", or a strong need for autonomy, control, and internal resilience (Bowlby, 1973, 1982; Mikulincer & Flroian, 1995). These strategies are compatible with PTSD symptoms that characterize the avoidance and negative alterations in cognitions and mood, symptom clusters identified in the *DSM-5*, thus highlighting the importance of attachment style to PTSD (American Psychiatric Association, 2013; Mikulincer & Shaver, 2003, 2007a, Mikulincer, Shaver, & Solomon 2015; Shaver & Mikulincer, 2002).

Trauma Appraisal. One way in which individuals may regulate their emotions following trauma is through cognitive reappraisal of the traumatic event (Rowland et al., 2013). Trauma appraisal has long been thought to be involved in PTSD, highlighted by DSM-IV A2 criterion requiring that individuals must experience "intense fear, helplessness, and horror" at the time of trauma for PTSD diagnosis (American Psychiatric Association, 1994, p. 428). Bowlby (1973) suggested that

individuals assimilate ongoing experiences, including distressing events, into their working models, which are activated in stressful circumstances and continue to influence how individuals appraise distressing events like trauma over their lifespan (Ogle, Rubin, & Siegler, 2016). There is evidence that peri- and post-trauma appraisals such as self-blame and shame can worsen and maintain PTSD symptoms (Barlow, Turow, & Gerhart, 2017; Uju, Shikai, Shono, & Kitamura, 2007; DePrince, Zurbriggen, Chu, & Smart, 2010). Further, some research suggests that the impact of trauma appraisals on PTSD symptom severity exceeds that of the influence of prior trauma exposure (Andrews, Brewin, Rose, & Kirk, 2000). There is also evidence that event centrality is one of the most reliable predictors of PTSD symptom severity (Bernsten & Rubin, 2006; Ogle et al., 2016). Consequently, the autobiographical model of PTSD model posits that the perceived event centrality of the trauma memory to one's identity and life narrative is a central mechanism implicated in the development and maintenance of PTSD (Rubin, Bernsten, & Bohni, 2008; Rubin et al., 2011).

There is evidence that attachment style influences individuals' appraisals of events such as traumas. Indeed, maladaptive appraisals in times of stress have been empirically associated with insecure attachment style, providing a potential mediator of the relation between attachment style and PTSD (Ogle et al., 2016; Sheinbaum et al., 2015). Mikulincer and Florian (1995) found that individuals with secure attachment style appraised stressful circumstances (combat training) as more benign, and appraised themselves as having the inner strength to cope. Conversely, individuals with insecure-ambivalent attachment style had exaggerated negative appraisal of threat, and appraised themselves as unable to cope. Insecure-avoidant individuals reported appraisals of being capable of coping, but still appraised the

event as more threatening than individuals with secure attachment style. Others have found that individuals with insecure attachment style had more negative interpretations of distressing events, and viewed traumatic events as more severe and central to their identity compared to individuals with secure attachment style (Collins, 1996; Mikulincer & Shaver 2014; Ogle et al., 2016). Appraising traumas as more severe and central to ones' identity was in turn associated with more severe PTSD symptoms (Ogle et al., 2016).

Social cognitive explanations. Social cognition, which is defined as "the ability to recognize, manipulate, and behave with respect to socially relevant information", is a skill that has implications for both emotion regulation and cognitive factors such as trauma reappraisal (p. 231, Adolphs, 2001). Social cognition facilitates emotion regulation abilities; for example, effective social cognition may enhance one's ability to seek social support following trauma. Higher levels of emotion recognition have been linked to greater use of the strategy of putting into perspective, and better performance in a social inference task (Rowland et al., 2013). In addition, social cognition may help individuals reappraise traumatic events, for example integrating social inferences to make meaning of the event, and better regulating one's emotions (Green and Malhi, 2006). Thus, there has been interest in examining social cognition as another potential explanation of the relationship between PTSD and attachment style.

Sharp, Fonagy, & Allen (2012) hypothesize a social-cognitive explanation for the relationship between PTSD and attachment style. Based on Bowlby's (1973) internal working model, Sharp and colleagues propose that early caregiving interactions produce attachment schemas that inform individuals' understanding of themselves and others. They suggest that insecure attachment negatively influences

the development of social cognition, in turn obstructing effectiveness of processing social information and seeking social support when confronted by trauma, increasing risk for PTSD. In evidence, there is research linking social-cognitive deficits to PTSD (Benight & Bandura, 2004; Carlson, Egeland, & Sroufe, 2009) and other social impairments (*e.g.*, Carlson et al., 2009; Foa, Hembree, Rothbaum, 2007). Two recent meta-systematic reviews, one of which performed a meta-analysis, found evidence that theory of mind is significantly impaired in individuals with PTSD, that social cognitive deficits precede the development of PTSD, and that alterations in social cognition affect the perception of threat based on neuroimaging findings (Stevens & Jovanovic, 2020; Couette, Mouchabac, Boula, Nuss, & Ferreri, 2019).

There is also empirical support for a relationship between insecure attachment style and social cognition. For example, relative to individuals with a secure attachment style, those with an insecure attachment style have been found to be less attentive to positive feedback, have more negatively biased interpersonal memories, greater expectations of rejection, less positive and flexible expectations of peers, less positive attributions of friendships, and reduced performance on theory of mind and emotion recognition tasks (Cassidy, Ziv, Mehta, and Feeney, 2003; Feeney & Cassidy, 2003; Humfress, O'Connor, Slaughter, Target, & Fonagy, 2002; Hünefeldt, Laghhi, Ortu, & Belardinelli, 2013; Vanwoerden, Kalpakci, & Sharp, 2015). Notably, many of these deficits are also more common in individuals with PTSD (Altunblas, Dilara, Unsalver, & Yasar, 2019; Bomyea, Johnson, & Lang, 2017; Castro-Vale et al., 2020). Further, Sharp et al. (2016) have provided preliminary evidence for this social cognitive theory in a sample of adolescents, finding a link between PTSD symptoms and attachment security via social cognitive impairment. Specifically, they found that improvement in PTSD symptoms as a function of treatment was partially mediated by

baseline attachment security and social-cognitive capacities.

In sum, attachment has been hypothesized to predict PTSD, with support from a strong body of research (*e.g.* Benoit et al., 2007; Lahav et al., 2015; MacDonald et al., 2008). However, not every individual with an insecure attachment style who is exposed to trauma will develop PTSD (Lahav et al., 2015). It is possible that attachment style interacts with other factors, such as genes, to predict risk for PTSD (Luijk et al., 2012). Next steps require us to determine how attachment interacts with genetic risk variants to predict PTSD, to elucidate the complex etiology of the disorder.

Gene-attachment interactions

To date, a small number of studies have found that affiliation factors such as social support and secure attachment style interacts with genes such as *FKBP5* and *OXTR* to predict reduced cortisol reactivity and less severe PTSD symptoms, suggesting that secure attachment style may buffer against genetic risk among trauma-exposed individuals (Luijk et al., 2010; Tamman et al., 2017; Sippel et al., 2017). Lian et al. (2014) found that glucocorticoid receptor polymorphisms rs41423247 and rs258747 interacted with the number of stressful life events, traumatic events, and social support to predict a more than three-fold increased risk of developing PTSD compared to low risk individuals. Kilpatrick et al. (2007) also found a gene-social support interaction. Specifically, low social support, high hurricane exposure, and having the low-expression variant of the *5-HTTLPR* of the serotonin transporter gene increased risk of PTSD following a hurricane (Kilpatrick et al., 2007). Further, Luijk et al. (2010) examined a large population-based sample of infants using the Strange Situation paradigm. The authors found that risk (homozygous T) alleles of the SNP rs136070 of the *FKBP5* gene were associated with increased cortisol reactivity. In

addition, there was a significant interaction between insecure avoidant attachment and *FKBP5* SNP rs136070 predicting a twofold greater risk for heightened cortisol reactivity in infants. However, it has yet to be examined whether secure attachment style may buffer polygenic risk for PTSD.

Attachment style represents a potentially malleable moderator of the association between polygenic risk and PTSD. Although attachment has traditionally viewed as stable, attachment theory acknowledges that attachment style may be modified when individuals have experiences that contradict their existing internal working models, resulting in their revision (Bowlby, 1988; Gillath, Karantas, & Fraley, 2016). This transition may operate in both directions, with individuals who have insecure attachment style able to transition to secure attachment style, and *vice versa*. Bowlby (1982) has suggested that a number of events, such as negative life events, birth of a sibling, and depression, may produce change in infant attachment style. He indicated that alterations in attachment style could be both necessary and adaptive responses to traumatic events. Some studies have found only moderate test-retest correlations on various attachment style measures (approximately 0.5; Collins & Read, 1990; Cozzarelli et al., 2003; Feeney & Noller, 1992). For example, Baldwin & Fehr (1995) conducted a meta-review and found that 30% of people reported a different attachment style when surveyed more than once, even within a period of a few weeks.

Research has suggested that attachment style may be altered in approximately 30% of adults in cases of significant life changes (*e.g.,* Baldwin & Fehr, 1995; Cozzarelli et al., 2003; Davila, Burge, & Hammen, 1997; Hazan, Hutt, & Markus, 1991; Guðmundsdóttir, Guðmundsdóttir & Elkit, 2006; Keelan, Dion & Dion, 1994; Kirkpatrick & Hazan, 1994; Lopez & Gormley, 2002; Ruvolo, Fabin, & Ruvolo,

2001; Scharfe & Bartholomew, 1994; Shaver & Brennan, 1992). There is evidence that certain individuals may be more susceptible to having an unstable or fluctuating attachment style. For example, Davila, Burge, and Hammen (1997) found that people with greatest changes in attachment style security over two years were more likely to have a history of psychopathology and personality pathology.

The implications for attachment style of major life transitions, such as parenthood, breakups and transition to college, have garnered considerable attention *(e.g.* Lopez & Gormley, 2002; Simpson, Rholes, Campbell, Tran & Wilson, 2003a). This is because such events expose individuals to new experiences that may provide opportunities for one's core assumptions to be challenged. One four-year longitudinal study found that romantic relationship dissolution predicted changes in attachment style from secure the insecure (Kirkpatrick & Hazan, 1994). The authors found that 90% of individuals who did not experience a breakup had secure attachment four years later, whereas only 50% of those who had a breakup had secure attachment. Previous research, including a meta-analysis by Fraley (2002), found that stressful life events were associated with a shift from secure to insecure attachment styles (Lewis et al., 2000; Waters et al., 2000).

Particularly relevant to PTSD, traumatic life events may also be associated with changes in attachment style. For example, Mikulincer et al. (2011) examined Israeli veterans from the Yom Kippur war. In this 17-year longitudinal study, the authors compared veterans who were ex-prisoners of the war to veterans who had not been held captive, with the latest measure obtained 35 years after the war. This study found evidence that being a prisoner of war predicted a greater likelihood of insecure attachment at the outset. However, whereas the control group generally became increasingly secure in their attachment styles over time, ex-prisoners of war became

more insecure in their attachment styles over time. Thus, results of this study suggest that war-related trauma may lead to alterations in attachment security, as well as the developmental trajectory of attachment security, even 35 years after the trauma.

Relationships with others may alter an existing attachment style when they challenge pre-existing internal working models (Bowlby, 1988). Security of attachment is derived from the knowledge that a significant other can be relied upon as being supportive, responsive, and accessible. Thus, when a significant other is not perceived as reliable in these ways, this may cause fluctuations in attachment security. In evidence, Holman and colleagues (2009) found that the extent to which individuals felt partners were responsive and accessible predicted attachment style security one year later. Further, Green, Furrer and McAllister (2011) found that increases in social support in low-income mothers were associated with decreases in insecure-ambivalent attachment style. Responses of others in the face of stressful life events (*e.g.,* spousal support during the birth of a first child) may also be associated with greater attachment security (Simpson, Rholes, Campbell, & Wilson, 2003).

Attachment style may also be modified with psychotherapy (Bateman & Fonagy, 2004; Fonagy & Bateman, 2006). Bowlby (1988) theorized that psychotherapists might provide a corrective attachment experience by constructing their own secure relationship with patients and facilitating patients' reframing of past attachment experiences. A meta-analysis by Taylor, Rietzschel, Danquah and Berry (2015) found that in the majority of studies reviewed, there was some form of improvement in attachment style. Though findings were inconsistent for insecure-avoidant attachment style, they found that prevalence of secure attachment style increases following therapy, and insecure-ambivalent attachment style decreases. For instance, one study found that there was a 39% increase in the number of people

classified with secure attachment style following 16 sessions of psychotherapy (Stovall-McClough & Cloitre, 2003). Further, some studies reviewed in this meta-analysis found that changes from insecure to secure attachment were maintained at follow-up, for instance 12 months after completing therapy in one study (*e.g.* Muller & Rosenkranz, 2009). Taken together, these findings indicate that attachment style may be a potentially modifiable moderator of polygenic risk for PTSD, may help inform the genetic-environmental etiology of PTSD, and may represent a target for prevention and treatment efforts in trauma-exposed individuals.

Gene Enrichment Analyses

Although examining PRSs can be more informative than single genes, we may still have difficulty interpreting and deriving biological meaning from the scores. It seems logical that risk alleles for any disorder are not randomly distributed among genes, but are instead distributed among functionally related sets of genes. Thus, there are limitations to single locus analyses, as these genes may not share a single unifying biological function, and a single gene may have multiple functional roles (Holmans et al., 2009). To address these limitations, novel methods such as gene enrichment analysis have been developed to identify underlying biological pathways and molecular mechanisms implicated in the relationship between genetic susceptibility and a given disorder.

In gene enrichment analysis, instead of examining a number of individual genes that are differentially expressed between two groups (*e.g.,* individuals with and without PTSD), one examines differential expressions of pathways or groups of genes. Simply put, gene enrichment approaches test for the overrepresentation of gene categories rather than individual genes. 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. These analyses have been conducted by using categories defined by databases such as the Gene Ontology (GO) database. These categories include biological processes, cellular components, and molecular functions (*e.g.* Polimanti et al., 2018; Rammos et al., 2019; Segman et al., 2005). The percentage of GO annotation[1] is calculated among genes that separate the disorder of interest (*e.g.*, PTSD) from controls, and tests for overrepresentation of members of groups within lists of genes containing significantly associated SNPs from GWAS studies.

Gene ontology and pathway enrichment analyses may then be conducted for gene-environment interaction results. One study using this approach found a polygenic risk score by trauma interactions predicting bipolar disorder in a sample of over 10,000 veterans (Polimanti et al., 2018). The variants included in the interaction showed strong enrichments for gene ontologies related to high voltage-gated calcium channel activity. It has long been thought that calcium signaling is implicated in bipolar disorder (Carmen and Wyatt, 1978; Cipriani et al., 2016). This study thus provides insight into the biological mechanisms that may underpin PRS-by-trauma interactions in predicting risk for bipolar disorder. Bioinformatics approaches such as gene enrichment and gene pathway analyses are thus crucial to advancing understanding of the complex etiology of mental disorders, including PTSD (Sheerin, Lind, Bountress, Nugent, & Amstadter, 2017).

[1] An annotation is "the statement of a connection between a type of gene product and the types designated by terms in an ontology such as the GO" p.2, Hill, Smith, McAndrews-Hill & Blake, 2008)

PTSD Symptom Clusters

Prior studies of polygenic risk for PTSD have generally focused on overall severity of PTSD symptoms of PTSD diagnosis, instead of PTSD symptom clusters (Misganaw et al., 2019). Given that intrusions and hyperreactivity to stress may be transdiagnostic features of psychiatric disorders (Bryant, O'Donnell, Creamer, McFarlane, & Silove, 2011) and considerable heterogeneity in PTSD symptom presentation (Pietrzak et al., 2014; Seligowski & Orcutt, 2015; Zoladz & Diamond, 2013), it is important to examine associations among polygenic risk and specific PTSD symptom clusters. This dimensional approach may highlight potential pleiotropic substrates for comorbidities and overlap between other psychiatric disorders and PTSD, as well as unique correlates of the PTSD phenotype (Misganaw et al., 2019).

The Present Study

The present study aimed to address the aforementioned gaps in the literature by examining main effects and interactions of re-experiencing PRS and attachment style on overall PTSD symptom severity and PTSD symptom clusters. Specifically, the present study aimed to examine whether adult attachment style moderates polygenic risk for PTSD in a large, nationally representative sample of U.S. European-American (EA) military veterans. PRS were derived from the largest GWAS of PTSD conducted to date, which consisted of 146,660 EA veterans in the US Million Veteran Program (Gelernter et al., 2019). Given that re-experiencing symptoms are largely unique and definitive of PTSD, with other symptom clusters such as hyperarousal and avoidance common to many anxiety disorders, the aim was to examine PRS associated with re-experiencing symptoms (Gelernter et al., 2019). Because there is not sufficient literature to suggest which PTSD symptom clusters

would have the strongest association with re-experiencing PRS and attachment style, these associations were explored without any specific hypotheses. The present study also aimed to examine re-experiencing PRS enrichment to identify possible biological mediators of the link between re-experiencing PRS, attachment style and PTSD symptoms.

Hypotheses

1. First, it was hypothesized that higher re-experiencing PRS would be associated with greater severity of lifetime and past-month PTSD symptoms (Gelernter et al., 2019).
2. Second, based on prior work it was hypothesized that veterans with an insecure attachment style would have greater severity of lifetime and past-month PTSD symptoms (Besser, Neria, & Haynes, 2009; Costa-Martins et al., 2016; Isaacs et al., 2017; Johnson & Williams-Keele, 1998; Lahav, Kanat-Maymon & Solomon, 2015; McDonald et al., 2008; Muller et al., 2008; Muller & Rosenkranz, 2009; Ogle, Rubin, & Siegler, 2016).
3. Third, it was hypothesized that among veterans with higher re-experiencing PRS, those with a secure attachment style will have significantly lower severity of PTSD symptoms relative to those with an insecure attachment style, based on previous studies of candidate gene x attachment interaction (Luijk et al., 2010; Sippel et al., 2017; Tamman et al., 2017).

Methods

Participants

The sample consisted of 2,030 EA veterans who participated in the National Health and Resilience in Veterans Study (NHRVS), which surveyed two separate nationally representative samples of U.S. military veterans. The sample was ascertained from a nationally representative survey research panel of more than 50,000 U.S. households that is maintained by GfK Knowledge Networks (now Ipsos). All participants were EA trauma-exposed male veterans whose data were meta-analyzed from two independent cohorts of the NHRVS that were collected in 2011 (n=1,509) and 2013 (n=521). The sample was limited to male EA veterans to avoid biases due to population structure (Kelleher, Thornton, Ashander & Ralph, 2018). To permit generalizability of study results to the entire population of U.S. veterans, post-stratification weights were applied to inferential analyses. The Human Subjects Subcommittee of the VA Connecticut Healthcare System approved the study.

Assessments

Attachment style was assessed using the Adult Attachment Style Questionnaire (Hazan & Shaver, 1987; ASQ). Veterans were asked to select which of three statements best describes their feelings and attitudes in relationships;

Item one, "*I am somewhat uncomfortable being close to others. I find it difficult to trust them completely and to allow myself to depend on them. I am nervous when anyone gets too close, and often romantic partners want me to be more intimate than I feel comfortable being*", describes insecure-avoidant attachment style.

Item two, "*I find it relatively easy to get close to others and am comfortable depending on them and having them depend on me. I do not often worry about being*

abandoned or about someone getting too close to me", describes secure attachment style.

Item three, "*I find that others are reluctant to get as close as I would like. I often worry that my partner does not really love me or will not want to stay with me. I want to merge completely with another person, but this desire sometimes scares people away",* describes insecure-ambivalent attachment style.

ASQ responses correlate highly with five other attachment style measures (Sperling et al., 1996). 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 category.

Trauma history

The Trauma History Screen (Carlson et al., 2011) was used to assess the occurrence of fourteen potentially traumatic life events across the lifespan, and which of the endorsed events was the worst experienced. This measure has good reliability and convergent validity (Carlson et al., 2011).

PTSD symptoms

Lifetime and past-month PTSD symptoms were assessed by self-report using two versions of the PTSD Checklist (PCL). The 17-item *Diagnostic and Statistical Manual of Mental Disorders IV* (*DSM-IV*) version of the PCL (PCL-IV, Weathers et al., 1993) was administered in the 2011 sample (Cronbach's a=0.94) and the 20-item *DSM-5* version (PCL-5, Bovin et al., 2016) was administered in the 2013 sample (Cronbach's a=0.95). The PCL-IV and PCL-5 contain items about PTSD symptoms related to an individual's index or worst traumatic event, which was assessed using the Trauma History Screen (Carlson et al., 2011, described above). On a scale of one (*not at all*) to five (*extremely*), participants rated the extent to which they were

bothered by each of symptoms in their lifetime and in the past month. The PCL is a commonly used and well-validated measure of PTSD, with good temporal stability, internal consistency, test-retest reliability, and convergent validity (Wilkins, Lang & Norman, 2011). A crosswalk algorithm developed by Moshier et al. (2019) was used to convert *DSM-IV* PCL scores to *DSM-5* PCL scores (see Table 1 for crosswalked scores). For the 2013 sample who had completed the *DSM-5* version of the PCL, a cutoff score of ≥ 13, which is equivalent to a score ≥ 30 on the *DSM-IV* version of the PCL, was used to indicate a positive screen for PTSD; this cutoff score has been recommended for non-treatment-seeking, population-based samples (McDonald & Calhoun, 2010).

Comparability of the symptom clusters on the *DSM-IV* and *DSM-5* versions of the PCL was achieved by using the four-factor *DSM-IV* model of re-experiencing, avoidance, emotional numbing, and hyperarousal symptoms, and the *DSM-5* model of intrusions, avoidance, negative cognitions and mood, and alterations in arousal and reactivity (American Psychiatric Association, 2013; King et al., 1998). Responses on items comprising each symptom cluster were summed to yield severity measures and then standardized to provide a single aggregate score for the meta-analyzed sample. Lifetime and past-month severity of overall PTSD symptoms, and PTSD symptom clusters were analyzed as dependent variables.

Genotyping

Participants provided saliva for DNA extraction. Saliva was collected using Oragene DNA (OG-250) kits. DNA was extracted using prepIT-L2 P reagent (DNA Genotek, Ontario, Canada) according to manufacturer's directions. All samples were genotyped with the PsychChip GWAS array (Illumina, San Diego, CA, USA) in the Gelernter lab at VA Connecticut Healthcare System in West Haven, CT. Genotypes

were called using GenomeStudio software V2011.1 and genotyping module V1.8.4 (Illumina, San Diego, CA, USA. Criteria for including SNPs were as follows: minor allele frequency (MAF)>0.01, missing genotyping rate per SNP <5% and Hardy-Weinberg equilibrium (HWE) *p*-value > 10^{-5}. To investigate population stratification of the remaining unrelated EA samples, principal components (PC) were computed from GWAS data using EIGENSOFT (Price et al., 2006) based on a common set of Hapmap3 SNPs (64,219), which were in low linkage disequilibrium (LD) with one another and have a MAF>0.01. Data retained after the initial quality control steps were imputed using SHAPEIT (Delaneau, Marchini, & Zagury, 2012; Howie, Donnelly, & Marchini 2009) for pre-phasing, IMPUTE2 (1000 Genomes Project Consortium, 2015) for imputation, and the 1,000 Genomes Project Phase 3 for EAs only (48) as the reference panel. High quality markers (genotype probability > 0.8, MAF>0.01, SNP missingness < 0.01) were used to make best guess estimates of genotypes (6,724,271 markers with high imputation quality).

Polygenic risk scoring

Re-experiencing PRS were calculated using PRSice 1.25 software (Eusden, Lewis & O'Reilly, 2015). Summary statistics were generated from the recent GWAS of PTSD re-experiencing symptoms conducted on the MVP cohort (Gelernter et al., 2019). To avoid biases due to population structure (Kelleher et al., 2018), this analysis was performed using MVP EA participants. Additionally, it was verified that no overlap is present between NHRVS and MVP. Multiple genome-wide association *p*-value thresholds were considered (PT=5×10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 0.001, 0.05, 0.3, 0.5, 1) for SNP inclusion. Correlations between various re-experiencing PRSs and PTSD symptom severity scores were examined. PRSs defined at PT=0.3 were selected, because these had the largest magnitude association with PCL scores

(r^2=0.09, p=9.3 × 10^{-5}). Selection of this re-experiencing PRS survived multiple testing after Bonferroni correction for the number of re-experiencing PRSs examined (0.05/10=0.005).

Data Analysis

A Spearman correlation analysis was conducted to evaluate the relation between re-experiencing PRS and attachment style to examine the potentially confounding presence of gene-environment correlation (*r*GE); results revealed that these variables were not statistically significantly correlated (r = -0.04, p = 0.10). Two sets of multiple regression analyses were then conducted to evaluate associations between re-experiencing PRS, attachment style, and their interaction in relation to lifetime and past-month PCL scores. Secondary multiple regression analyses were then conducted to examine how re-experiencing PRS, attachment style, and their interaction related to lifetime and past-month PTSD symptom clusters of a) intrusions; b) avoidance; c) negative alterations in cognitions and mood; and d) alterations in arousal and reactivity. To correct for multiple comparisons, the false discovery rate was adjusted using the Benjamini-Hochberg procedure for the two preliminary analyses and the eight secondary analyses respectively (Thissen, Steinberg & Kuang, 2002).

Covariates

These analyses were adjusted for age, the top 10 ancestry principal components (PCs), combat veteran status, number of lifetime traumas, and nature of index trauma (assaultive *vs.* non-assaultive). Covarying for ancestral proportion scores corrects for stratification in genome-wide studies, to prevent population stratification from confounding the study (Price et al., 2006). Age, gender, and the

number of lifetime traumas are common covariates used in genetic analyses of PTSD (Watkins et al., 2016; Xie et al., 2010). Variables relevant to veterans include combat veteran status and the nature of the worst traumatic event, which are linked to increased PTSD symptoms (*e.g.* Smith, Summers, Dillon, & Cougle, 2016; Stevelink et al., 2019). Other variables that were controlled for include nature of index trauma, because PTSD rates are higher among survivors of assaultive trauma compared to non-assaultive trauma, to determine those effects above and beyond assaultive trauma (Breslau et al. 1999; Kessler et al. 1995; Tolin & Foa, 2006).

PRS enrichment

The re-experiencing PRS variants were categorized for variants surviving multiple testing threshold ($p = 3.19 \times 10^{-7}$) and nominally significant variants ($p \leq 0.05$) for both PTSD and PTSD-by-attachment. Nominally significant variants that displayed concordant direction of effect between PTSD and PTSD-by-Attachment style 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 (Ge, Jung, & Yao, 2019) and functional profiling using g:Profiler (Reimand et al., 2016) with FDR *p*-value (p_{FDR}) < 0.05. The variants were annotated using DeepSEA (Zhou & Troyanskaya, 2015), 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 (Dayem et al., 2018).

Results

Descriptive Statistics

Sociodemographics.

A summary of sample characteristics for the 2011, 2013, and merged samples is provided in Table 2. Sample characteristics were similar between the 2011 and 2013 samples. The mean age in the merged sample was 63.9 years, with the majority married or cohabitating, some college or higher educated, retired, and with household income of less than $60,000. The majority of the sample was non-combat veterans, and had spent an average of 6.9 years in the military.

Trauma exposure

On average, veterans in the merged sample reported exposure to 3.4 traumatic events. The most commonly reported index or worst traumatic event was the sudden death of a close family member or friend (33.8%), followed by life threatening illness or injury (17.1%), and military-related trauma (8.9%). Mean (*M*) lifetime PCL-5 score in the merged sample was 10.6 (standard deviation [*SD*]=12.7). Thirty percent screened positive for probable lifetime PTSD with a cut score of 13 or higher. As expected, mean past-month PTSD score was lower (*M*=6.7, *SD*=10.9), with 16.0% screening positive for probable past-month PTSD.

Attachment style

In the merged sample, 73.1% of veterans reported having a secure attachment style, which is higher than proportions of secure attachment style reported in general adult populations (approximately 60-65% secure; Ainsworth, 1979; Doherty, Hatfield, Thompson, & Choo, 1994; Mickelson, Kessler, & Shaver, 1997). This difference may be because in these studies, approximately 5% of individuals are unclassified for methodological reasons (Ainsworth, 1979; Doherty, Hatfield, Thompson, & Choo,

1994; Mickelson, Kessler, & Shaver, 1997). In total, 23.1% (n=885) reported having an avoidant attachment style; and 3.8% (n=132) reported having an ambivalent attachment style. Proportions of those with insecure-avoidant attachment were similar to other studies performed in general population samples (typically 20-25% avoidant, *e.g.* Ainsworth et al., 1978; Doherty et al., 1994; Mickelson et al., 1997). However, proportions of insecure-ambivalent attachment were slightly lower than other studies (typically 8-11% ambivalent, *e.g.* Ainsworth et al., 1978; Doherty et al., 1994; Mickelson et al., 1997).

Relationship Between Re-Experiencing PRS, Attachment Style, and PTSD Symptoms

To assess for the main and interaction effects of re-experiencing PRS and attachment on PCL scores, a multiple linear regression was conducted. Table 3 shows the results of these analyses. Overall, for lifetime PCL scores, the model was significant ($F(17,1538)=53.65$, $p<0.001$). This multiple regression accounted for 36.5% of the variance in lifetime PCL scores, as indexed by the adjusted R^2. Veterans' predicted lifetime PCL score was equal to 13.71 + 1.78 (standardized re-experiencing PRS) - 8.58 (attachment style) -1.74 (interaction), where attachment style is coded as insecure = 0, secure = 1, and a higher standardized re-experiencing PRS score indicating greater risk for PTSD.

Findings for past-month PCL scores were similar, with a significant regression equation of $F(17,1423)=44.18$, $p<0.001$, and 34.0% of variance predicted by the model. Veterans' predicted past-month PCL score is equal to 6.79 + 1.93 (standardized re-experiencing PRS) – 8.01 (attachment style).

Hypothesis 1: Main effect of PRS

There was a statistically significant main effect of re-experiencing PRS, with higher PRS being independently associated with greater severity of lifetime (β=0.14) and past-month (β=0.17) PTSD symptoms (both $p<0.001$). Participants' lifetime and past month PCL scores increased by 1.78 and 1.93 points respectively for each one-point standard deviation increase in polygenic risk.

Hypothesis 2: Main effect of attachment style

There was also a statistically significant main effect of attachment style; insecure attachment style was independently associated with greater severity of both lifetime PTSD symptoms (β= -0.30, $p<0.001$) and past-month PTSD symptoms (β= -0.32, $p<0.001$). Veterans with an insecure attachment style scored 8.58 points higher than those with a secure attachment style on lifetime PCL, and 8.01 points higher on the past-month PCL.

Hypothesis 3: Interaction effects of PRS and attachment

The interaction of re-experiencing PRS and attachment style also emerged as a significant predictor of severity of lifetime (β= -0.11, $p=0.003$) and past-month (β= -0.11, $p=0.005$) PTSD symptoms. In particular, the interaction revealed a positive association between PRS and severity of PTSD symptoms for veterans with an insecure, but not secure, attachment style.

Each standard deviation increase in PRS predicted a 1.78-point increase in lifetime PCL score for veterans with an insecure attachment style. Conversely, for those with a secure attachment style, each standard deviation unit increase in PRS, there was a 1.74-point decrease in lifetime PCL score. This decrease neutralized the 1.78-point increase in PCL scores observed for those with an insecure attachment style and re-experiencing PRS of 1.

Findings for past-month PCL scores were similar. For each standard deviation unit increase in polygenic risk score, there was a 1.93-point increase in PCL for veterans with an insecure attachment style. This effect was somewhat mitigated by the presence of a secure attachment style; for each standard deviation unit increase in PRS, there was a 1.50-point *decrease* in past-month PCL scores for veterans with a secure attachment style.

As shown in Figures 1 and 2, there was a linear R^2 value of 0.13 and 0.19 between polygenic risk score and lifetime and past-month severity of PTSD symptoms, respectively, for veterans with an insecure attachment style; in contrast, these R^2 values were 0.01 and 0.02, respectively, for veterans with a secure attachment style.

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

Table 3 shows results of secondary multiple regression analyses examining the effects of re-experiencing PRS and attachment style on lifetime PTSD symptom clusters.

Statistically significant main effects of re-experiencing PRS were observed for lifetime intrusions (β=0.15, p<0.001), negative alterations in cognitions and mood (β=0.14, p<0.001), and alterations in arousal and reactivity (β=0.14, p=0.001), but not avoidance (β=0.04, p>0.05). However, for past-month PTSD, only the effect of re-experiencing PRS on negative alterations in cognitions and was statistically significant (β =0.16, p=0.013).

Attachment style had a statistically significant independent effect on all four of the lifetime PTSD clusters (β=-0.21 to -0.34, all p<0.001). There was also a statistically significant effect of attachment style on all four past-month PTSD symptom clusters, with similar effect sizes (β=-0.15 to -0.27, all p<0.001).

Statistically significant interactions between re-experiencing PRS and attachment style showed that secure attachment style moderated the impact of PRS on lifetime intrusions (β=-0.16, p<0.001), negative alterations in cognitions and mood (β=-0.11, p=0.004), and alterations in arousal and reactivity (β=-0.10, p=0.01); and of past-month intrusions (β=-0.15, p=0.02), avoidance (β=-0.17, p=0.009) and negative alterations in cognitions and mood (β=-0.15, p=0.02).

Functional Annotation and Enrichment of PRS Variants

Of the re-experiencing PRS variants, one (rs151177743 on chromosome 3, $p=2.07 \times 10^{-7}$) survived multiple-testing correction when testing for PTSD-by-attachment style interaction. This variant was not significantly associated with PTSD. A total of 731 SNPs among 1,628 nominally significant variants had concordant effect directions between phenotype-PTSD and the PTSD-by-attachment interaction. Sixty-four SNPs of the re-experiencing PRS variants had > 0.7 probability for expressive quantitative trait loci (eQTL). One hundred and seventy five SNPs have been previously associated with psychiatric disorders either directly or via proxy-SNPs. 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). 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. 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.

Discussion

The aim of the current study was to investigate whether adult attachment style moderates polygenic risk for severity of lifetime and past-month PTSD symptoms in U.S. military veterans. Overall, results of the study supported the hypotheses under investigation. Significant effects of polygenic risk, attachment style, and their interaction were observed for severity of lifetime and past-month PTSD symptoms. This is the first known study to examine polygenic prediction of PTSD symptom clusters, as opposed to examining polygenic influences on an overall PTSD diagnosis (Salvatore et al., 2015), as well as the role of an environmental moderator—attachment style—of this association.

Hypothesis 1

As predicted, the present study found that a re-experiencing PRS obtained from an independent GWAS cohort of >146,000 veterans predicted severity of lifetime and past-month PTSD symptoms (Gelernter et al., 2019). Specifically, each standard deviation unit increase in PRS predicted a 1.78 and 1.93-point increase in severity of lifetime and past-month PTSD symptoms, respectively. These findings are consistent with prior research indicating that PRS scores for PTSD predict PTSD onset and severity (Misganaw et al., 2019). The present findings also confirm those of Gelernter et al. (2019), suggesting that the risk variants constructed from this large GWAS are associated with severity of PTSD symptoms in an independent sample. However, consistent with prior studies, the independent effect of PRS was small and not sufficient to be used clinically as a biomarker of PTSD prognosis (Misganaw et al., 2019). The full potential of PRS may be fulfilled with accelerations in methodologies that increase power of univariate association studies, and enhance polygenic prediction performance (Krapohl et al., 2017; Maier et al., 2018; Turley et

al., 2018). For instance, statistical methods such as Multi-Trait Analysis of GWAS can increased the number of genome-wide significant loci in GWASs by two to four times (Turley et al., 2018). In addition, the present study only examined single-nucleotide polymorphisms of polygenic risk for re-experiencing PTSD. Future polygenic work may incorporate other complex structural polymorphisms, such as copy number variations, which have been found to be predictive of risk for psychiatric disorders (Levy, Xu, Gogos, & Karayiorgou, 2005). This may improve prediction accuracy of PRS for PTSD, and enhance the potential to use information from PRS for clinical purposes, such as biomarkers for PTSD diagnosis and symptom severity.

Hypothesis 2

As hypothesized, a main effect of adult attachment style on lifetime severity of PTSD symptoms was found, such that veterans with insecure attachment style had more severe lifetime PTSD symptoms than veterans with secure attachment style. Specifically having an insecure attachment style was associated with a PTSD symptom increase of 8.58 (lifetime) and 8.01 (past month) points. Therefore, the present study supports theories indicating that insecure attachment style is associated with the development and maintenance of PTSD (Mikulincer & Shaver, 2013). Potential mechanisms underlying the link between attachment style and severity of PTSD symptoms are described below.

Emotion regulation

Attachment style theories have suggested that different attachment styles are associated with distinct emotion regulation strategies that confer risk or resilience to PTSD. Given theories and research suggesting that re-experiencing symptoms drive other PTSD symptoms (*e.g.* McNally et al., 2015), one possibility is that individuals

with an insecure attachment style respond to their re-experiencing symptoms with maladaptive emotion regulation, thereby giving rise to other PTSD symptoms and maintaining the chronicity of the disorder. For example, insecure avoidant individuals may respond to re-experiencing symptoms with avoidant strategies, facilitating avoidance symptoms (Mikulincer & Shaver, 2015). Insecure ambivalent individuals may respond with exaggerations of distress to obtain the support of others, facilitating negative cognitions and mood (Mikulincer & Shaver, 2015)

Emotion regulation difficulties are associated with both insecure attachment style and PTSD symptoms. Individuals with PTSD have been found to have general emotion dysregulation, which includes difficulty identifying, recognizing and understanding emotions (Bardeen et al., 2013; Castro-Vale, Severo, & Carvalho, 2020; Miles et al., 2016). Such difficulties are linked to PTSD development, maintenance, symptom severity, and even intergenerational implications (Bardeen et al., 2013; Castro-Vale et al., 2020; Chesney & Gordon, 2017; Seligowski et al., 2015). For example, in one recent study, it was found that even 40 years after trauma exposure, and after adjusting for potential confounders like depression, veterans with PTSD had impaired emotion recognition of all emotions, as did their offspring (Catro-Vale et al., 2020). These findings suggest that emotion dysregulation may mediate the relation between insecure attachment style and PTSD.

The development of attachment relationships may represent an essential component of emotion regulation, as we learn from infancy to seek trusted others in times of distress (Bryant, 2016). In the context of an impoverished environment where caregivers are unresponsive and unavailable, emotion regulation may not develop appropriately, resulting in diminished ability to regulate physiological arousal to distressing traumatic events, among other aspects of emotion (Lanius et al., 2011).

Mikulincer et al. (2006) have hypothesized that individuals with secure attachment style have positive representations and expectations of themselves and others in relationships. Therefore, they have learned to seek proximity to others to alleviate distress following trauma (Bowlby, 1973; Mikulincer, 1995). In contrast, individuals with insecure attachment styles may develop secondary, maladaptive emotion regulation strategies due to negative internalized models and expectations of themselves and others in relationships (Barazzone et al. 2018; Mikulincer & Shaver, 2015). These beliefs and expectations may make them less likely to seek comfort from attachment figures, or they may do so inappropriately (Bowlby, 1973; Mikulincer et al., 2015). Indeed, Ainsworth and colleagues identified these secondary emotion regulation strategies in early work. They found that erratic and emotionally distant responses by caregivers to infants resulted in children having either blunted or exaggerated emotional expression to conserve their relationship and augment their caregiver's availability (Bryant, 2016; Ainsworth, 1979; Ainsworth, Boston, Bowlby & Rosenbluth, 1956).

Mikulincer and colleagues' have further specified these secondary attachment strategies by insecure attachment subtype (Mikulincer & Shaver, 2003; Shaver & Hazan, 1993). Specifically, they postulate that insecure-ambivalent individuals use *hyperactivating* attachment strategies such as overdependence on partners for protection and perceiving the self as helpless at regulating emotion (Mikulincer & Shaver, 2003; Shaver & Hazan, 1993). Such strategies may facilitate rumination about the traumatic experience, and thus engender negative cognition and mood symptoms. Insecure-avoidant individuals may use *deactivating* strategies, down-regulating their attachment systems, rather than risking painful rejection, punitive responses to emotional expression, or abandonment. These deactivating strategies

include avoiding dependence on partners, denying threats, failing to acknowledge distress, and keeping emotional distance. Such strategies may cause the individual to deny pain and avoid trauma reminders, which may encourage posttraumatic avoidance symptoms (Mikulincer, Shaver & Solomon, 2015; Barazzone, et al., 2018). The maladaptive strategies used by individuals with insecure attachment may consequently prevent adequate processing and resolution of the trauma, and contribute to the development and maintenance of PTSD symptoms.

Secondary attachment style strategies may also impact PTSD symptoms through intent to seek mental health treatment. Research suggests that individuals with insecure attachment style are less inclined to seek treatment for psychiatric symptoms than individuals with secure attachment style (Irkörücü & Demir, 2015; Vogel & Wei, 2005). Though some studies suggest that both insecure attachment style subtypes are equally associated with inhibited help seeking, others have found that this tendency is strongest in those with insecure-avoidant attachment style (Bartholomew & Horowitz, 1991; Collins & Feeney, 2000; Vogel & Wei, 2005; Irkörücü & Demir, 2015; Mallinckrodt, Gantt & Coble, 1995). This inhibition of treatment-seeking behavior may be because insecure-avoidant individuals deny distress, devalue the importance of others to increase autonomy, view others as unreliable or indifferent, have poor expectations of the level of support they would receive, and perceive a lack of social resources (Sarason, Pierce, & Sarason, 1990; Vogel & Wei, 2005). In contrast, individuals with secure attachment style may have more positive attitudes about sharing emotional difficulties and vulnerabilities with a psychotherapist, and may be more inclined to seek mental health support (Irkörücü & Demir, 2015). Thus, it may be that veterans with insecure attachment style had more severe PTSD symptoms due not seeking mental health treatment following trauma

exposure compared to veterans with secure attachment style.

Of note, secondary attachment strategies may be adaptive in some contexts, providing an evolutionary rationale for the presence of insecure attachment style in one third of individuals (Belsky, 1999). Insecure attachment styles are developed in context and calibrated to the environment, for instance having an erratic, inaccessible caregiver (Widom, Czaja, Sepulveda Kozakowski, & Chaunan, 2018; Weinfield, Sroufe, Egeland & Carlson, 1999). These experiences may signal an unsafe, unpredictable environment to an infant. In precarious, volatile environments, having an insecure attachment style may protect individuals and the group from imminent physical danger. For example, those with insecure-ambivalent attachment style may detect early or ambiguous threat before individuals with secure attachment style, who are less vigilant and more trusting (Ein-Dor, Mikulincer, & Shaver, 2010).

Social cognition

Another potential mechanism of the relation between attachment style and severity of PTSD symptoms lies in social cognitive abilities. Social cognitive abilities are thought to enhance emotion regulation (Rowland et al., 2013). Sharp and colleagues outline how social cognition may contribute to the development and maintenance of PTSD following trauma exposure. According to their social-cognitive model, social cognition mediates the relation between attachment style and PTSD symptoms. They theorize that early caregiving and attachment schemas form the foundation of social cognitive abilities, including mentalization abilities or "the ability to think about and interpret the actions of the self and others in terms of intentional mental states" (p. 49, Huang et al., 2020). Caregivers teach mentalization by their mirroring of the child's own emotional experience back to them, facilitating the ability for the child to mentally represent his or her own emotions, and later, others'

emotions. The close relationship between attachment insecurity and impaired mentalization abilities is believed to continue into adulthood (Huang et al., 2020). Sharp et al. (2016) suggest that in context of insecure attachment, such social cognitive deficits impair the individual's ability to effectively process social information and request social support from others following trauma.

The present findings support both Mikulincer and colleagues (2015) and Sharp and colleagues (2012) theories' in revealing that attachment predicts considerable variance in the severity of PTSD symptoms, although the present study cannot elucidate which (if any) of these psychological mechanisms may mediate the interaction of re-experiencing PRS x attachment in predicting severity of PTSD symptoms. Further research is needed to clarify the mechanisms underlying these associations.

Hypothesis 3

Results of the current study extend prior research examining candidate gene x attachment interactions to suggest that the association between higher re-experiencing PRS and greater severity of PTSD symptoms is observed only in veterans with an insecure attachment style. The re-experiencing PRS-by-attachment style interaction was specifically associated with greater severity of lifetime and past-month intrusions and negative alterations in cognition and mood, lifetime alterations in arousal and reactivity symptoms, and past-month avoidance symptoms. These findings suggest that the effects of the PRS x attachment style x interaction are most reliable for symptoms of a) intrusions and b) negative alterations in cognition and mood. The present results support findings from the MVP cohort that re-experiencing PRS is strongly related to intrusion symptoms, and extends the findings to an independent and nationally representative sample of veterans (Gelernter et al., 2019).

Gene enrichment findings

Among the variants included in the significant re-experiencing PRS (PT = 0.3), rs151177743 showed an interaction with attachment style that survived multiple-testing correction. This variant 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 (Jang et al., 2016). Variants mapped to *IGSF11* have previously been associated with pleiotropic effects linking schizophrenia and cognitive ability (Lam et al., 2019). Consistent with *IGSF11* involvement in synaptic adhesion, the PRS enrichment 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 (Kilinc, 2018; Missler, Südhof, & Biederer, 2012).

These synaptic processes may have important implications for PTSD via their mediation of fear conditioning and extinction learning, which have been found to be abnormal in individuals with PTSD compared with controls (Jovanovic & Ressler, 2010; Mahan & Ressler, 2012; Milad et al., 2008). Evidence from animal models that imitate the behavioral aberrancies observed in PTSD, such as over-generalization of fear associations and impaired fear extinction, suggest that abnormal synaptic plasticity may be one mechanism for the development of PTSD (Jovanovic & Ressler, 2010; Mahan & Ressler, 2012; Milad et al., 2008). Though synaptic plasticity was not examined in the present 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. Veterans with secure attachment style may better engage adaptive affect-regulation strategies such as accessing social support, thus

mitigating polygenic risk for PTSD after trauma exposure (Mikulincer et al., 2003; Mikulincer et al., 2015).

These gene enrichment findings may also explain why re-experiencing was one of the two most reliably predicted symptom clusters by the re-experiencing PRS x attachment interaction. Deficits in fear extinction learning have specifically been related to re-experiencing symptoms, with some authors conceptualizing re-experiencing the traumatic event via intrusive memories as a conditioned response to trauma-related cues (Visser, 2020). For instance Miedl et al., 2020 found that deficient fear extinction, indexed by hyperactivation of the anterior insula and dorsal anterior cingulate cortex, predicted subsequent intrusions. Thus, deficiencies in synaptic processes may mediate failures to extinguish these conditioned responses in individuals at high genetic risk for PTSD, resulting in more severe re-experiencing symptoms. Negative alterations in cognition and mood symptoms such as emotional numbing may be a compensatory mechanism to suppress these unpleasant conditioned responses. Having a secure attachment style may mediate the relationship between re-experiencing PRS and intrusion symptoms by enhancing fear extinction processes. There is evidence that exposure to social support stimuli during fear extinction inhibits the return of fear (Hornstein et al., 2016). Further, recent work showed that pairing a social support stimulus *(i.e.,* images of social support figures) with a fearful stimulus during fear extinction predicted less return of fear following extinction and 24 hours after extinction compared to fearful images that had been paired with images of strangers (Hornstein, Haltom, Shirole, & Eisenberger, 2018). Similarly, Toumbelekis and colleagues found that thinking about a supportive attachment figure reduced the acquisition of fear-potentiated startle, and this had

long-term effects on fear extinction 48 hours later (Toumbelekis, Liddell, & Bryant, 2018).

Thus, secure attachment style may counteract the effects of genetically-mediated aberrant synaptic plasticity in those with high re-experiencing PRS, as veterans with secure attachment style may better engage adaptive affect-regulation strategies such as accessing social support, thus counteracting polygenic risk for PTSD after trauma exposure (Mikulincer et al., 2003; Mikuliner et al., 2015). Further research is needed to directly examine the biological underpinnings that underlie this moderating effect (*e.g.* Luijk et al., 2010), for example, potential genetic overlap in polygenic risk for attachment style and PTSD.

The nature of the gene-environment interaction

One biopsychosocial aspect of polygenic risk scores that could not be examined in this study was the nature and directionality of the gene-environment interaction. There may be other explanations for the observed interaction. Gene-environment correlations may be one such alternative explanation, though this is made unlikely by the finding of no statistically significant correlation between re-experiencing PRS and attachment style.

Firstly, there may be an evocative gene-environment correlation, whereby individuals' genetically influenced behavior evokes specific environmental responses (Avinun and Hariri, 2019; Fearon et al., 2015; Scarr & McCartney, 1983). For instance, greater re-experiencing polygenic risk may predispose individuals to anxious behavior, or greater stress reactivity, and may evoke rejecting responses from caregivers, thus giving rise to an insecure attachment style. Conversely, individuals with lower re-experiencing polygenic risk may be predisposed to more stable, well-adjusted behavior that evokes responses of warmth and sensitive responsiveness, thus

giving rise to a secure attachment style. Therefore, whereas the attachment theories discussed thus far suggest that attachment style leads to individual differences in affect regulation that predispose individuals to PTSD, an alternative explanation is that individual differences such as re-experiencing polygenic risk scores that predispose individuals to PTSD may also influence attachment styles.

A related potential explanation is the presence of a passive gene-environment interaction, whereby the individual's genotype is correlated with the rearing environment created by their biological caregivers (Price & Jaffee, 2008). This is because the family childrearing environment can depend on heritable parental characteristics. Thus, parents can provide children not only with their genotype but also with an environment that correlates with their own genotype. For example, a recent study by Cheesman and colleagues (2019) found that polygenic scores explained much less variance in educational attainment in individuals who were adopted away from biological caregivers, compared to non-adopted individuals who were raised by biological caregivers; *i.e.* polygenic impact on educational achievement was increased in context of rearing by close genetic relatives with whom non-adopted individuals share both genotype and family environment. This provides support for a passive-gene environment correlation. Therefore an individual's genotype (polygenic risk scores) and their environmentally mediated dispositional qualities (attachment) may be correlated, making the extent to which genes or the environment is having an effect unclear. Genotype-environment correlation studies are mostly performed in child and adolescent samples. Few such studies have been performed in young adults, and fewer still in older adults who comprise the majority of this study (Deater-Deckard & Mayr, 2005).

Clinical Implications

Diagnosis and preventative intervention

The present study has several clinical implications for PTSD diagnosis and preventative intervention. A profile of high polygenic risk and insecure attachment style may be used in risk stratification models to identify at-risk veterans who should be followed closely and monitored for PTSD symptoms following trauma exposure. In correspondence with the Research Domain Criteria (RDoC) approach proposed by the National Institute of Mental Health, PRS and attachment style may be two of many factors—specifically, genes and social processes related to affiliation and attachment—that contribute to the etiology of PTSD (Kapur, Phillips & Insel, 2012). Such information may inform diagnostics of trauma-related mental disorders by considering key biological and environmental factors (Kapur, Phillips & Insel, 2012). In addition, assessing for the combination of high PRS and insecure attachment style may help to identify an at-risk group who benefit from preventative treatment following trauma exposure.

Interpersonally-oriented treatment modalities

Although the present study did not examine treatments for PTSD, the findings have clinical implications for treatment that should be explored by future research. Traditional evidence-based treatments for PTSD such as cognitive behavioral therapy (CBT) typically involve imaginal exposure to trauma memories or *in vivo* confrontation of trauma reminders (Foa, Rothbaum, & Furr, 2003; Joseph & Gray, 2008). Exposure-based psychotherapies have received considerable attention in the literature, and there is evidence for their efficacy and effectiveness in treating PTSD (Lely, Smid, Jongedijk, Knipscheer, & Kleber, 2019; Lewis, Roberts, Andrews, Starling, & Bisson, 2020). However, Markowitz and colleagues have suggested "an

unfortunate consequence of the success of the exposure-based therapy model has been the neglect of other potentially useful treatment paradigms for PTSD" (p. 2, Markowitz et al., 2009). Such treatment paradigms, according to these authors, include an explicit focus on interpersonal functioning. Although exposure-based therapies may indirectly help alter interpersonal relationships, *e.g.* via challenging cognitions about trust and intimacy, and improving PTSD symptoms that can impair social functioning, they do not have explicit focus on interpersonal relationships or improving social cognition (Reich, Nemeth, & Acierno, 2019). This is despite central features of PTSD being inherently interpersonal, a large body of work documenting the role of interpersonal variables impacting PTSD chronicity, and strong protective effect of secure attachment style (Galea et al., 2002; Silver et al., 2002; Markowitz, Milrod, Bleiberg, & Marshall, 2009).

Although the association between attachment style and PTSD is most likely bidirectional (Mikulincer et al., 2014), results of the current study suggest that modification of attachment style through psychotherapies specifically directed at interpersonal relationships may help mitigate high polygenic risk for PTSD (Chopik, Edelstein, & Grimm, 2019; Fonagy & Bateman, 2006; Hogan, Linden, & Najarian, 2002; Main, Kaplan & Cassidy, 1985; Kernberg, Diamond, Yeomans, Clarkin, & Levy, 2008; Levy et al., 2006; Lipsitz & Markowitz, 2013; Waters, Hamilton & Weinfield, 2000). Such therapies focus on the reparative therapist-patient relationship as an attachment bond, and other key relationships (Mallinckrodt, 2010). Their goal is to develop more adaptive and flexible templates of interpersonal relationships, build social support, and improve social cognition and social skills such as mentalizing abilities (Fonagy & Bateman, 2006; Hogan, Linden, & Najarian, 2002; Kernberg, Diamond, Yeomans, Clarkin, & Levy, 2008; Levy et al., 2006; Lipsitz & Markowitz,

2013). Thus, targeted treatment of PTSD for individuals with high polygenic risk for this disorder may include a specific focus on strategies to help bolster security of interpersonal relationships and social support (Chopik, Edelstein, & Grimm, 2019; Fonagy & Bateman, 2006; Hogan, Linden, & Najarian, 2002; Main, Kaplan & Cassidy, 1985; Kernberg, Diamond, Yeomans, Clarkin, & Levy, 2008; Levy et al., 2006; Lipsitz & Markowitz, 2013; Waters, Hamilton & Weinfield, 2000).

One such interpersonally oriented therapy that is the subject of expanding research is interpersonal psychotherapy (IPT). The core principle of IPT for PTSD is that "trauma impairs the individual's ability to use the social environment to process environmental trauma, shattering perceived environmental safety and poisoning trust in interpersonal relationships" (p. 136, Markowitz et al., 2009). IPT for PTSD aims to improve social skills, lessen emotions of helplessness, augment self-efficacy and agency, enable corrective emotional experiences, and help to construct adaptive coping techniques. This treatment does not require exposure, and may be a reasonable alternative treatment option for patients who are adamantly opposed to exposure (Sharpless & Barber, 2011)

Precision medicine

Although PTSD symptom outcomes have been found to be similar for CBT and interpersonally oriented treatments like IPT (*e.g.* see meta-analysis by Althobaiti et al., 2019; Luborsky et al., 2002; Markowitz et al., 2015), future research should examine whether outcomes differ for patients on measures of social cognition, social functioning, and social support. In addition, such studies should examine whether the relative effectiveness of these treatments may vary as a function of attachment style or existing social supports to assist in treatment matching. Precision medicine approaches emphasize integrating individual differences across a number of areas into

prevention and treatment, rather than simply basing clinical decisions on what is effective for the average patient (Hudson et al., 2015; Norr et al., 2018). The present study highlights two domains—polygenic risk and attachment style—that should be investigated in precision medicine treatment studies. For example, patients with secure attachment or several social supports may not have need for an interpersonally oriented treatment, and therefore may benefit more from exposure-based treatments. Individuals with completely impoverished social support networks and insecure attachment style may not have any relationships to build upon (Weissman, Markowitz, & Klerman, 2017). Patients with insecure attachment style and some social network, however, might be ideally matched to IPT (Weissman, Markowitz, & Klerman, 2017). Aberrant fear extinction processes in individuals with high PRS may make them more suited to exposure-based therapies that specifically target fear extinction compared to individuals with low PRS (Liddell & Jobson, 2016). Such research may help to guide treatment matching based on individual patient profiles.

Limitations and Future Directions

Sample and measure considerations

Methodological limitations of the present study must be noted. First, the population-based nature of the study permitted a large number of measures to be obtained from a large sample, but measures themselves had to be very brief. As a result, attachment was measured using one question consisting of three items, which is less comprehensive than the Adult Attachment Interview (George, Kaplan & Main, 1985). This may explain why proportions secure attachment styles (73.1%) were higher than in other studies of general population samples (typically 60-65%), and proportions of insecure-ambivalent attachment (3.8%) was slightly lower than general population samples (typically 8-11%, *e.g.* Ainsworth, 1979; Doherty, Hatfield,

Thompson, & Choo, 1994; Mickelson, Kessler, & Shaver, 1997). This difference may be because in other studies, approximately 5% of individuals are unclassified for methodological reasons. The present study used a simple forced-choice paradigm; if a more multi-dimensional, comprehensive attachment style interview had been administered, similar classification difficulties may have emerged. Other differences in proportions of subtypes may be due to the fact that this was an older veteran sample, so results may not generalize to general population samples. Nevertheless, Sperling, Foelsch and Grace (1996) found high scale and subscale reliability of the three-item measure, as well as moderate correlation with five other longer attachment subscales. Therefore, there is evidence that the measure is a valid indicator of attachment.

Second, there are limitations in the sample composition. Although the sample is a nationally representative sample of EA male U.S. veterans, it may not be representative of other non-veteran populations that experience PTSD. The present study should be replicated in the general population and more diverse samples of veterans to determine the generalizability of the results of the current study.

Attachment subtypes

Another limitation of the present study is categorization of attachment style. To increase statistical power, the two insecure attachment style subtypes (insecure-avoidant and -ambivalent) were collapsed into one insecure attachment style group. Future studies should compare effects of these attachment style subtypes in moderating the effect of re-experiencing PRS and severity of PTSD symptoms. This is particularly important given relatively untested propositions that hyperactivating emotion regulation strategies linked to insecure-ambivalent attachment style (*e.g.* overdependence on partners) may promote intrusions and re-experiencing symptoms,

and deactivating strategies linked with insecure-avoidant attachment style (*e.g.* keeping emotional distance) may facilitate avoidance symptoms (Mikulincer, Shaver, & Pereg, 2003; Mikulincer, Shaver, & Solomon, 2015).

Trauma type

An additional weakness of the present study is that the potentially mediating/moderating effect of trauma type was not examined, though trauma type (assaultive *vs.* non-assaultive) was adjusted for in multivariable analyses. The most prevalent index traumas for veterans in the present study were sudden death of a close family member or friend, and life threatening illness/injury. The former is interpersonal in nature, and may entail loss of an attachment figure, for example a spouse. Thus, the attachment insecurity may have arisen as a consequence of managing loss-related trauma.

Beyond the influence of managing the potential traumatic loss of attachment figures, there is evidence for stronger relationships between interpersonal trauma and attachment insecurity compared to non-interpersonal trauma (Aspelmeier et al., 2007; Huang et al., 2017; Mikulincer et al., 2011; Muller, Thornback, & Bedi, 2012). In addition, there may be differing effects of attachment style on PTSD depending on trauma type (Barazzone et al., 2018). In support of this, a systematic review by Barazzone et al. (2018) found that the relationship between PTSD and trauma varied as a function of trauma type and attachment style. For instance, one study reviewed found that in the context of severe captivity-related trauma, secure attachment was associated with worsened PTSD symptoms (Kanninen, Punamaki, & Qouta, 2003). There may also be a bidirectional relationship between attachment insecurity and PTSD; for example, a longitudinal study by Mikulincer, Ein-Dor, Solomon, & Shaver (2011) found that attachment insecurity increased in prisoner of war veterans, and

decreased in non-prisoner-of-war veterans over a period of 17 years. The authors suggested that being held captive may have disrupted individuals' trust in the intentions of others and consequently impacted on their attachment security (Kanninen et al., 2003). In addition, social support-seeking strategies associated with secure attachment style would likely be impossible in captivity. Similarly, Mikulincer et al. (2015) indicate that "the constant mental reactivation of a trauma, particularly a man-made trauma that shatters one's trust in others' goodwill and one's sense of personal value and lovability, can gradually increase the strength of negative working models of self and other, thereby heightening attachment insecurities and reducing the likelihood of attaining a calmer, more secure mental state" (p. 13). In addition, interpersonal trauma may diverge with formerly held beliefs about the world and others being safe, making habitual coping strategies ineffectual, and diminishing individuals' assurance in attachment figure's safety and availability (Barazzone et al., 2018; Mikulincer, Shaver, & Horesh, 2006).

Thus, prior theories and findings suggest that interpersonal trauma may affect both attachment style, as well as the relationship between attachment style and PTSD. Therefore, it is important that future studies examine trauma type as a potential moderator of the relationship between attachment style and PTSD.

Causality of attachment

Further research is also needed to evaluate causal associations between attachment style and PTSD. A significant challenge in PTSD research is disentangling risk factors and consequences of the disorder and of trauma itself. Longitudinal designs that monitor individuals before the onset of the disorder, or optimally before trauma exposure, provide one way of informing causal associations. However, like most studies in the PTSD literature, the present study is cross-sectional, thus

preventing us from drawing causal conclusions about the negative impact of attachment on PTSD symptoms.

There may also be a reciprocal relationship between attachment security and posttraumatic stress symptoms. Instead of secure attachment reducing vulnerability to posttraumatic stress symptoms, trauma may erode secure attachment style, disrupting the protective functions of attachment (Barrazzone et al., 2018). According to this social support deterioration model, trauma may lead to a degradation of social support, which can be exacerbated by individuals' changes in expectations of social support, in turn further diminishing interpersonal relationships (Bryant, 2016; Barrera, 1988; Wheaton, 1985).

Additionally, the experience of having PTSD in itself can invoke helplessness and vulnerability that worsens existing attachment insecurities (Mikulincer et al., 2015). For instance, individuals with PTSD are more likely to divorce and have multiple divorces (Rodriguez et al., 2012). Hyperarousal symptoms can cause veterans to leave social events prematurely before their partners are ready to leave, creating discomfort for partners and others (Reich et al., 2019; Rodriguez, Holowka, & Marx, 2012). Individuals with PTSD may also have restricted friendships because they have difficulty sharing emotions, demonstrating emotional support, or resolving arguments (Rodriguez et al., 2012). Veterans' difficulties may also extend to parenting difficulties, as hyperarousal can be associated with volatile parent-child interactions, and avoidance and numbing symptoms may result in emotional detachment and lack of interest in children's activities (Gewirtz, Polusny, DeGarmo, Khaylis, & Erbes, 2010; Ruscio, Weathers, King, & King, 2002). This may place increased burden on their partners, estranging them further (Baptist et al., 2011; Galovski & Lyons, 2004).

There are several studies suggesting that there is a bidirectional relationship between perceived interpersonal relationships and support and PTSD symptoms. For example, Mikulincer et al. (2011) found that higher levels of post-traumatic stress symptoms across three time points (18, 30, and 35 years) following the Gulf War predicted higher attachment insecurity in both prisoners of war and non-prisoners of war. Further, Kaniasty and Norris (2008) found that more social support correlated with reduced PTSD symptoms in the early post-trauma phase, however increased PTSD predicted eroded social support 18 to 24 months post-trauma (Kaniasty & Norris, 2008). Similarly, in a sample of male veterans, King and colleagues found that greater PTSD severity two years post-combat was related to reductions in positive social support five years later (King, King, Taft, Hammond, & Stone, 2006). A more recent longitudinal study by Platt, Low, Galea, Norris, and Koenen (2016) found that one specific aspect of social support—emotional support—predicted subsequent decreased PTSD symptoms, but PTSD symptoms were also associated with later decreases in social support. Further, Sippel and colleagues also observed a reciprocal relationship between PTSD and social support with greater PTSD dysphoric arousal symptoms (*i.e.,* irritability/anger) pre-treatment predicting greater distress related to interpersonal conflict post-treatment; and greater pre-treatment conflict-related distress predicting greater severity of all five PTSD symptom clusters at post-treatment (Sippel, Watkins, Pietrzak, Hoff, & Harpaz-Rotem, 2019).

Thus, rather than insecure attachment conferring risk for PTSD symptoms, there may be alternative explanations for the observed findings. The symptoms associated with more severe PTSD, especially increased severity of dysphoric symptoms such as anger/irritability, which are particularly deleterious to relationships, may erode social relationships more than less severe PTSD symptoms;

there may be a bidirectional relationship between PTSD, trauma and attachment style. Therefore, a causal role of attachment cannot be determined in the present study, although there is some longitudinal support for a causal role of insecure attachment on PTSD (*e.g.* MacDonald et al., 2008; Mikulincer et al., 2008).

Epigenetics

Longitudinal research is also important for clarifying developmental contributors and temporal dynamics of trauma, attachment and re-experiencing PRS to examine how and when re-experiencing PRS influences risk for PTSD. One such developmental factor is the impact of environmental factors throughout the lifespan on gene expression. Although PRS are generally considered to provide a stable measure of polygenic risk, they may be altered by epigenetic regulation, a mechanism by which environmental influences regulate gene activity without altering the underlying gene sequence (Holliday, 2006). The present study examined PRS at one point in time; however a risk score that includes epigenetic markers would need to be evaluated at several time points to follow alterations in DNA methylation.

Attachment style is one factor that moderates DNA methylation. Prior work has found evidence for altered DNA methylation and attachment style. For example, Ein-Dor, Verbekeb, Mokry and Vrtička (2018) found that insecure-avoidant attachment style score was positively correlated with *OXTR* and glucocorticoid receptor (*NR2C1*) gene promoter methylation. Thus, it is possible that attachment itself may be an environmental factor that causes epigenetic changes to polygenic risk indicators, which may have further implications for PTSD (Yehuda et al., 2010). In addition, maltreatment could be a third variable that influences both epigenetic changes and attachment (Ramo-Fernandez et al., 2019; Jiang, Postovit, Cattaneo, Binder, & Aitchison, 2019; Lo, Chan & Ip, 2017). This may be one potential

biological mechanism for the interaction between re-experiencing PRS, attachment style, and PTSD. Future work should examine whether epigenetic modification of the expression of PRS indicators may influence the interaction of attachment style and PRS in predicting PTSD risk.

Longitudinal research is also needed to examine how the timing of trauma exposure interacts with re-experiencing PRS and attachment style in determining PTSD symptoms. Most veterans' index trauma occurred many years earlier ($M > 20$ years), making it important to consider how timing of trauma plays into the observed results. In particular, timing of trauma exposure may be an important factor in regulating polygenic activity and setting attachment style in place. There is evidence that epigenetic modifications may be developmentally time-sensitive, with sensitive periods for optimal induction of DNA methylation changes (Bornstein, 1989; Knudsen, 2004). For example, Dunn and colleagues (2020) found that the developmental timing of adversity accounted for greater variability in DNA methylation than even recency or accumulation of traumatic events. In sum, future longitudinal research investigating epigenetic alterations of polygenic risk scores, in particular in relation to attachment style and sensitive periods for trauma, may inform understanding of the relation between polygenic risk and PTSD.

Conclusion

Notwithstanding the aforementioned limitations, results of this study suggest that re-experiencing PRS scores for PTSD re-experiencing symptoms derived from the MVP cohort—the largest and best-powered studied GWAS to date for PTSD—interact with adult attachment style to predict past-month and lifetime PTSD symptoms in a nationally representative sample of veterans, with these effects most pronounced for symptoms of intrusions and negative alterations in cognition and

mood. 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 risk; and evaluate the efficacy of attachment style- and social support-focused interventions in mitigating risk for PTSD in veterans at high polygenic risk for this disorder.

Table 1.

Crosswalk of corresponding Posttraumatic Stress Disorder Checklist for DSM-IV (PCL-4) and PCL for DSM-5 (PCL-5) total scores with 95% confidence intervals from 10,000 bootstrapped samples, adapted from Moshier et al., 2019.

PCL-4 Total(95% CI)	PCL-5 Total(95% CI)	PCL-4 Total(95% CI)	PCL-5 Total(95% CI)
17←----------	----------→ 0(-1,0)	52←----------	----------→38(35,41)
18←----------	----------→1(0,2)	53←----------	----------→40(37,43)
19←----------	----------→2(0,3)	54←----------	----------→41(38,44)
20←----------	----------→3(1,4)	55←----------	----------→42(39,45)
21←----------	----------→4(2,5)	56←----------	----------→43(40,46)
22←----------	----------→4(3,6)	57←----------	----------→45(42,48)
23←----------	----------→5(3,7)	58←----------	----------→46(43,49)
24←----------	----------→6(4,9)	59←----------	----------→47(44,50)
25←----------	----------→7(5,10)	60←----------	----------→48(45,51)
26←----------	----------→8(6,11)	61←----------	----------→50(46,53)
27←----------	----------→9(7,12)	62←----------	----------→51(48,54)
28←----------	----------→11(8,13)	63←----------	----------→52(49,55)
29←----------	----------→12(9,14)	64←----------	----------→53(50,57)
30←----------	----------→13(10,15)*	65←----------	----------→55(51,58)
31←----------	----------→14(11,16)	66←----------	----------→56(53,59)
32←----------	----------→15(12,18)	67←----------	----------→57(54,60)
33←----------	----------→16(13,19)	68←----------	----------→58(55,62)
34←----------	----------→17(14,20)	69←----------	----------→60(56,63)
35←----------	----------→18(15,21)	70←----------	----------→61(58,64)
36←----------	----------→19(17,22)	71←----------	----------→62(59,65)
37←----------	----------→21(18,23)	72←----------	----------→63(60,67)
38←----------	----------→22(19,24)	73←----------	----------→65(61,68)

39←----------	----------→23(20,26)	74←----------	----------→66(63,69)
40←----------	----------→24(21,27)	75←----------	----------→67(64,70)
41←----------	----------→25(22,28)	76←----------	----------→68(65,72)
42←----------	----------→26(23,29)	77←----------	----------→70(67,73)
43←----------	----------→28(25,30)	78←----------	----------→71(68,74)
44←----------	----------→29(26,32)	79←----------	----------→72(69,75)
45←----------	----------→30(27,33)	80←----------	----------→74(71,76)
46←----------	----------→31(28,34)	81←----------	----------→75(72,77)
47←----------	----------→32(29,35)	82←----------	----------→76(74,79)
48←----------	----------→34(31,37)	83←----------	----------→77(75,79)
49←----------	----------→35(32,38)	84←----------	----------→79(77,80)
50←----------	----------→36(33,39)	85←----------	----------→80(78-81)
51←----------	----------→37(34,40)		

*_Note:_ Cutoff for probable PTSD diagnosis is shaded in light gray. This cutoff is $\geq$30 for the DSM-IV (2011 sample), and $\geq$13 for the DSM-5 (2013 sample).

Table 2

Sociodemographic, military, trauma, and clinical characteristics of 2011, 2013, and merged samples

	2011 Sample (*n*=1,509)	2013 Sample (*n*=521)	Merged Sample (*n*=2,030)
	Weighted *M* (*SD*) or unweighted *n* (weighted %)		
Sociodemographic Characteristics			
Age	64.03 (13.71)	63.35 (15.18)	63.9 (14.1)
Some college or higher	1292 (66.5%)	432 (62.8%)	1,724 (65.5%)
Married/living with partner	1207 (77.1%)	399 (74.5%)	1,606 (76.4%)
Currently employed	554 (35.5%)	193 (38.6%)	748 (36.3%)
Household income ≥ 60,000 a year	796 (32.8%)	275 (45.3%)	1,072 (43.4%)
Military Characteristics			
Combat status	535 (32.7%)	216 (40.8%)	751 (34.8%)
Years in military	6.85 (7.5)	7.12 (7.5)	6.9 (7.3)
Trauma and Clinical Characteristics			
Number of lifetime traumatic events	3.28 (2.6)	3.72 (2.6)	3.4 (2.6)
Index (worst) traumatic event			
Sudden death of close family member or friend	429 (30.3%)	135 (31.8%)	564 (33.8%)
Life-threatening illness or injury	232 (17.9%)	82 (15.2%)	314 (17.1%)

Military-related trauma	119 (8.5%)	40 (8.8%)	159 (8.9%)
Child physical or sexual abuse	44 (2.7%)	18 (4.3%)	62 (3.2%)
Lifetime PCL Score	9.18 (11.96)	14.66 (14.7)	10.6 (12.7)
Positive screen for lifetime PTSD	572 (25.2%)	171 (42.1%)	549 (30.0%)
Past-Month PCL Score	6.14 (10.69)	9.24 (12.15)	6.7 (10.9)
Positive screen for past-month PTSD	283 (14.8%)	79 (23.3%)	249 (16.0%)
Attachment			
Secure	1141 (73.5%)	385 (71.9%)	1,526 (73.1%)
Insecure	366 (26.4%)	131 (28.1%)	497 (26.9%)
Polygenic Risk Score	-0.000807 (0.000061)	-0.000808 (0.000059)	-0.00186 (10.91148)

*_Note._ In total, 23.1% (_n_=885) reported having an avoidant attachment style; and 3.8% (_n_=132) reported having an ambivalent attachment style.

**_Note._ Probable PTSD in the main sample 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 (McDonald & Calhoun, 2010).

Table 3.

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.

	Lifetime PTSD Symptoms				Past-Month PTSD Symptoms			
	B(*SE*)	β	*t*	*p*	B(*SE*)	β	*t*	*p*
PRS	1.78(.050)	0.14	3.55	<0.001*	1.93(0.46)	0.17	4.23	<0.001*
Attachment Style	-8.58(0.62)	-0.30	13.90	<0.001*	-8.01(0.58)	-0.32	13.91	<0.001*
PRS x Attachment Style	-1.74(0.59)	-0.11	2.96	0.003*	-1.50(0.10)	-0.11	2.79	0.005*

	Intrusions				Avoidance				Negative Alterations in Cognition and Mood				Alterations in Arousal and Reactivity			
Lifetime	B(*SE*)	β	*t*	*p*	B(*SE*)	β	*t*	*p*	B(*SE*)	β	*t*	*p*	B(*SE*)	β	*t*	*p*
PRS	0.14(0.04)	0.15	3.82	<0.001*	0.04(0.04)	0.04	1.01	0.31	0.14(0.04)	0.14	3.62	<0.001*	0.12(0.04)	0.14	3.50	<0.001*
Attachment Style	-0.42(0.05)	-0.21	9.27	<0.001*	-0.46(0.05)	-0.22	9.46	<0.001*	-0.72(0.05)	-0.34	15.24	<0.001*	-0.51(0.04)	-0.26	11.54	<0.001*
PRS x Attachment Style	-0.17(0.04)	-0.16	4.07	<0.001*	-0.02(0.05)	-0.02	0.39	0.70	-0.11(0.01)	-0.11	2.86	0.004*	-0.11(0.04)	-0.10	2.56	0.010*
Past month	**B(SE)**	**β**	***t***	***p***	**B(SE)**	**β**	***t***	***p***	**B(SE)**	**β**	***t***	***p***	**B(SE)**	**β**	***t***	***p***
PRS	0.08(0.06)	0.09	1.45	0.15	0.12(0.06)	0.12	1.95	0.051	0.15(0.06)	0.16	2.50	0.013*	0.05(0.06)	0.06	0.90	0.37
Attachment Style	-0.39(0.06)	-0.20	6.19	<0.001*	-0.32(0.07)	-0.15	4.69	<0.001*	-0.57(0.07)	-0.27	8.43	<0.001*	-0.52(0.07)	-0.25	7.69	<0.001*
PRS x Attachment Style	-0.08(0.06)	-0.15	2.34	0.020*	-0.18(0.07)	-0.17	2.61	0.009*	-0.16(0.07)	-0.15	2.32	0.020*	-0.06(0.07)	-0.05	0.81	0.42

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

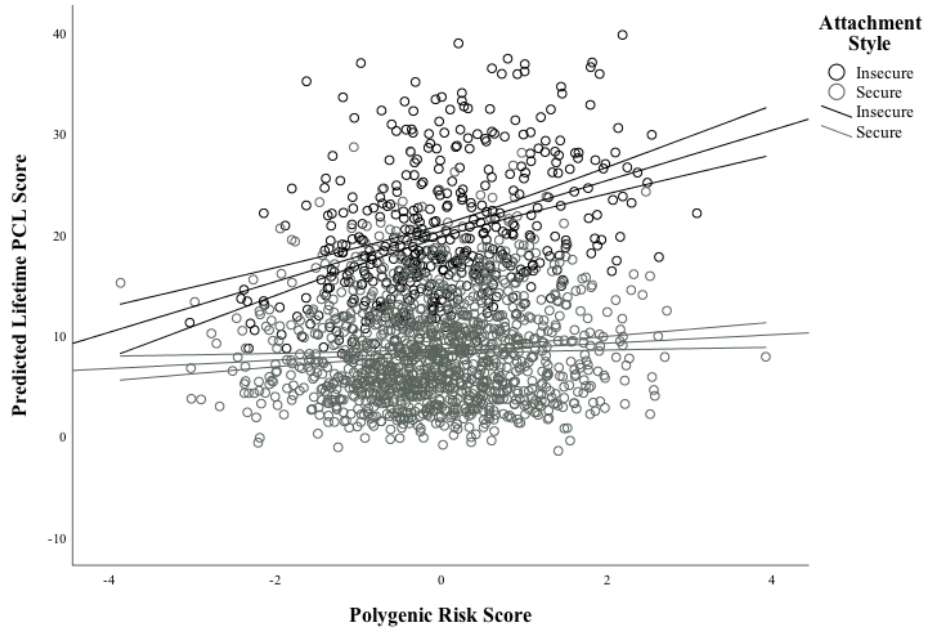
β represent standardized beta coefficients, with insecure attachment = 0 as the reference group.

B represents unstandardized coefficients.

SE represents standard error of the coefficients.

Figure 1.

Weighted predicted unstandardized lifetime PCL scores as a function of Z-scored PRS moderated by attachment style.



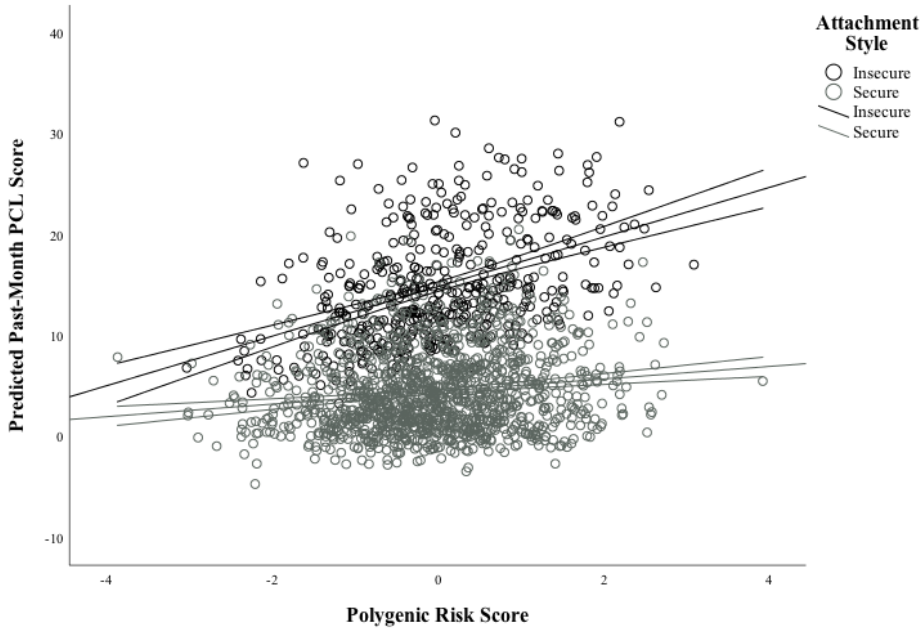
Model adjusted for age, sex, ancestral proportion scores, combat veteran status, cumulative trauma burden, and nature of index trauma (assaultive vs. non-assaultive).

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, and nature of index trauma (assaultive vs. non-assaultive).



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

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