PTSD, alcohol dependence, and conduct problems: Distinct pathways via lability and disinhibition

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HIGHLIGHTS

• PTSD is associated with symptoms of alcohol dependence via affect lability.
• PTSD is associated with conduct problems via behavioral disinhibition.
• 5-HTTLPR genotype moderates associations between childhood stress and PTSD.

ARTICLE INFO

Article history:
Received 1 April 2016
Received in revised form 27 August 2016
Accepted 31 August 2016
Available online 4 September 2016

Keywords:
Alcohol use disorder
Affect dysregulation
PTSD
SLC6A4
rs25531

ABSTRACT

This study tested the role of affect lability and disinhibition in mediating associations between PTSD symptoms and two forms of alcohol-related problems, dependence syndrome symptoms (e.g., impaired control over consumption) and conduct problems (e.g., assault, risk behaviors). Genotype at the serotonin transporter linked polymorphic region (5-HTTLPR) was hypothesized to moderate associations between traumatic stress and PTSD symptoms. In addition, the study tested whether childhood traumatic stress moderated associations between combat trauma and PTSD symptoms. Participants were 270 OIF/OEF/OND veterans. The hypothesized model was largely supported. Participants with the low expression alleles of 5-HTTLPR (S or L) exhibited stronger associations between childhood (but not combat) traumatic stress and PTSD symptoms. Affect lability mediated the associations between PTSD symptoms and alcohol dependence symptoms. Behavioral disinhibition mediated associations between PTSD symptoms and conduct related problems. Conditional indirect effects indicated stronger associations between childhood traumatic stress and lability, behavioral disinhibition, alcohol consumption, AUD symptoms, and associated conduct problems via PTSD symptoms among those with the low expression 5-HTTLPR alleles. However, interactions between combat trauma and either childhood trauma or genotype were not significant. The results support the hypothesis that affect lability and behavioral disinhibition are potential intermediate traits with distinct associations with AUD and associated externalizing problems.

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Posttraumatic stress disorder (PTSD) is a debilitating condition that affects OEF (Operation Enduring Freedom)/OIF (Operation Iraqi Freedom) veterans (Hoge, Auchterlonie, & Milliken, 2006). Prevalence of PTSD among OEF/OIF veterans has increased substantially since 2002 to a current estimate of 23% (Fulton et al., 2015; Seal et al., 2009). PTSD diagnosis increases the odds of alcohol use disorder (AUD) 4-fold (Seal et al., 2011); 41%–79% of those with PTSD have an AUD (Hoge et al., 2004; Pietrzak, Goldstein, Southwick, & Grant, 2011; Scherrer et al., 2008). Patients with comorbid PTSD and substance use disorder (SUD) are at a greater risk for health problems, suicide attempts, violent behavior, and legal problems (Driessen et al., 2008; Tate, Norman, McQuaid, & Brown, 2007). Patients with PTSD and comorbid SUD are less likely to benefit from substance use treatment

http://dx.doi.org/10.1016/j.addbeh.2016.08.044
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and more likely to relapse compared to those with SUD alone (Ouimette, Brown, & Najavits, 1998). Given the social, health and economic impact associated with PTSD and AUD, understanding risk mechanisms is critical for advancing prevention and treatment efforts. Environmental, genetic, temperament, and social-cognitive factors each act as predisposing, precipitating, or maintaining factors in the development and expression of symptoms and behavior. Research on the etiology and treatment of comorbid PTSD and AUD can be advanced by an integrative approach that includes multiple important domains. This study integrates the study of environmental factors (i.e., traumatic stress), genetic factors that contribute to stress reactivity, and individual differences in behavioral and emotional regulation.

1. Mediators of associations between PTSD symptoms and externalizing problems

AUD and other externalizing behaviors are hypothesized to be associated with different regulatory deficits, with behavioral disinhibition underlyng conduct problems and affect lability conferring risk for dependence syndrome (Simons, Carey, & Wills, 2009; Simons, Oliver, et al., 2005b; Simons, Wills, & Neal, 2014). The affective processing model of negative reinforcement posits that fluctuation in negative affect is the core mechanism driving substance dependence (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; McCarthy, Curtin, Piper, & Baker, 2010). Given the importance of sensitization to negative affective states, high levels of negative affect, and rapid changes in negative affect in this model, we propose that individuals characterized by high levels of affective lability are at increased risk for the compulsive drinking patterns characteristic of AUD. PTSD is associated with pronounced emotional dysregulation. We posit that labile affect will mediate associations between PTSD and dependence syndrome symptoms.

Disinhibition has been linked to alcohol use and associated conduct problems (e.g., assault, interpersonal conflict; Carver, 2005; Fernie et al., 2013; Giancola, Parrott, & Roth, 2006; Sher & Trull, 1994; Wills et al., 2013). Disinhibition mediates associations between PTSD and alcohol-related problems (Miller, Vogt, Mozley, Kaloupek, & Keane, 2006), predicts externalizing problems over and above the effects of alcohol consumption (Simons et al., 2009, 2005a), and moderates the relationship between alcohol use and conduct problems, increasing the strength of associations (Neal & Carey, 2007; Simons, Gaer, et al., 2005). Hence, we hypothesize that disinhibition will mediate associations between PTSD symptoms and conduct related problems.

2. Gene-by-environment (G × E) interactions

Individual differences in the risk for developing psychiatric disorders, including PTSD and AUD, are likely the product of an individual’s genetic predisposition and exposure to environmental risk (e.g., stress; Ducci & Goldman, 2008; Koenen, Nugent, & Amstadter, 2008; Sher et al., 2010; Tarter, 2002). There has been substantial interest in characterizing such genetic vulnerabilities, yet the findings have been mixed. A critical barrier to progress in this area has been the focus on categorical diagnoses as phenotypes. We hypothesize that individuals who carry the low expression “S” allele of the serotonin transporter (SLC6A4) regulatory region polymorphism (5-HTTLPR) will exhibit stronger associations between traumatic stress and PTSD symptoms. This is consistent with previous findings on 5-HTTLPR and PTSD (Kimbel et al., 2015; Liu et al., 2015; Pietrzak, Galea, Southwick, & Gelernter, 2013; Wald et al., 2013; Walsh, Uddin, Soliven, Wildman, & Bradley, 2014). Results of two recent meta-analyses found limited evidence of direct effects of 5-HTTLPR on PTSD, indicate that effects are limited to individuals with high degrees of trauma exposure, and call for more research on G × E interactions (Gressier et al., 2013; Navarro-Mateu, Escamez, Koenen, Alonso, & Sanchez-Meca, 2013). The present study seeks to advance previous work by testing moderating effects of the serotonin transporter (SLC6A4) regulatory region polymorphism on associations between both childhood traumatic stress and combat related traumatic stress and a continuous latent PTSD factor in a sample of veterans. Further, to better genetically characterize the expression (i.e., transcriptional efficiency) of 5-HTTLPR we also genotyped rs25531 and utilized the “triallelic” coding scheme, whereby “low” expression is indicated by carrying one or more copies of 5-HTTLPR “S” or rs25531 Lc (Nakamura, Ueno, Sano, & Tanabe, 2000).

3. Stress sensitization versus stress inoculation

Theoretical models on the role of premorbid stress in traumatic stress reactions have posited different relationships. These models vary in respect to the level of premorbid stress that is studied (i.e., manageable stressors versus severe stressors) and the nature of the effect (i.e., buffering versus vulnerability). The stress inoculation model (i.e., early exposure to manageable stressors) suggests that early life stress, especially experiences that are not overwhelming, may act as a protective factor making individuals more resilient to later stressful events (Fergus & Zimmerman, 2005; Garonez, 1991; Khoshaba & Maddi, 1999; Masten, 2001; Mortimer & Staff, 2004). Animal models have demonstrated early stress inoculation induced resiliency in monkeys (Lyons & Parker, 2007) and rats (Meany & Seyf, 2005) by reducing their behavioral and hormonal responses to stress in adult life. In contrast, traumatic life stress taxes the development of an adaptive stress response system, making individuals more vulnerable to the effects of later life stress (Dougherty, Klein, & Davila, 2004; Harkness, Bruce, & Lumley, 2006; Kendler, Kuhn, & Prescott, 2004; Shapiro et al., 2014). Exposure to extreme stress early in life leads to undesirable outcomes (e.g., anxiety, depression) through the interaction between genetic vulnerability and neural circuits responsible for emotion regulation (Gilliespie, Pifer, Bradley, & Ressler, 2009). In the current study, we focus on the vulnerability model and test whether childhood traumatic stress potentiates the association between combat stress and PTSD among veterans to better characterize the associations between combat stress and PTSD symptoms.

4. Summary

The proposed model is depicted in Fig. 1. Gender, combat stress, childhood stress, serotonin transporter 5-HTTLPR/rs25531 genotype, and the stress and genotype interactions were exogenous variables predicting a latent PTSD severity indicator. PTSD symptoms, in turn, predicted alcohol use, affect lability, and disinhibition. Associations between PTSD symptoms and symptoms of alcohol dependence syndrome were expected to be indirect via alcohol consumption and lability. Associations between PTSD symptoms and conduct problems were expected to be indirect via alcohol consumption and disinhibition. Gender was included as a covariate due its potential associations with the outcomes. Men tend to be at higher risk for externalizing problems (e.g., AUD; Hicks et al., 2007). In contrast, research on gender differences in affect lability (Samuel, South, & Griffin, 2015; Simons et al., 2014) and PTSD (Jacobson, Donoho, Crum-Cianflone, & Maguen, 2015) has been more equivocal.

5. Method

5.1. Participants

Participants were 270 OIF/OEF/OND (Operation New Dawn) veterans age 21–51 (M = 33.25, SD = 6.59). Thirteen percent were women. The sample was 81% white, 10% black, 3% multiracial, 1% Asian, and 5% other races or did not respond. Seven percent were Hispanic. The median number of deployments was 2. Approximately 47% were in the National Guard or Reserves when called up for their first
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