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Shared molecular genetic risk of alcohol dependence and PTSD

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Abstract

Alcohol use disorder (AUD) and posttraumatic stress disorder (PTSD) frequently co-occur, highlighting the importance of understanding the etiology of these comorbid conditions. While AUD and PTSD are moderately heritable with modest overlap in genetic risk as estimated from family studies, there has been a paucity of work using molecular genetic data to estimate shared genetic effects on these conditions. This study used large-scale genome-wide molecular data to examine shared genetic risk for PTSD and AUD, specifically alcohol dependence (AD), through cross-trait LD score regression (LDSC/LDSR). Summary statistics came from the Psychiatric

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Genomics Consortium (PGC) PTSD workgroup Freeze 2 (PGC2) European Ancestry (EA) participants (N=174,659), and AD summary statistics in EA participants (N=38,686) came from the PGC Substance Use Disorders (SUD) workgroup. We performed LDSC to estimate genetic correlation between AD and PTSD using HapMap3 variants and LD scores from the 1000 Genomes project. A moderate, significant correlation was observed between AD and PTSD ($r_g=.35$, $p=.02$), with sex differences identified through stratified analyses. Our results are the first to demonstrate evidence of a shared molecular genetic etiology for AD and PTSD. Further research is needed to better understand possible sex differences in shared heritability and extend these results to additional populations.

Keywords

molecular genetics; alcohol dependence; PTSD; comorbidity; heritability

Posttraumatic stress disorder (PTSD) is one of the most common disorders following trauma exposure, with lifetime rates of PTSD varying as a function of trauma type, from 4% - 17% (Liu et al., 2017, Kessler et al., 2017), and greater prevalence in females than males (20.4% versus 8.1%; Kessler et al., 1995). Alcohol dependence (AD; now included in the term alcohol use disorder [AUD]) is also common, with roughly 29% of individuals meeting lifetime criteria (Grant et al., 2015). While historically greater prevalence has been found in males than females (36% versus 22.7%; Grant et al., 2015), this sex difference has been diminishing in recent years (Keyes et al., 2008). Importantly, it is well-documented that PTSD and AUD frequently co-occur (see systematic review by Debell et al., 2014) and this comorbidity is associated with increased symptom severity, impairment, physical health concerns, and poor treatment prognosis (Jacobsen et al., 2001, Blanco et al., 2013, Evren et al., 2011, Shorter et al., 2015). As such, there is a need to understand the underlying mechanisms of this comorbidity. There are a number of phenotypic models of comorbidity of environmental and psychosocial mechanisms that have received much attention (Schumm and Chard, 2012). There is a smaller, but growing, literature examining the biological mechanisms of PTSD and AUD comorbidity, including dysregulation in certain neurotransmitters (e.g., dopamine, norepinephrine), the hypothalamic-pituitary-adrenal (HPA) axis more broadly, and shared genetic vulnerabilities (see Norman et al., 2012, for a review).

There have been relatively few studies of shared genetic risk, most of which have been conducted in twin studies. In terms of genetic risk for each disorder independently, PTSD is moderately and AD is substantially heritable (McLeod et al., 2001), with twin studies suggesting higher heritability of PTSD in females than males (True et al., 1993, Stein et al., 2002, Sartor et al., 2012) and no significant sex difference in heritability of AUD (Verhulst et al., 2015). Importantly, some of the latent (i.e., estimated using family studies) genetic risk for PTSD and AD is shared (approximately 30%; Sartor et al., 2011, Xian et al., 2000), but this has yet to be studied using molecular genetic data. Large consortia for genome-wide association studies (GWAS) of both disorders are now available (N = 206,655 for PTSD; N = 52,848 for DSM-IV AD), and significant variants have been found for both PTSD (Nievergelt et al., 2019) and AD (Walters et al., 2018).

In recent years, advanced statistical procedures such as LD score cross-trait regression (LDSC; also known as LDSR; Bulik-Sullivan et al., 2015a) have been developed to further analyze GWAS data and can be used to estimate the molecular heritability and the magnitude and direction of shared genetic effects, or genetic correlation. Genetic correlation is a key population parameter that describes the shared genetic architecture of complex traits and diseases (Ni et al., 2018). The work applying LDSC to PTSD is limited, but a recent study (Nievergelt et al., 2019) estimated SNP-based heritability of 5% among those of European ancestry (EA) and found differences in this estimate between males and females (1% and 10%, respectively). There is similarly scarce research applying LDSC to AD, with one study finding a heritability of 9% in a combined male/female sample of individuals of EA (Walters et al., 2018). While the genetic correlation between PTSD and other traits (e.g., schizophrenia; Duncan et al., 2018) and between AD and other traits (e.g., tobacco use, schizophrenia; Walters et al., 2018) have been examined, this has not been extended to the PTSD-AD association. It is hypothesized that there is a significant molecular genetic correlation between PTSD and AD. This study is the first to our knowledge to employ the cutting-edge statistical genetic technique of cross-trait LDSC to leverage genome-wide data for AD and PTSD using some of the largest available GWAS datasets (via the Psychiatric Genomics Consortium; PGC).

Material and Methods

This project was deemed exempt from research ethics committee approval, as it uses archival, summary statistics from consortia groups; included studies in these consortia have their own, independent IRB approvals.

Samples

Additional details on the datasets that comprise the PTSD and AD summary statistics (e.g., male/female breakdown, age, trauma type for PTSD) are available in the supplemental material. PTSD summary statistics came from the PGC-PTSD Freeze 2 dataset (PTSD-PGC2; Nievergelt et al., 2019) of GWAS summary statistics from EA participants, $N = 174,659$ (13.3% PTSD positive cases). Case status reflects primarily lifetime PTSD diagnosis (although it includes current diagnosis when lifetime was not available). PTSD-PGC2 includes subjects from 9 studies already reported in the initial paper (Duncan et al. 2018), 47 new studies (together forming Freeze 1.5) of which 42 were included in the EA summary files, and the large European ancestry UK Biobank study. The UK Biobank cohort is a population-based study and is comprised of few to no subjects who experienced military-related trauma. Conversely, the PGC1.5 cohort is made of a substantial portion of men from military cohorts, while most women in the sample are from civilian studies (Nievergelt et al., 2019).

AD summary statistics came from the PGC Substance Use Disorders (SUD) workgroup (Walters et al., 2018) EA participants, $N = 38,686$ (26.4% AD positive cases). Cases were defined as meeting criteria for a DSM-IV (DSM-IIIIR for one study) diagnosis of AD and all controls were alcohol exposed. The AD EA sample is comprised of individual genotypic data from 13 case/control studies and 9 family-based studies as well as summary statistics

from GWAS of AD from additional cohorts, including both inpatient and outpatient samples and population-based studies. Only one family member was included in the summary statistics from family-based studies; thus, the summary statistics are comprised of only unrelated individuals.

Analytic Plan

The cross-trait LDSC approach (Bulik-Sullivan et al., 2015a, Bulik-Sullivan et al., 2015b) requires only GWAS summary statistics in samples of unrelated individuals and is not biased by sample overlap (Bulik-Sullivan et al., 2015b). The approach replaces the χ^2 by the z scores from both studies (i.e., from sample summary statistics) and the genetic covariance is then estimated using the slope from the regression of both z scores on LD scores. Normalizing genetic covariance by SNP heritability yields genetic correlation. Analyses were conducted to estimate the genetic correlation between PTSD and AD using the open-source LDSC pipeline, version 1.0.0 (github.com/bulik/ldsc). Analyses were performed using HapMap3 variants and EA linkage disequilibrium (LD) scores from the 1000 Genomes project (Abecasis et al., 2010). The PGC summary statistic files have previously been processed through a comprehensive quality control pipeline (Sullivan, 2010) including filtering to remove SNPs with imputation information value < 0.90 and minor allele frequency < 0.01. The LDSC pipeline filtering process further removes SNPs based on a minimum N and variants that are either not SNPs or are strand-ambiguous.

The primary analysis examined the genetic correlation between the full PTSD and AD samples. Following the primary analysis, sex-stratified analyses were conducted using separate male ($n \sim 85,000$) and female ($n \sim 86,000$) summary statistics files for PTSD, as evidence suggests lower heritability (based on molecular and twin studies) for PTSD in males compared to females (Duncan, Cooper, & Shen, 2018). However, the combined sex AD sample was used for two reasons. First, meta-analyses of behavioral genetic studies on AUD has not found evidence of differential heritability for AUD in males compared to females (Verhulst, Neale, & Kendler, 2015). Second, the current sample size of the PGC AD data is modest and limited in power for sex-stratified analyses. As LDSC relies on molecular heritability to estimate genetic correlation, in cases of too low heritability or too small N, models will not converge. Thus, similar to the flagship AD analyses from the PGC from which the summary statistics are drawn from for the present analyses (Walters et al., 2018), sex-stratified analyses were not conducted for AD.

Finally, the male PTSD-PGC2 sample was examined separately by its components, PTSD-PGC1.5 ($n \sim 30,000$) and UK Biobank [UKB] PTSD data ($n \sim 55,000$; which comprise PTSD-PGC2) given recent findings that in males, significant heritability estimates were found in UKB data but not PTSD-PGC1.5 (Nievergelt et al., 2019), which would then impact genetic correlation estimates, as heritability must be demonstrated for LDSC to be conducted.

Results

In the present analysis, prior to determining genetic correlation, LD score based SNP-heritability was estimated, and is presented in Table 1. Next, genetic correlation was

estimated and a moderate, significant genetic correlation was observed between PTSD and AD ($r_g = 0.35$, $SE = 0.16$, $p = .02$).

In the PTSD sex-stratified analyses (see Table 1 for heritability estimates), the genetic correlation between AD and the female PTSD sample was again moderate and significant ($r_g = 0.34$, $SE = .14$, $p = .01$); however, the genetic correlation between AD and the male-only PTSD sample was not significant, and the point estimate was lower ($r_g = 0.14$, $SE = .44$, $p = .75$). An additional set of analyses was conducted in the male PTSD sample, as previous work (Nievergelt et al., 2019) identified different estimates of heritability in males based on samples that comprised the PTSD-PGC2 data (heritability estimates for the separate sub-samples are presented in Table 1). Thus, LDSC analyses were conducted separately for these two male sub-samples (PTSD-PGC1.5 and UKB PTSD). While there was no significant correlation between AD and PTSD in the PGC1.5 sample ($r_g = -0.25$, $SE = .60$, $p = .68$), there was a significant correlation between AD and PTSD in the UKB sample ($r_g = 0.51$, $SE = .24$, $p = .04$).

Discussion

While molecular genetic correlations with AD and other phenotypes and PTSD and other phenotypes have been previously demonstrated, and one recent study examined the association between PTSD and alcohol use and did not find a significant genetic correlation (Wang et al., 2019), this is the first study to demonstrate a shared molecular genetic basis for AD and PTSD. Using recently published GWAS data from the PGC, a moderate, significant correlation was observed between AD and PTSD ($r = .35$). Our findings are consistent with evidence of shared latent genetic liability estimated from twin and family studies (Sartor et al., 2011, Xian et al., 2000). Notably, consistent with the original heritability analyses using the PGC PTSD and AD data (Nievergelt et al., 2019; Walters et al., 2018), our LDSC SNP-based heritability estimates were smaller than those reported from twin studies. This is expected and has been observed in the literature for many other phenotypes (Vischer, Brown, McCarthy, & Yang, 2012), purported due to factors such as many more variants still needing to be identified, requiring larger GWAS samples; rare variants and structural variation that are not typically captured in existing genotypic arrays; low power to detect gene-gene interactions; and not accounting for shared environment among relatives (Manolio et al., 2009). Given the small heritability estimates, this correlation represents only a proportion of the heritability that overlaps between AD and PTSD. It is also noted that findings highlight the unique genetic influence for each trait (i.e., two thirds of the genetic risk is unique to each disorder). Overall, study findings are highly consistent with other molecular genetic studies of AD (Walters et al., 2018) and PTSD (Sumner et al., 2017) and related traits, and align with the twin literature on shared heritability (e.g., Sartor et al., 2011).

Findings of the present study also extend findings from the twin literature which provide more information on the liability for comorbidity (as they examine genetic risk within and between twins), and capture all inherited genetic variants shared by monozygotic twins. Thus, the source of any shared genetic effects cannot be discerned. Molecular genetic investigations in samples of unrelated individuals demonstrate genetic correlation, from common variants, and separate from phenotypic comorbidity. As such, molecular genetic

studies provide insight into shared genes that increase risk for both conditions, help clarify the genetic architecture, and lay the groundwork for risk prediction and functional examination of common variation underlying and shared between PTSD and AD (see review by Martin, Taylor, & Lichtenstein, 2017).

One limitation of the current state of the PGC AD data is that it is modest in sample size, and thus, sex-stratified analyses of AD are under-powered and models cannot converge. Thus, the present study was not able to fully examine sex differences in the shared risk between PTSD and AD. As larger samples become available, this will be an important area of investigation. We note that a recently published study of the largest AUD data to date with a sample over 200,000 (from the Million Veteran Program; Kranzler et al., 2019) was able to separately estimate sex-specific heritability in EA samples. However, even in this larger sample, while a nominally higher SNP-based heritability estimate was found for females than males, the authors stated that potential hypotheses for this difference (e.g., substantially smaller sample size and greater standard error, higher liability-threshold and burden or risk variants in females) could not be explicitly tested due to the still lower statistical power in the female sample, as the sample was predominately male (93%). Present study analyses did include sex-stratified PTSD subsamples, supported by previous findings of sex differences in PTSD heritability (Duncan et al., 2018; Nievergelt et al., 2019). Further, given previous findings of differences in heritability estimates within male PTSD subsamples (Nievergelt et al., 2019), we examined UKB male PTSD results separate from the PTSD-PGC1.5 male PTSD results. We found a moderate genetic correlation between combined AD and PTSD in females ($r_g = 0.34$, $SE = .14$) as well as between combined AD and the male sub-sample that demonstrated a significant heritability estimate (UKB sample; $r_g = 0.51$, $SE = .24$). While study findings suggest a fairly comparable PTSD-AD genetic correlation in these subsamples, considerable additional research will be needed to examine the nuances of sex differences in PTSD-AD/AUD shared genetic risk; at present, it remains unknown whether sex differences in the genetic correlation are to be expected. Further, the small, existing literature is mixed with regard to sex differences in the prevalence of comorbid PTSD-AUD (e.g., Kozaric-Kovacic et al., 2000, Pietrzak et al., 2011) and more work is needed to better understand factors that moderate the relation between sex and PTSD-AUD comorbidity.

We note that the etiological influences of molecular genetic overlap and phenotypic correlation are not mutually exclusive (i.e., shared risk can be operating through multiple pathways). Researchers have posited several frameworks linking the two disorders. In the high-risk hypothesis, for example, individuals with a genetic predisposition for AD have been shown to engage in a range of risky (externalizing) behaviors prior to the onset of alcohol use problems (Meyers et al., 2014), increasing exposure to potentially traumatic experiences. The self-medication hypothesis posits that individuals potentially self-medicate their PTSD with alcohol, ultimately increasing risk for AD (Haller and Chassin, 2014). Although present study findings suggest overlapping genetic risk may influence these different pathways linking PTSD and AD, the current study design does not allow us to disentangle these possible causal mechanisms. In an informative review of shared genetic risk across psychiatric disorders, Martin and colleagues (2017) describe the multiple, not mutually exclusive, interpretations of a given genetic correlation, which may signify: 1) the same risk variants are directly, causally impacting different phenotypes; 2) the same risk

variants could be impacting a third, unmeasured phenotype that underlies both conditions; 3) there are in fact different risk variants between the two disorders but these variants are highly correlated and acting through different mechanisms to result in the conditions; 4) one phenotype mediates the association between genetic risk and the other phenotype. At present, it is difficult to distinguish among these explanations. Therefore, the next step in research in this area is to conduct longitudinal prospective studies and/or Mendelian Randomization methods (e.g., Polimanti et al., 2018) that can disentangle causality, and for this, better-powered GWAS of these two phenotypes would be helpful. Current study results do support the common, third-variable approach and support new avenues for research, setting the stage for identification of common mechanisms that are genetically informed.

Study limitations include the fact that the current study relies on summary statistics from individuals of European ancestry only given that LDSC is currently only applicable to non-admixed samples. The inclusion of individuals of diverse ancestry is a critical next step to reduce disparities in the representation of, and applicability of genetic results to, global populations. Although the AD summary statistics used in the present study are from one of the largest publicly available AD GWAS datasets, it is noted that the sample size is still fairly small from a GWAS perspective. Related to this limitation, male and female specific AD summary statistics were not used in the current study due to the lack of statistical power for sex-stratified analyses noted by Walters et al. (2018). A related limitation is that it thus remains unknown whether sex differences in shared heritability are attributable to PTSD and/or AD. As GWAS sample sizes for AD increase, male and female specific AD heritability estimates and genetic correlations with PTSD should be examined. The current study relies on summary statistics from the two largest initiatives to examine DSM diagnoses of PTSD and AD, however ongoing efforts to examine non-diagnostic, quantitative phenotypes (e.g., frequency/quantity of drinking) and other substance use disorders (cannabis, opioids) will provide important extensions to this work. Finally, the reason for differences in heritability across the male PTSD sub-samples, which impacted estimation of genetic correlation (i.e., as a genetic correlation can only be estimated in the presence of heritability), remains unknown at present. However, it is hypothesized to be due to differences between the PGC1.5 cohorts and UK Biobank (see supplemental material for more details on the samples). Specifically, one way in which these two samples notably differ is in trauma type, which is known to be heterogeneous. In the PGC1.5, a substantial proportion of men were from military cohorts and most women were civilian samples, while the UKB cohort had few to no participants exposed to military-related trauma (Nievergelt et al., 2019). Other sample differences include measurement/diagnosis of the PTSD phenotype (i.e., UKB PTSD status was determined with a brief self-report survey screen, as compared to the typical PGC-PTSD samples from PTSD-focused studies which include more diagnostic interviews), as well as power (i.e., sample size for UKB was substantially larger than PGC1.5) and heterogeneity (i.e., age differences across samples, with UKB being on average older than the PGC1.5 samples). All will have notable impacts on both heritability and genetic correlation estimates. Planned analyses as samples continue to grow include examination of detailed trauma and phenotypic information and their impact on measurement variability and heritability estimates (Nievergelt et al., 2019).

In conclusion, using summary statistics from the two largest GWAS of PTSD and AD, this study demonstrates a shared molecular genetic basis for the two disorders. Future studies should explore mechanisms underlying the comorbidity and shared genetic liability, the nature of the genetic correlation for these disorders, and expand into other genetically-informed approaches (e.g., functional studies, gene x gene interaction studies) in diverse samples of men and women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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Table 1.

Heritability estimates from LDSC regression analyses

	Observed Scale			Liability Scale*		
	h^2 SNP	SE	p	h^2 SNP	SE	p
Full sample						
PTSD	0.04	0.01	$6.33e^{-5}$	0.18	0.02	$2.26e^{-19}$
AD	0.05	0.01	$5.73e^{-7}$	0.09	0.02	$6.80e^{-6}$
PTSD stratified analyses						
Sex-stratified						
Male PTSD-PGC2	0.004	0.01	.69			
Female PTSD-PGC2	0.08	0.02	$6.3e^{-5}$			
Male sample stratified						
PTSD-PGC1.5	0.01	0.03	.74			
UKB PTSD	0.03	0.01	.003			

Note:

* = Liability scales for PTSD used a sample prevalence of 28% and a population prevalence of 30%, as done in previously published work with this dataset. Liability scales for AD used a sample prevalence of 35% and a population prevalence of 16% as done in previously published work with this dataset.