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Evidence of Shared Genome-Wide Additive Genetic Effects on Interpersonal Trauma Exposure and Generalized Vulnerability to Drug Dependence in a Population of Substance Users

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Exposure to traumatic experiences is associated with an increased risk for drug dependence and poorer response to substance abuse treatment (Claus & Kindleberger, 2002; Jaycox, Ebener, Damesek, & Becker, 2004). Despite this evidence, the reasons for the observed associations of trauma and the general tendency to be dependent upon drugs of abuse remain unclear. Data ($N = 2{,}596$) from the Study of Addiction: Genetics and Environment were used to analyze (a) the degree to which commonly occurring single nucleotide polymorphisms (SNPs; minor allele frequency $> 1\%$) in the human genome explains exposure to interpersonal traumatic experiences, and (b) the extent to which additive genetic effects on trauma are shared with additive genetic effects on drug dependence. Our results suggested moderate additive genetic influences on interpersonal trauma, $h^2_{\text{SNP-Interpersonal}} = .47$, 95% confidence interval (CI) [.10, .85], that are partially shared with additive genetic effects on generalized vulnerability to drug dependence, $h^2_{\text{SNP-DD}} = .36$, 95% CI [.11, .61]; $r_{\text{G-SNP}} = .49$, 95% CI [.02, .96]. Although the design/technique does not exclude the possibility that substance abuse causally increases risk for traumatic experiences (or vice versa), these findings raise the possibility that commonly occurring SNPs influence both the general tendency towards drug dependence and interpersonal trauma.

The identification of genetic and environmental risk factors for drug dependence remains a critical issue in problem substance use and abuse, with implications for understanding etiology as well as prevention and intervention. Converging evidence across epidemiological and twin and family studies support the existence of a generalized vulnerability to drug

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dependence as an alternative to the theory that distinct risk and protective factors influence individual substances of abuse (Kendler, Myers, & Prescott, 2007; Palmer et al., 2012, 2015; Rhee et al., 2006). Generalized vulnerability to drug dependence represents the underlying tendency to use and become dependent upon both licit (e.g., alcohol) and illicit (e.g., cannabis) substances. Prior research examining genetic influences on measures of drug dependence (e.g., factor score or sum score of drug-dependence symptoms) have shown moderate to high heritability estimates ranging from 40% to 64% (Palmer et al., 2012, 2015). For example, Button et al. (2006) estimated the heritability of dependence vulnerability at 40.0% in a community-based sample of twins with rates of drug use and dependence similar to those observed in U.S.-based population samples. Further, a longitudinal study of drug dependence in the same sample suggested that genetic influences persist from adolescence into young adulthood (Palmer et al., 2013).

In addition to the evidence for moderate (.30 to .60) to high (>.60) genetic influences on substance use/abuse, most studies also find a substantial role for environmental influences (Agrawal & Lynskey, 2008; Button, et al., 2006). Research characterizing the influence of genes and environment on drug dependence is needed to better understand whether genes and environment contribute unique additive risks, confer unique synergistic risks (i.e., the combination of genetic and environmental risk factors have a greater effect on risk than a single risk factor alone), or are themselves interrelated such that aspects of environment are influenced by genetics (Salvatore et al., 2014; Young-Wolff, Enoch, & Prescott, 2011).

Exposure to traumatic experiences, in particular, has been linked to problem substance use and even to poor response to substance abuse treatment (Huang, Schwandt, Ramchandani, George, & Heilig, 2012; Sacks, McKendrick, & Banks, 2008). Although explanatory models generally include a role for biological/genetic influences (i.e., gene–environment interplay), relatively few genetic studies have attempted to characterize this overlap. Available studies point to the need for further study. For example, one recent investigation used a co-twin control method in a large sample ($N = 2{,}776$) of adult twin pairs, including twin pairs discordant for exposure to Criterion A trauma ($N = 449$; Brown et al., 2014) according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., *DSM-IV*; American Psychiatric Association, 1994). Within the full sample, participants with a history of trauma were found to be more likely to meet criteria for a substance abuse disorder; among twins discordant for trauma, there was evidence that trauma was directly related to a substance abuse disorder. The pattern of findings (the lower bound of the confidence interval [CI] in the discordant twin analyses included one), however, could not rule out the possibility of shared familial influences (i.e., either additive genetic and shared environment) on the relationship between trauma and substance use disorders (Brown et al., 2014). Accordingly, research with a complementary approach is needed to continue to inform shared genetic influences on trauma and substance use disorders.

Exposure to a range of traumatic events such as violence, abuse, life-threatening accidents, and disasters is common, with more than 80% of individuals reporting exposure to at least one traumatic event (Miller et al., 2013). Importantly, the ways in which an individual selects and shapes their own environment means that many seemingly environmental influences are themselves heritable (Kendler & Baker, 2007). Twin studies have shown that a range of environmental exposures, including trauma exposure, are influenced by genetic factors (Koenen et al., 2002; Lyons et al., 1993; Sartor et al., 2011; Stein, Jang, Taylor, Vernon, & Livesley, 2002). Genetic influences on trauma exposure have been shown in veteran and community samples. For example, data from the Vietnam Era Twin Registry produced estimates of heritability of combat exposure ranging from 35% to 47% (Eisen, True, Goldberg, Henderson, & Robinette, 1987; Goldberg, True, Eisen, Henderson, & Robinette, 1987; Lyons et al., 1993). Heritability of exposure to interpersonal trauma in a civilian sample was estimated to be more modest (≈20%) in one investigation (Stein et al., 2002). Although studies have tested the overlap of genetic influences on trauma exposure and risk for posttraumatic stress disorder (PTSD), few studies have incorporated both genetic and trauma history influences in heritability models of drug dependence. One exception is an investigation with the Swedish Twin Registry, which reported moderate heritability (55%) for alcohol dependence and concluded that the effects of physical trauma on alcohol dependence were largely attributable to familial factors, whereas the association of childhood sexual abuse with alcohol dependence was attributable to both familial and specific environmental effects (Magnusson et al., 2012).

In addition to twin and family studies, a few molecular candidate gene studies have examined genetic influences on the association between PTSD and substance use/abuse, with some evidence pointing to markers (e.g., carriers of the major alleles of a haplotype block in the corticotropin-releasing hormone type I receptor [*CRHR1*] gene that is defined by rs110402 and rs242924, protects against the risk for alcoholism among individuals with a history of adult traumatic stress exposure; Ray et al., 2013) implicated in major stress system modulation (Ducci et al., 2008; Enoch et al., 2010; Nelson et al., 2010; Nugent, Lally, Brown, Knopik, & McGeary, 2012). Studies linking genetic variation to both trauma exposure and substance problems are limited, with most studies focusing on the moderation of genetic influences on substance behaviors by trauma exposure (Enoch et al., 2010; Ray et al., 2013). Candidate molecular studies are also limited by the small effects of single markers. Merging many of the strengths of molecular studies and family studies, Yang, Lee, Goddard, and Visscher (2013) developed a method for estimating the phenotypic variance explained by all genotyped single nucleotide polymorphisms (SNPs; genomic relatedness-maximum likelihood [GREML]; implemented in the software package genome-wide complex

trait analysis [GCTA]; version 1.21). GCTA decomposes the phenotypic variance into the effects due to environmental influences as well as the effects of unmeasured genetic variants (V_E; i.e., variance not explained by the model) and additive influences of all measured SNPs (i.e., V_A—variance attributable to genomewide SNP similarity; SNP-heritability, h^2_{SNP}—proportion of the total phenotype variance due to V_A). Although GREML does not provide a direct estimation of individual marker effects on a phenotype, observed SNP-heritability estimates likely comprise effects from variants with the largest effect sizes observed in GWASs (Moser et al., 2015). Hence, SNP-heritability estimates provide a basis for beginning to understand the genetic architecture of complex traits. Using GREML, we recently showed that common SNPs account for approximately 25% to 36% of the variance across several drug-dependence phenotypes (Palmer et al., 2015). Questions remain, however, regarding the role of commonly occurring (i.e., minor allele frequency >1%) genetic variants on trauma exposure and their overlap with the genetic influences on drug dependence.

This research aimed to examine the proportion of variance in trauma exposure that could be accounted for by common SNPs in a sample of participants reporting drug use. Further, we sought to examine the overlap in genomewide genetic effects on drug dependence and trauma. The current analyses focused on the measure of generalized vulnerability to drug dependence because of the heterogeneity of genetic effects generally observed when assessing each substance separately. Although vulnerability to drug dependence can be operationalized/scored in multiple forms, the current study examined genetic influences on the measure that aligns best with the common pathway model that has been previously examined and replicated in different samples (Vanyukov & Ridenour, 2012; Vanyukov et al., 2012). Generalized vulnerability to drug dependence (derived from a latent factor) was recently examined in a sample of drug users and showed significant promise for being sensitive to genetic effects (Palmer et al., 2015).

Method

Participants, Procedure, and Measures

The current study used previously collected data from subjects in the Study of Addiction: Genetics and Environment (SAGE), which is part of the National Human Genome Research Institute's Gene Environment Association Study Initiative (Database for Genotypes and Phenotypes [dbGaP] study accession phs000092.v1.p1). As part of the public use agreement from dbGAP, subjects in each dataset provided informed consent for genetic studies of drug and alcohol addiction. The SAGE study comprised three large, complementary datasets (i.e., the Collaborative Study on the Genetics of Alcoholism [COGA], the Family Study of Cocaine Dependence [FSCD], and the Collaborative Genetic Study of Nicotine Dependence [COGEND]) of mixed ethnic background. More information for these projects may be found at http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000092.v1.p1.

For the current study, we restricted analyses to unrelated SAGE participants of European descent (N = 2,596; 44.6% male, mean age = 38.58 years, SD = 9.80). One of any pair of individuals who had a mean genetic relationship >.025 (i.e., maximum relatedness approximately corresponding to cousins two to three times removed) was randomly removed (Lee, Wray, Goddard, & Visscher, 2011). Thus, analyses adjusted for cryptic relatedness, which could inflate SNP-heritability estimates by including shared environmental variance or genetic variance not usually tagged by SNPs. We confirmed ancestry using principal component analysis (PCA; described below; Palmer et al., 2015) to adjust for the possibility of heterogeneity in SNP effects and low power in detecting effects across ethnicities with small sample sizes. The Institutional Review Board for Rhode Island Hospital reviewed and approved the scope of work for secondary data analyses of our subset of the SAGE data. Genotyping had been conducted with the Illumina 1M platform. Blood samples deposited at the Rutgers University Cell and DNA Repository (http://www.rucdr.org) had been genotyped at the Johns Hopkins Center for Inherited Disease Research (CIDR) using Illumina Human1Mv1_C BeadChips and the Illumina Infinium II assay protocol. SNP calls were made using Illumina BeadStudio Genotyping Module v3.1.14. Strict quality-control standards were implemented, and genotypes were released by CIDR for 1,040,106 SNPs (99.15% of attempted). Further details are provided in the comprehensive data cleaning report at dbGaP http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/document.cgi?study_id=phs000092.v1.p1&phv=22928&phd=2274&pha=&pht=116&phvf=&phdf=20&phaf=&phtf=&dssp=1&consent=&temp=1.

Using a random sample of 30,000 SNPs from the SAGE dataset to generate a genomic similarity matrix, we performed a PCA to extract estimates of genetic variation due to ancestry (as in Palmer et al., 2015). In addition, we added SNP calls from 128 HapMap individuals (one per family) to anchor results for the PCA.

For genetic analyses using individuals of European descent, we retained 796,125 autosomal markers with a minor allele frequency >1%, a call rate ≥99%, and a Hardy–Weinberg equilibrium (HWE) p value >.0001.

Analyses focused on generalized vulnerability to drug dependence and interpersonal forms of traumatic experiences. Self-report *DSM-IV* symptom endorsement for dependence on alcohol, nicotine, cocaine, cannabis, and other illicit drugs (i.e., dependence on drugs other than cannabis or cocaine (e.g., opiates, phencyclidine, hallucinogens, sedatives) had been gathered using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994) in addition to modified versions of the Semi-Structured Assessment of Nicotine Dependence (SSAND; Saccone, Saccone, et al., 2009; Saccone, Wang, et al., 2009) and the Semi-Structured Assessment for Cocaine Dependence (SSACD), which is a modified

version of the SSAGA for studying cocaine dependence (available at: http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/variable.cgi?study_id=phs000092.v1.p1&phv=22925).

As described in Palmer et al. (2015), vulnerability to drug dependence is best represented by a standardized factor score ($M = 0$, $SD = 1$) based on five dichotomous *DSM-IV* diagnoses of drug dependence for alcohol, nicotine, cocaine, cannabis, and other illicit drugs (e.g., opiates, phencyclidine, hallucinogens, sedatives). Briefly, we conducted an exploratory and confirmatory factor (EFA and CFA, respectively) analyses on separate random halves of the SAGE dataset using weighted least squares mean variance estimation. Parallel analysis, substantive interpretation, and previous empirical findings suggested a 1-factor solution (Zwick & Velicer, 1986). The common factor model fit the data well (root mean square error of approximation = .060, comparative fit index = .995) with loadings on the observed factor >.67. The single latent factor was extracted and factor scores computed. The standardized factor is interpreted as the level of severity of drug-related problems where higher scores on the latent factor are indicative of more diagnostic-level problems across substances.

Exposure to traumatic events was assessed during research interviews, specifically queries incorporated into the SSAGA (Bucholz et al., 1994), the SSAND (Saccone, Saccone, et al., 2009; Saccone, Wang, et al., 2009), and the SSACD (trauma exposure assessment is publically available at the dbGaP website http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/document.cgi?study_id=phs000092.v1.p1&phv=22899&phd=1219&pha=2907&pht=116&phvf=8&phdf=&phaf=&phtf=&dssp=1&consent=&temp=1#V4137). The interviewer handed the participant a list of potential traumas and then asked whether they had ever "experienced or witnessed something that is so horrible that it would be distressing or upsetting to almost anyone?" Interviewers then verbally restated examples on the list: military combat; an assault, rape, or kidnapping; seeing someone seriously injured or killed; a flood, earthquake, large fire, or other disaster; an airplane crash or serious car accident; a shooting or bombing; or any situation where you feared there was a serious threat to your life or to the life of another person. For participants who reported any event, interviewers then recorded each reported event. For analyses in the current study, trauma was considered a dichotomous lifetime event such that both reported childhood and adult traumas contributed to whether an individual was considered to have experienced a trauma. Trauma was operationalized as either interpersonal ($n = 1{,}760$; i.e., physical assault and rape or sexual assault) or noninterpersonal trauma ($n = 1{,}725$; i.e., trauma that did not involve direct physical or sexual encounters, e.g., earthquake) to maximize power given low rates of individual responses. Interpersonal trauma and noninterpersonal trauma were treated as separate events so that individuals who endorsed both a tornado and sexual assault would be coded as having experienced both interpersonal and noninterpersonal trauma.

Data Analysis

Phenotypic statistics and data manipulation were conducted using SAS (Version 9.4, R2; Steiger & Fouladi, 1997), MPlus (Version 7; Muthén & Muthén, 1998–2012), and SVS (Version 8.3.0, Version 8.x; SNP & Variation Suite [version 8.4.1]).

Genome-wide complex trait analysis (GCTA; Yang, Lee, Goddard, & Visscher, 2011) was used to decompose phenotypic variance measured by the drug-dependence factor and the trauma-exposure outcomes that is due to additive effects of all genotyped SNPs. This approach consists of two steps in which the genetic similarity between individuals was obtained via a pairwise genetic relationship matrix (GRM), followed by construction of a mixed effects model. Univariate and bivariate GREML models were fitted to the phenotypic data while adjusting for age, gender, study origin, and the first five genetic principal components to account for stratification effects within individuals of European descent (Price et al., 2006). In bivariate GREML, the covariance between two traits is described by a standard bivariate linear mixed model such that the genetic correlation ($r_{G\text{-}SNP}$) is estimated using the covariance between the genetic and environmental/residual factors influencing each trait. Accordingly, $r_{G\text{-}SNP}$ can be interpreted as the extent to which the genetic factors influencing each phenotype are correlated. Consistent with the core properties of correlation metrics, the genetic correlation can take on values ranging from −1.0 to 1.0 (Lee, Yang, Goddard, Visscher, & Wray, 2012). See Supplementary Materials for analyses repeated using *DSM-IV* diagnostic measures.

Results

The most prevalent form of trauma was noninterpersonal (61.8%, $n = 1{,}066/1{,}725$). Interpersonal trauma was present among 36.2% ($n = 637/1{,}760$) of the three samples. Findings supported an association between drug dependence and report of having experienced interpersonal trauma, $r^2 = .05$, 95% CI [.03, .07], $p < .001$.

Estimates of the phenotypic variance/covariance (i.e., in drug dependence, interpersonal trauma, and noninterpersonal trauma) explained by all autosomal SNPs are shown in Table 1. The SNP-based heritability of generalized drug-dependence was 36%, 95% CI [.11, .61], h^2_{SNP}. The effects for individual substances are provided in Supplemental Table 1. Likewise, a significant proportion of the phenotypic variance in interpersonal trauma, $h^2_{SNP\text{-}Interpersonal} = .47$, 95% CI [.10, .85], was captured by common SNPs; additive genetic effects on noninterpersonal trauma were limited, $h^2_{SNP\text{-}Noninterpersonal} = .11$, 95% CI [−.26, .49]. Bivariate GREML analyses between trauma and drug dependence suggested that genetic factors for interpersonal traumatic events and generalized drug dependence are positively correlated, $r_{G\text{-}SNP} = .49$, 95% CI [.02, .96]. In other words, partially overlapping genetic factors influence both phenotypes; see Supplemental Table 2 for bivariate results stratified by substances that comprise drug dependence.

Table 1
Bivariate Model (rG:DD-Trauma) of Shared and Nonshared Genetic Effects Across Measures

		$r_{DD\text{-}Trauma}$		$V_{A\text{-}DD}$		$V_{A\text{-}Trauma}$		$cov_{A\text{-}DD\text{-}Trauma}$		$r_{G\text{-}SNP}$		
Variable	*n*	*r*	95% CI	*r*	95% CI	*r*	95% CI	*r*	95% CI	*r*	95% CI	SNP-C
INT	4,356	.05	[.03, .07]	.17	[.05, .28]	.11	[.02, .19]	.07	[−.01, .14]	.49*	[.02, .96]	.20
NONINT	4,321	.00	[.00, <.01]	.18	[.06, .29]	.03	[−.04, .09]	.04	[−.02, .11]	.69	[−.76, 1.00]	.14

Note. DD = generalized vulnerability to drug dependence; $r_{DD\text{-}Trauma}$ = phenotypic correlation between drug dependence and trauma variables; $V_{A\text{-}DD}$ = genetic variance for drug dependence phenotype; $V_{A\ Trauma\text{-}}$ = genetic variance for trauma phenotype; $cov_{A\text{-}DD\text{-}Trauma}$ = the genetic covariance; $r_{G\text{-}SNP}$ = the genetic-single nucleotide polymorphism correlation; SNP-C = SNP-coheritability; CI, confidence interval; INT = interpersonal trauma; NONINT = noninterpersonal trauma.
*$p < .05$.

Discussion

The present research aimed to describe the extent to which common genetic variation is associated with liability to both trauma exposure and drug dependence. The first contribution of this research is evidence that, in these samples of drug users, exposure to interpersonal trauma was heritable. This is consistent with evidence from twin models (Koenen et al., 2002; Lyons et al., 1993; Sartor et al., 2011; Stein et al., 2002) and extends/complements twin approaches to show that a significant proportion of genetic liability for interpersonal trauma exposure is captured by common SNPs. Although the present design does not permit explanations for observed effects, one possibility is that the heritability of trauma exposure may be explained by genetic influences on personality (Afifi, Asmundson, Taylor, & Jang, 2010; Jang, Stein, Taylor, Asmundson, & Livesley, 2003). Certain traits may increase the likelihood that an individual experiences trauma. An individual with externalizing traits might choose social networks or environmental settings that increase risk for experiencing trauma; further, someone with an externalizing style might behave in a manner that places them at risk for trauma. Accordingly, a seemingly environmental event such as assault or combat exposure may be determined in part by genetic influences.

The second contribution of the investigation was evidence that a significant portion of the genetic liability to interpersonal trauma exposure may be shared with liability to drug dependence; notably, noninterpersonal trauma did not share common genetic liability with drug dependence. Again, the present methods cannot disentangle the underpinnings of this overlapping genetic liability, but this molecularly based finding is consistent with prior twin literature (Koenen et al., 2005; Sartor et al., 2011; Xian et al., 2000). For example, one twin study has shown that PTSD shares genetic etiology with both externalizing (defined as drug and alcohol dependence and antisocial personality disorder; $h^2 = 69\%$) and internalizing (defined as dysthymia, generalized anxiety disorder, panic disorder, and major depression; $h^2 = 41\%$) disorders (Wolf et al., 2010).

One limitation of this study was an inability to determine (from the significant $r_{G\text{-}SNP}$) whether the same genetic factors influenced both trauma liability and drug-dependence traits directly. This application of GREML to retrospective data was unable to disentangle direct causal mechanisms such as trauma increasing risk for drug dependence, drug dependence increasing trauma risk, or a shared phenotype increases risk for both trauma and drug dependence. It is possible that associations between trauma and drug dependence are explained by a common underlying constitutional difference that places the same individuals at risk for trauma and for drug dependence (Reed, Anthony, & Breslau, 2007). Alternatively, individuals with drug dependence may be at greater risk for experiencing trauma by virtue of their context: Individuals using illicit substances may risk assault secondary to behaviors enacted to obtain drugs or by interacting with others who are more likely to be physically (or sexually) aggressive (Afful, Strickland, Cottler, & Bierut, 2010). Likewise, being under the influence of a substance(s) increases risk for experiencing a range of traumatic events (Clark, Lesnick, & Hegedus, 1997; Giaconia et al., 2000; Perkonigg, Kessler, Storz, & Wittchen, 2000). It is also possible that trauma-exposed individuals are at increased risk for drug dependence because they are self-medicating to address trauma-related symptoms/diagnoses such as PTSD.

Inclusion of a PTSD assessment would have provided some indication of individual differences in response to these traumatic experiences. Research suggests that trauma (particularly PTSD diagnosis) increases the risk of developing a substance use disorder, and many substance use disorders precede the onset of trauma exposure. Findings from twin and molecular genetic studies also suggest that PTSD shares moderate overlapping genetic risk (≈40%) with drug-dependence phenotypes, such as alcohol and drug dependence (Sartor et al., 2011; Xian et al., 2000) and nicotine dependence (Koenen et al., 2005). Candidate molecular genetic research has reported associations between the mu opioid receptor (Type 1; *OPRM1*) variation and PTSD and enhancement motives for drinking (Nugent et al., 2012). Further, consistent with a self-medication hypothesis of substance abuse, PTSD symptom severity in that sample was significantly associated with drinking motives for coping, enhancement, and socialization. In short, it is possible that unmeasured PTSD may partly account for the associations observed here. These same studies also highlight the complex multidirectional nature of the relationship between trauma exposure and drug dependence. It is possible that the observed $r_{G\text{-}SNP}$ may be due to indirect effects, mediation effects (i.e., mediated by

either drug dependence or trauma exposure), or even both (i.e., a bidirectional causal model).

It is also important to recognize a few other limitations. Specifically, observed SNP heritability estimates of the trauma exposure measures may not generalize to population-based estimates because this study was conducted with differentially ascertained samples of substance users; reported genetic effects are all on the observed scale. Further, we employed a broad indicator of trauma that encompassed physical and sexual trauma across the lifespan. This bias may affect observed estimates from the current study depending on the ratio of phenotypic distributions in the general population. The SAGE sample was selected based on alcohol (COGA), nicotine (COGEND), and cocaine (FSCD) dependence, thereby including individuals who reported involvement with multiple substances. Consequently, estimates of SNP-heritability for drug dependence in the current study are likely slightly inflated compared to the general population. Though this may limit generalizability to individuals with low likelihood of substance dependence, it provides enhanced power. In addition, the study utilized dichotomous measures of lifetime trauma, which are less sensitive to the cumulative effects of trauma. Finally, the observed $r_{G\text{-}SNP}$ was bounded by a large 95% CI. Although this study was in agreement with prior twin and family studies, the results need replication. Overall, these findings suggested a genetic relationship between drug dependence and trauma, but it did not provide a clear indication of the risk for drug dependence given a person's trauma history or vice versa, as that is dependent upon the direction of causation between drug dependence and trauma. Future work would benefit from additional trauma measures and trauma-related diagnoses, as well as assessments of other domains of the vulnerability to drug dependence. Likewise, more studies are needed to determine the causal relationship between drug dependence and trauma and to test whether there are shared genome-wide additive genetics over what would occur indirectly via a causal relationship between drug dependence and trauma.

Importantly, there is evidence from substance abuse treatment programming that individuals with a trauma history (particularly in childhood) show poorer treatment response than those without a trauma history (Sacks et al., 2008). Given our findings regarding a shared genetic liability for both drug dependence and trauma exposure, prevention and treatment researchers alike may be well served to focus on risk factors that might be common to trauma exposure and drug dependence (e.g., impulsivity, sensation seeking, and failure to assess long-term consequences of immediate behavior); research on this question is needed. Even for individuals who do not yet report a trauma history, the combination of their genetic liability and aspects of a substance use/abuse lifestyle render individuals with drug dependence at increased risk for experiencing future trauma. Accordingly, treatments for substance use/abuse could be well served by incorporating components of intervention that are aimed at reducing risk for future trauma.

References

Afful, S. E., Strickland, J. R., Cottler, L., & Bierut, L. J. (2010). Exposure to trauma: A comparison of cocaine-dependent cases and a community-matched sample. *Drug and Alcohol Dependence*, *112*, 46–53. doi:10.1016/j.drugalcdep.2010.05.012

Afifi, T. O., Asmundson, G. J., Taylor, S., & Jang, K. L. (2010). The role of genes and environment on trauma exposure and posttraumatic stress disorder symptoms: A review of twin studies. *Clinical Psychology Review*, *30*, 101–112. doi:10.1016/j.cpr.2009.10.002

Agrawal, A., & Lynskey, M. T. (2008). Are there genetic influences on addiction: Evidence from family, adoption and twin studies. *Addiction*, *103*, 1069–1081. doi:10.1111/j.1360-0443.2008.02213.x

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Brown, R. C., Berenz, E. C., Aggen, S. H., Gardner, C. O., Knudsen, G. P., Reichborn-Kjennerud, T.,. . . Amstadter, A. B. (2014). Trauma exposure and Axis I psychopathology: A co-twin control analysis in Norwegian young adults. *Psychological Trauma: Theory, Research, Practice, and Policy*, *6*, 652–660. doi:10.1037/a0034238

Bucholz, K. K., Cadoret, R., Cloninger, C. R., Dinwiddie, S. H., Hesselbrock, V. M., Nurnberger, J. I., . . . Schuckit, M. A. (1994). A new, semi-structured psychiatric interview for use in genetic linkage studies: A report on the reliability of the SSAGA. *J. Stud. Alcohol Journal of Studies on Alcohol*, *55*(2), 149–158. doi:10.15288/jsa.1994.55.149

Button, T. M., Hewitt, J. K., Rhee, S. H., Young, S. E., Corley, R. P., & Stallings, M. C. (2006). Examination of the causes of covariation between conduct disorder symptoms and vulnerability to drug dependence. *Twin Research and Human Genetics: The Official Journal of the International Society for Twin Studies*, *9*, 38–45. doi:10.1375/183242706776402993

Clark, D. B., Lesnick, L., & Hegedus, A. M. (1997). Traumas and other adverse life events in adolescents with alcohol abuse and dependence. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*, 1744–1751. doi:10.1097/00004583-199712000-00023

Claus, R. E., & Kindleberger, L. R. (2002). Engaging substance abusers after centralized assessment: Predictors of treatment entry and dropout. *Journal of Psychoactive Drugs*, *34*, 25–31. doi:10.1080/02791072.2002.10399933

Ducci, F., Enoch, M., Hodgkinson, C., Xu, K., Catena, M., Robin, R., & Goldman, D. (2008). Interaction between a functional MAOA locus and childhood sexual abuse predicts alcoholism and antisocial personality disorder in adult women. *Molecular Psychiatry*, *13*, 334–347. doi:10.1038/sj.mp.4002034

Eisen, S., True, W., Goldberg, J., Henderson, W., & Robinette, C. (1987). The Vietnam Era Twin (VET) Registry: Method of construction. *Acta Geneticae Medicae et Gemellologiae: Twin Research*, *36*, 61–66. http://dx.doi.org/10.1017/S0001566000004591

Enoch, M. A., Hodgkinson, C. A., Yuan, Q., Shen, P. H., Goldman, D., & Roy, A. (2010). The influence of GABRA2, childhood trauma, and their interaction on alcohol, heroin, and cocaine dependence. *Biological Psychiatry*, *67*, 20–27. doi:10.1016/j.biopsych.2009.08.019

Giaconia, R. M., Reinherz, H. Z., Hauf, A. C., Paradis, A. D., Wasserman, M. S., & Langhammer, D. M. (2000). Comorbidity of substance use and posttraumatic stress disorders in a community sample of adolescents. *American Journal of Orthopsychiatry*, *70*, 253–262. doi:10.1037/h0087634

Goldberg, J., True, W., Eisen, S., Henderson, W., & Robinette, C. (1987). The Vietnam Era Twin (VET) Registry: Ascertainment bias. *Acta Geneticae Medicae et Gemellologiae: Twin Research*, *36*, 67–78. http://dx.doi.org/10.1017/S0001566000004608

Huang, M. C., Schwandt, M. L., Ramchandani, V. A., George, D. T., & Heilig, M. (2012). Impact of multiple types of childhood trauma exposure on risk of psychiatric comorbidity among alcoholic inpatients. *Alcoholism:*

Clinical and Experimental Research, *36*, 1099–1107. doi:10.1111/j.1530-0277.2011.01695

Jang, K. L., Stein, M. B., Taylor, S., Asmundson, G. J., & Livesley, W. J. (2003). Exposure to traumatic events and experiences: Aetiological relationships with personality function. *Psychiatry Research*, *120*, 61–69. doi:10.1016/s0165-1781(03)00172-0

Jaycox, L. H., Ebener, P., Damesek, L., & Becker, K. (2004). Trauma exposure and retention in adolescent substance abuse treatment. *Journal of Traumatic Stress*, *17*, 113–121. doi:10.1023/B:JOTS.0000022617.41299.39

Kendler, K. S., & Baker, J. H. (2007). Genetic influences on measures of the environment: A systematic review. *Psychological Medicine*, *37*, 615–626. doi:10.1001/archpsyc.64.11.1313

Kendler, K. S., Myers, J., & Prescott, C. A. (2007). Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. *Archives of General Psychiatry*, *64*, 1313–1320. doi:10.1097/00005053-200204000-00001

Koenen, K. C., Harley, R., Lyons, M. J., Wolfe, J., Simpson, J. C., Goldberg, J.,. . . Tsuang, M. (2002). A twin registry study of familial and individual risk factors for trauma exposure and posttraumatic stress disorder. *The Journal of Nervous and Mental Disease*, *190*, 209–218. doi:10.1001/archpsyc.62.11.1258

Koenen, K. C., Hitsman, B., Lyons, M. J., Niaura, R., McCaffery, J., Goldberg, J.,. . . Tsuang, M. (2005). A twin registry study of the relationship between posttraumatic stress disorder and nicotine dependence in men. *Archives of General Psychiatry*, *62*, 1258–1265. doi:10.1016/j.ajhg.2011.02.002

Lee, S. H., Wray, N. R., Goddard, M. E., & Visscher, P. M. (2011). Estimating missing heritability for disease from genome-wide association studies. *American Journal of Human Genetics*, *88*, 294–305. doi:10.1016/j.ajhg.2011.02.002

Lee, S. H., Yang, J., Goddard, M. E., Visscher, P. M., & Wray, N. R. (2012). Estimation of pleiotropy between complex diseases using single-nucleotide polymorphism-derived genomic relationships and restricted maximum likelihood. *Bioinformatics*, *28*, 2540–2542. doi:10.1093/bioinformatics/bts474

Lyons, M. J., Goldberg, J., Eisen, S. A., True, W., Tsuang, M. T., Meyer, J. M., & Henderson, W. G. (1993). Do genes influence exposure to trauma? A twin study of combat. *American Journal of Medical Genetics*, *48*, 22–27. doi:10.1017/s0033291711001310

Magnusson, Å., Lundholm, C., Göransson, M., Copeland, W., Heilig, M., & Pedersen, N. (2012). Familial influence and childhood trauma in female alcoholism. *Psychological Medicine*, *42*, 381–389. doi:10.1017/S0033291711001310

Miller, M. W., Wolf, E. J., Kilpatrick, D., Resnick, H., Marx, B. P., Holowka, D. W.,. . .Friedman, M. J. (2013). The prevalence and latent structure of proposed *DSM-5* posttraumatic stress disorder symptoms in US national and veteran samples. *Psychological Trauma: Theory, Research, Practice, and Policy*, *5*, 501–512. doi:10.1037/a0029730

Moser, G., Lee, S. H., Hayes, B. J., Goddard, M. E., Wray, N. R., & Visscher, P. M. (2015). Simultaneous discovery, estimation and prediction analysis of complex traits using a bayesian mixture model. *PLoS Genetics*, *11*, e1004969. doi:10.1371/journal.pgen.1004969

Muthén, L. K., & Muthén, B. O. (1998–2012). *Mplus user's guide* (7th ed.). Los Angeles, CA: Author.

Nelson, E. C., Agrawal, A., Pergadia, M. L., Wang, J. C., Whitfield, J. B., Saccone, F. S.,. . .Rice, J. P. (2010). Genetic study: H2 haplotype at chromosome 17q21. 31 protects against childhood sexual abuse-associated risk for alcohol consumption and dependence. *Addiction Biology*, *15*, 1–11. doi:10.1007/s10461-011-0095-8

Nugent, N. R., Lally, M. A., Brown, L., Knopik, V. S., & McGeary, J. E. (2012). OPRM1 and diagnosis-related posttraumatic stress disorder in binge-drinking patients living with HIV. *AIDS and Behavior*, *16*, 2171–2180. doi:10.1007/s10461-011-0095-8

Palmer, R. H., Brick, L., Nugent, N. R., Bidwell, L. C., McGeary, J. E., Knopik, V. S., & Keller, M. C. (2015). Examining the role of common genetic variants on alcohol, tobacco, cannabis and illicit drug dependence: Genetics of vulnerability to drug dependence. *Addiction*, *110*, 530–537. doi:10.1111/add.12815

Palmer, R. H., Button, T. M., Rhee, S. H., Corley, R. P., Young, S. E., Stallings, M. C.,. . .Hewitt, J. K. (2012). Genetic etiology of the common liability to drug dependence: Evidence of common and specific mechanisms for *DSM-IV* dependence symptoms. *Drug and Alcohol Dependence*, *123*(Suppl 1), S24–S32. doi:10.1016/j.drugalcdep.2011.12.015

Palmer, R. H., Young, S. E., Corley, R. P., Hopfer, C. J., Stallings, M. C., & Hewitt, J. K. (2013). Stability and change of genetic and environmental effects on the common liability to alcohol, tobacco, and cannabis *DSM-IV* dependence symptoms. *Behavior Genetics*, *43*, 374–385. doi:10.1007/s10519-013-9599-5

Perkonigg, A., Kessler, R. C., Storz, S., & Wittchen, H. U. (2000). Traumatic events and post-traumatic stress disorder in the community: Prevalence, risk factors and comorbidity. *Acta Psychiatrica Scandinavica*, *101*, 46–59. doi:10.1034/j.1600-0447.2000.101001046.x

Price, A. L., Patterson, N. J., Plenge, R. M., Weinblatt, M. E., Shadick, N. A., & Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics*, *38*, 904–909. doi:10.1038/ng1847

Ray, L. A., Sehl, M., Bujarski, S., Hutchison, K., Blaine, S., & Enoch, M. A. (2013). The CRHR1 gene, trauma exposure, and alcoholism risk: A test of G × E effects. *Genes, Brain and Behavior*, *12*, 361–369. doi:10.1111/gbb.12032

Reed, P. L., Anthony, J. C., & Breslau, N. (2007). Incidence of drug problems in young adults exposed to trauma and posttraumatic stress disorder: Do early life experiences and predispositions matter? *Archives of General Psychiatry*, *64*, 1435–1442. doi:10.1001/archpsyc.64.12.1435

Rhee, S. H., Hewitt, J. K., Young, S. E., Corley, R. P., Crowley, T. J., Neale, M. C., & Stallings, M. C. (2006). Comorbidity between alcohol dependence and illicit drug dependence in adolescents with antisocial behavior and matched controls. *Drug and Alcohol Dependence*, *84*, 85–92. doi:10.1016/j.drugalcdep.2005.12.003

Saccone, N. L., Saccone, S. F., Hinrichs, A. L., Stitzel, J. A., Duan, W., Pergadia, M. L., ... Bierut, L. J. (2009). Multiple Distinct Risk Loci for Nicotine Dependence Identified by Dense Coverage of the Complete Family of Nicotinic Receptor Subunit (CHRN) Genes. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*, *150B*(4), 453–466. doi:10.1002/ajmg.b.30828

Saccone, N. L., Wang, J. C., Breslau, N., Johnson, E. O., Hatsukami, D., Saccone, S. F., ... Bierut, L. J. (2009). The CHRNA5-CHRNA3-CHRNB4 Nicotinic Receptor Subunit Gene Cluster Affects Risk for Nicotine Dependence in African-Americans and in European-Americans. *Cancer Research*, *69*(17), 6848–6856. doi:10.1158/0008-5472.can-09-0786

Sacks, J. Y., McKendrick, K., & Banks, S. (2008). The impact of early trauma and abuse on residential substance abuse treatment outcomes for women. *Journal of Substance Abuse Treatment*, *34*, 90–100. doi:10.1016/j.jsat.2007.01.010

Salvatore, J. E., Aliev, F., Edwards, A. C., Evans, D. M., Macleod, J., Hickman, M.,. . . Korhonen, T. (2014). Polygenic scores predict alcohol problems in an independent sample and show moderation by the environment. *Genes*, *5*, 330–346. doi:10.3390/genes5020330

Sartor, C., McCutcheon, V., Pommer, N., Nelson, E., Grant, J., Duncan, A.,. . . Heath, A. (2011). Common genetic and environmental contributions to post-traumatic stress disorder and alcohol dependence in young women. *Psychological Medicine*, *41*, 1497–1505. doi:10.1017/S0033291710002072

SNP & Variation Suite (Version 8.3.0, Version 8.x) [Computer software]. Bozeman, MT: Golden Helix. Retrieved from http://www.goldenhelix.com

Steiger, J. H., & Fouladi, R. T. (1997). Noncentrality interval estimation and the evaluation of statistical models. In L. L. Harlow, S. A. Mulaik, & J. H. Steiger (Eds.), *What if there were no significance tests*? (pp. 221–257). Mahwah, NJ: Erlbaum.

Stein, M. B., Jang, K. L., Taylor, S., Vernon, P. A., & Livesley, W. J. (2002). Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: A twin study. *American Journal of Psychiatry*, *159*, 1675–1681. doi:10.1176/appi.ajp.159.10.1675

Vanyukov, M. M., & Ridenour, T. A. (2012). Common liability to drug addictions: Theory, research, practice. *Drug and Alcohol Dependence*, 123. doi:10.1016/j.drugalcdep.2012.01.005

Vanyukov, M. M., Tarter, R. E., Kirillova, G. P., Kirisci, L., Reynolds, M. D., Kreek, M. J., . . . Ridenour, T. A. (2012). Common liability to addiction and "gateway hypothesis": Theoretical, empirical and evolutionary perspective. *Drug and Alcohol Dependence*, 123. doi:10.1016/j.drugalcdep.2011.12.018

Wolf, E. J., Miller, M. W., Krueger, R. F., Lyons, M. J., Tsuang, M. T., & Koenen, K. C. (2010). Posttraumatic stress disorder and the genetic structure of comorbidity. *Journal of Abnormal Psychology*, *119*, 320–330. doi:10.1037/a0019035

Xian, H., Chantarujikapong, S. I., Scherrer, J. F., Eisen, S. A., Lyons, M. J., Goldberg, J.,. . . True, W. R. (2000). Genetic and environmental influences on posttraumatic stress disorder, alcohol and drug dependence in twin pairs. *Drug and Alcohol Dependence*, *61*, 95–102.

Yang, J., Lee, S. H., Goddard, M. E., & Visscher, P. M. (2011). GCTA: A tool for genome-wide complex trait analysis. *American Journal of Human Genetics*, *88*, 76–82. doi:10.1016/j.ajhg.2010.11.011

Yang, J., Lee, S. H., Goddard, M. E., & Visscher, P. M. (2013). *Genome-wide complex trait analysis (GCTA): Methods, data analyses, and interpretations genome-wide association studies and genomic prediction* (pp. 215–236). Heidelberg, Germany: Springer.

Young-Wolff, K. C., Enoch, M.-A., & Prescott, C. A. (2011). The influence of gene–environment interactions on alcohol consumption and alcohol use disorders: A comprehensive review. *Clinical Psychology Review*, *31*, 800–816. doi:10.1016/j.cpr.2011.03.005

Zwick, W. R., & Velicer, W. F. (1986). Comparison of five rules for determining the number of components to retain. *Psychological Bulletin*, *99*, 432–442.