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An α-synuclein gene (*SNCA*) polymorphism moderates the association of PTSD symptomatology with hazardous alcohol use, but not with aggression-related measures

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ABSTRACT

Posttraumatic stress disorder (PTSD) often precedes comorbid substance use disorder and has been associated with aggression. Prior research has evidenced that alcohol use and other externalizing behaviors share genetic factors with PTSD; however, few studies have examined if specific genes are associated with externalizing behaviors in PTSD. The purpose of the current study was to investigate whether an α-synuclein gene polymorphism (*SNCA* rs356195) moderates the association of PTSD symptomatology with externalizing behaviors. We examined the separate and combined effects of PTSD symptomatology and *SNCA* rs356195 on alcohol- and aggression-related measures in nonclinical participants ($N = 138$ European Americans; 15 diagnosed with probable PTSD). Probable PTSD status and *SNCA* were both associated with externalizing measures. *SNCA* also moderated the association of PTSD symptomatology with hazardous alcohol use, but not with aggression-related measures. Current findings suggest that variations in *SNCA* may increase the likelihood that PTSD symptomatology results in excessive alcohol use.

1. Introduction

Posttraumatic stress disorder (PTSD) is a common psychiatric disorder that develops following a traumatic event and is estimated to affect approximately 9% of individuals in their lifetime (Kessler et al., 2005). The range of responses that can follow exposure to a traumatic event is broad and includes emotional numbing, hypervigilance, irritability, recklessness, and unwanted re-experiencing of the event through intrusive memories and flashbacks (American Psychiatric Association, 2013). Notably, PTSD frequently co-occurs with substance use disorders (Jacobsen, Southwick, Kosten, 2001; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). For instance, estimated rates of lifetime alcohol use disorder range from about 22% to 52% in individuals with PTSD (Breslau, Davis, Andreski, & Peterson, 1991; Breslau, Davis, Peterson, & Schultz, 1997; Kessler et al., 1995), compared to 8–21% in individuals without PTSD (Breslau et al., 1991, 1997). Where temporal data are available, PTSD usually precedes comorbid substance use disorder (Chilcoat & Breslau, 1998; Jacobsen et al., 2001; Kessler et al., 1995; Kline et al., 2014). PTSD has also been associated with interpersonal aggression (Jakupcak et al., 2007; Jordan et al., 1992; Kulka et al., 1990; Taft et al., 2009), and the robustness of this association has been supported by a meta-analysis of 39 studies (Orth & Wieland, 2006). Other studies have reported elevated rates of thrill-seeking behavior, risky sexual behavior, and unsafe driving associated with PTSD (Fear et al., 2008; Strom et al., 2012), and these risky and impulsive behaviors frequently co-occur (Fear et al., 2008 Jakupcak et al., 2007; Strom et al., 2012).

Importantly, cluster analytic studies have revealed distinct patterns of personality and behavior among individuals who have been exposed to trauma (Forbes, Elhai, Miller, & Creamer, 2010; Miller, Greif, Smith, 2003; Miller, Kaloupek, Dillon, & Keane, 2004;

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Miller & Resick, 2007). One pattern is characterized by *externalizing* psychopathology, including high negative emotionality, low constraint, high levels of aggression, and elevated comorbidity with substance use disorders and antisocial personality disorder. This contrasts with an *internalizing* pattern characterized by low positive emotionality and high negative emotionality. The nature of the genetic and environmental influences on these outcomes is an area of ongoing research.

Twin studies using the Vietnam Era Twin Registry have revealed that PTSD and alcohol use disorder share common genetic influences (McLeod et al., 2001; Xian et al., 2000). However, examination of individual genes is better suited to determining which individuals with PTSD tend to display externalizing psychopathology following traumatic exposure (Norman et al., 2012). The *ANKK1/DRD2* A1 allele, which is associated with alcohol expectancies (Connor et al., 2008 Young, Lawford, Feeney, Ritchie, & Noble, 2004) and risk for alcohol dependence in general (Wang, Simen, Arias, Lu, & Zhang, 2013), has been shown to be more frequent in combat veterans with PTSD who were harmful drinkers compared to those who were not harmful drinkers (Young et al., 2002). The ankyrin 3 gene (*ANK3*) has also been studied for its possible influence on externalizing behavior and PTSD: Logue et al. (2013) reported that a single-nucleotide polymorphism (SNP; rs9801490T allele) was associated with a reduced likelihood of PTSD and externalizing behavior, suggesting that it may reflect a common genetic factor underlying the development of both PTSD and externalizing behavior. Finally, variations in *5-HTTLPR* have been found to interact with early life and family stress to predict alcohol use in maltreated children and adolescents (Kaufman et al., 2007; Nilsson et al., 2005). Overall though, little is known about specific genes that are associated with externalizing behaviors in PTSD.

α-Synuclein is a presynaptic protein that attenuates dopamine (DA) biosynthesis and release (Venda, Cragg, Buchman, & Wade-Martins, 2010), and DA neurotransmission is known to play an important role in reward and addiction (Berridge, 2007; Wise, 2004). With regard to addictive behavior, the α-synuclein gene (*SNCA*) has been shown to be more highly expressed in the hippocampus and nucleus accumbens of alcohol-naïve rats bred to prefer alcohol compared to alcohol-naïve rats bred to not prefer alcohol (Liang et al., 2003; Pelkonen, Hiltunen, Kiianmaa, & Yavich, 2010). In humans, blood α-synuclein levels have been positively correlated with alcohol and cocaine craving (Bonsch et al., 2004; Mash et al., 2008), and several SNPs of *SNCA* have been associated with alcohol craving (Agrawal et al., 2013; Foroud et al., 2007) and alcohol use disorder (Levey et al., 2014). Recent studies have also linked *SNCA* to impulsivity in mice (Pena-Oliver et al., 2012; Pena-Oliver, Sanchez-Roige, Stephens, & Ripley, 2014) and humans (Guillot, Fanning, Liang, & Berman, 2014a). In regard to specific SNPs of *SNCA*, the C-allele of *SNCA* rs356195 has been associated with negative history of alcohol craving (Foroud et al., 2007), and *SNCA* rs356195 T-allele carriers have displayed greater impulsivity than individuals with the CC genotype (Guillot et al., 2014a). Given the involvement of DA and impulsivity in aggressive behavior (Lesch & Merschdorf, 2000; Yanowitch & Coccaro, 2011), it is possible that *SNCA* is also associated with aggression. However, no study to date has examined this relationship.

Externalizing symptoms (e.g., aggression), characterized by behavioral disconstraint, have been prospectively associated with alcohol problems in individuals with PTSD (Haller & Chassin, 2013; Miller, Vogt, Mozley, Kaloupek, & Keane, 2006). The purpose of the current study was to investigate whether the *SNCA* rs356195 polymorphism, which has previously been associated with impulsivity, moderates the association of PTSD symptomatology with externalizing behaviors. To this end, we examined the separate and combined effects of PTSD symptomatology and *SNCA* rs356195 on alcohol- and aggression-related measures in a nonclinical sample. We hypothesized that *SNCA* T-allele carriers would display evidence of greater impairment in behavioral control in domains related to alcohol use and aggression relative to C homozygotes. Based on past research, we expected that probable PTSD status would be associated with more severe alcohol use and greater aggression and alcohol-related aggression expectancies. We also hypothesized that *SNCA* would moderate these relationships, such that PTSD symptomatology would be more strongly related to higher levels of hazardous alcohol use, aggression, and alcohol-related aggression expectancies in T-allele carriers.

2. Method

2.1. Participants and Procedures

Using the same methodology as a prior study (Guillot, Fanning, Liang, & Berman, 2014b), a total of 222 participants were recruited from the university and community through university-based e-mail announcements, on- and off-campus fliers, and newspaper and online advertisements and were genotyped for *SNCA* rs356195. Blood samples for genotyping were obtained by puncturing the index finger with an automatic fingerstick lancet device and then storing three small blots of blood with 3MM chromatography paper (Whatman, Inc. Florham Park, NJ). Dried blood samples were analyzed at the Indiana Alcohol Research Center. DNA was isolated using the HotSHOT method (Truett et al., 2000), after which TaqMan probes were used for allelic discrimination (Applied BioSystems, Inc. Foster City, CA). Thermocycling was carried out in MJ Research PTC-200 thermocyclers, and the PCR products were analyzed in an ABI PRISM® 7300 Sequence Detection System (SDS) instrument.

In order to limit the potentially confounding effects of population stratification, only participants who self-identified as "Caucasian" were retained. Of the remaining 145 participants, 7 were excluded because of incomplete self-report data, leaving a total sample of 138 European Americans (77 men and 61 women) between the ages of 21 and 55 ($M = 25.96$, $SD = 7.48$). The project was approved by The University of Southern Mississippi Human Subjects Protection Review Committee. Written informed consent was obtained prior to participation.

2.2. Measures

2.2.1. PTSD Checklist Civilian Version (PCL-C)

The PCL-C was used to diagnose probable PTSD (McDonald & Calhoun, 2010). The self-report instrument consists of 17 items corresponding to symptoms from PTSD Criterion B (trauma re-experiencing), Criterion C (trauma-related avoidance and general numbing), and Criterion D (increased arousal) of the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*). (American Psychiatric Association, 2000) Test-takers are asked to respond to each symptom consistent with how much they have been bothered by that problem during the past month, and items are answered on a 5-point severity scale scored from 1 (*not at all*) to 5 (*extremely*). Using the symptom cluster method, individuals are given a presumptive diagnosis of PTSD if they score 3 (*moderately*) or higher on at least one Criterion B item, three Criterion C items, and two Criterion D items (thus meeting Criterion B, C, and D, respectively). The symptom cluster method has yielded a sensitivity of 39–100% and a specificity of 79–94% in relation to interviewer-diagnosed PTSD.(McDonald & Calhoun, 2010) In addition, PCL-C Criterion B–D subscale scores and Total Scale scores were also computed.

2.2.2. Alcohol Use Disorders Identification Test (AUDIT)

The AUDIT is a self-report measure of hazardous and harmful alcohol use (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001).