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Brain Structure and Problematic Alcohol Use: A Test of Plausible Causation Using Latent Causal Variable Analysis

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Abstract

Associations between brain structure and problematic alcohol use may reflect alcohol-induced toxicity and/or preexisting risk. Here, we applied a latent causal variable approach to genome-wide association study summary statistics of problematic alcohol use (n=435,563) and magnetic resonance imaging-derived brain structure phenotypes (e.g., cortical volume, cortical thickness, white matter volume; ns ranging from 17,706 to 51,665) to test whether variability in brain structure may plausibly contribute to problematic alcohol use and/or whether problematic alcohol use influences brain structure. After correction for multiple testing within each modality, we find evidence that greater volume of the pars opercularis, greater thickness of the cuneus, and lower volume of the basal forebrain may plausibly contribute to problematic alcohol use. All other nominally-significant associations identify brain structure as a potential causal contributor to problematic alcohol use; there was no evidence suggesting that problematic alcohol use may cause differences in brain structure. Collectively, these results challenge common interpretations that associations between alcohol use and brain structure reflect consequences of alcohol, instead supporting emerging work suggesting that brain structure may reflect a predispositional risk factor for alcohol involvement.

Introduction

Problematic alcohol use (PAU) has been robustly associated with smaller global and regional measures of brain structure (1). While these associations have been widely purported to arise from alcohol-induced brain atrophy, it is also possible that variability in brain structure may reflect predispositional liability (2). Mendelian Randomization (MR) approaches, which represent a form of instrumental variable analysis, have been widely used to assess whether genomic liability to one phenotype may cause another (e.g., alcohol and hypertension (3, 4)). However, MR approaches can be confounded by genetic correlations between the phenotypes. A recent method that uses a latent causal variable (LCV) approach (5) was developed to address this concern. LCV can be used to assess putatively causal relationships between pairs of phenotypes while accounting for genetic correlation and sample overlap.

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Here, we applied LCV to summary statistics generated from the largest GWASs of PAU and brain structure phenotypes to test whether variability in brain structure may plausibly contribute to PAU and/or whether PAU may contribute to brain structure.

Methods

Problematic Alcohol Use (PAU) genetic association summary statistics came from the Zhou et al GWAS meta-analysis of three PAU phenotypes: ICD-derived Alcohol Use Disorder (AUD) from the Million Veteran Program n= 286,202, Alcohol Use Disorder Identification Test-problem subscale (AUDIT-P) GWAS from the UK biobank, n=121,604, and DSM-III/DSM-IV alcohol dependence from the Psychiatric Genomics Consortium n=27,757; total n= 435,563)(6). The PAU GWAS had a significant heritability estimate of 0.068 (SE = 0.004).

GWAS summary statistics for global and regional magnetic resonance imaging (MRI)-derived brain structure phenotypes for cortical thickness and surface area, were obtained from analyses conducted by the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) consortium (cortex gray matter n = 51,665 (7). Measures of gray matter volume (cortical and subcortical) and white matter volume were derived from an independent GWAS of UK biobank data (subcortical and gray matter volume n = 19,629 (8), white matter n = 17,706 (9)). N's reflect the total number of individuals in the original study for each GWAS, with 278 imaging phenotypes total. All GWAS summary statistics include adjustments for population structure using ancestrally-informative principal components, as well as additional standard covariates (for example, sex and age).

Linkage Disequilibrium Score Regression (LDSR) (10) is commonly used to estimate the heritability of complex traits using genome-wide association study summary statistics, such as those available herein (10). As LDSR does not require raw data, this method can be extended to estimate the genetic correlation (SNP-rg) between traits measured in two different GWAS, while accounting for any sample overlap between the traits. Additionally, LDSR includes control for population structure and sample confounding.

Models built off LDSR can be parameterized to test for causality by constraining the SNP effect sizes and testing whether a latent causal variable mediates the association (5). Briefly, the GWAS summary data serve as instruments for a series of techniques that are called "genetic instrumental variable analysis". Normally, genetic instrumental variable analysis selects the top SNPs for trait 1 and uses those as an instrumental variable "exposure". If the SNPs that contribute to trait 1 are also associated with differences in trait 2 to a similar degree and effect size, then there is evidence for a plausibly causal association. LCV expands this analysis by using genome-wide SNPs, i.e. not only the "top" associations, as instruments. To do this, LCV models a latent "causal" variable that represents the pattern of consistency that would be observable if a causal relationship existed. LCV then tests the degree to which the latent "causal" variable mediates the correlation between both traits, so the degree of causality is measured as a ratio of sharing between the measured trait and the latent variables, giving us a two-tailed test of causality that simultaneously tests bi-directional causal effects. This ratio is known as the genetic causality proportion (GCP), an estimate of the degree to which each trait is correlated with the latent genetic variable,

i.e., the extent to which each trait is potentially genetically causal for the other trait (ranging from 0 reflecting no genetic causality to |1| indicating full genetic causality). An advantage of LCV over MR is that it accounts for unknown amounts of sample overlap between the GWAS of the two traits in the model.

To evaluate our results for evidence of correlation and causality, we evaluate both the direction of effect of the SNP-rg and the direction of effect of the GCP. We can evaluate the direction of the LDSR genetic correlation as we would any other correlation measure, with a positive SNP-rg providing evidence of a positive relationship between the traits, and a negative SNP-rg suggesting an inverse correlation. If the GCP is positive, it suggests that the first trait in the model is causal for trait 2; if the GCP is negative, it means the second trait is causal for trait 1. For example, if trait 1 in our model is PAU and trait 2 is volume of a brain region, a negative genetic correlation would imply that lower volume for the brain region is correlated with greater risk for problematic alcohol use; furthermore, a negative GCP would imply that volume of the brain region has a causal effect on problematic alcohol use.

Latent causal variable (LCV) analyses (5) between PAU and the 278 MRI imaging phenotypes were conducted using the MASSIVE pipeline (https://view.genoma.io/) (11). For each of the 278 imaging phenotypes, we tested for putatively causal associations and genetic correlations with PAU; we corrected for multiple testing using Bonferroni correction within each modality. The major histocompatibility complex (MHC) region was removed for all analyses.

Results

Three GCP estimates were significant after multiple corrections. Increased cortical volume of the left pars operculais (GCP = −0.643(0.173)) was significant after multiple corrections within modality (P =0.00019, N regions= 62, Bonferroni threshold = 0.00081). Enigma cortical surface metrics were averaged across the hemisphere, and greater thickness of the cuneus (GCP −0.226(0.066), P= 0.00059) was significant when correcting within modality (N regions = 35, Bonferroni threshold= 0.001429). Finally, lower subcortical brain volume of the left basal forebrain (GCP = −0.489(0.144)) was implicated when correcting within number of subcortical brain areas (p = 0.00067, N regions = 35, Bonferroni Threshold = 0.001429). No results were significant after a conservative correction for all brain regions (0.05/278, correction = 0.00018). All nominally significant results were in line with deviations in brain areas causing PAU, rather than PAU causing changes in brain area (Table 1 and Figure 1).

Discussion

We used LCV analyses to estimate putative causal relationships between brain structure and problematic alcohol use (PAU). In contrast to speculation that neuroimaging-derived brain structure correlates of PAU reflect neurotoxic consequences of alcohol (12), our analyses revealed evidence that brain structure phenotypes may, at least partially, contribute to PAU (Table 1; Figure 1). We found no evidence that PAU contributes to brain structure. After correction for multiple testing, there was evidence that lower basal forebrain volume as

well as greater volume of the pars opercularis and thickness of the cuneus may genetically contribute to PAU.

Reduced volume of the basal forebrain has been linked to chronic alcohol use disorder as well as working memory performance (13). Alongside evidence from non-human animal models that binge drinking can reduce basal forebrain volume (14) this has led to speculation that heavy alcohol use may cause these reductions, and, in turn, underlie behavioral impairments associated with PAU (e.g., executive control (13)). Our findings provide a counterpoint to this interpretation and suggest that lower basal forebrain volume may, at least partially, represent a genetically associated predisposing risk factor for problematic alcohol use. Such findings are consistent with emerging research suggesting that genomic liability to executive function is shared with PAU (15).

In contrast to evidence linking reduced inferior frontal gyrus volume to AUD, we find evidence that greater pars opercularis volume is associated with PAU. It is likely that Pars Opercularis is playing a role through language (16). Better language ability may contribute to initial escalations in alcohol use that provide the foundation for the development of alcohol use disorder (17). We are unaware of any prior findings linking cortical thickness of the cuneus to alcohol, though cuneus functional activation has been related to impulsive choice in AUD cases (18).

Some limitations are worth noting. First, as the GWAS were conducted in individuals of European ancestry, findings may not generalize to other ancestral groups. Second, we were unable to evaluate whether our findings replicate using independent GWAS summary statistics. As most GWASs gather and meta-analyze the largest possible datasets for discovery, there are limited opportunities to use well-powered GWAS summary statistics generated from independent samples for replication. Nonetheless, related approaches assessing the plausibility of causality (e.g., longitudinal data, discordant twin/sibling designs) may be leveraged to assess convergence of results (2). Limitations notwithstanding, our estimation of putatively causal bidirectional genetic relationships between brain structure and PAU using GWAS data yielded evidence that brain structure may contribute to the development of PAU, but that PAU may not contribute to brains structure.

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the study and take responsibility for the integrity of the data and accuracy of the data analyses. Conflict of interest disclosures: No disclosures were reported.

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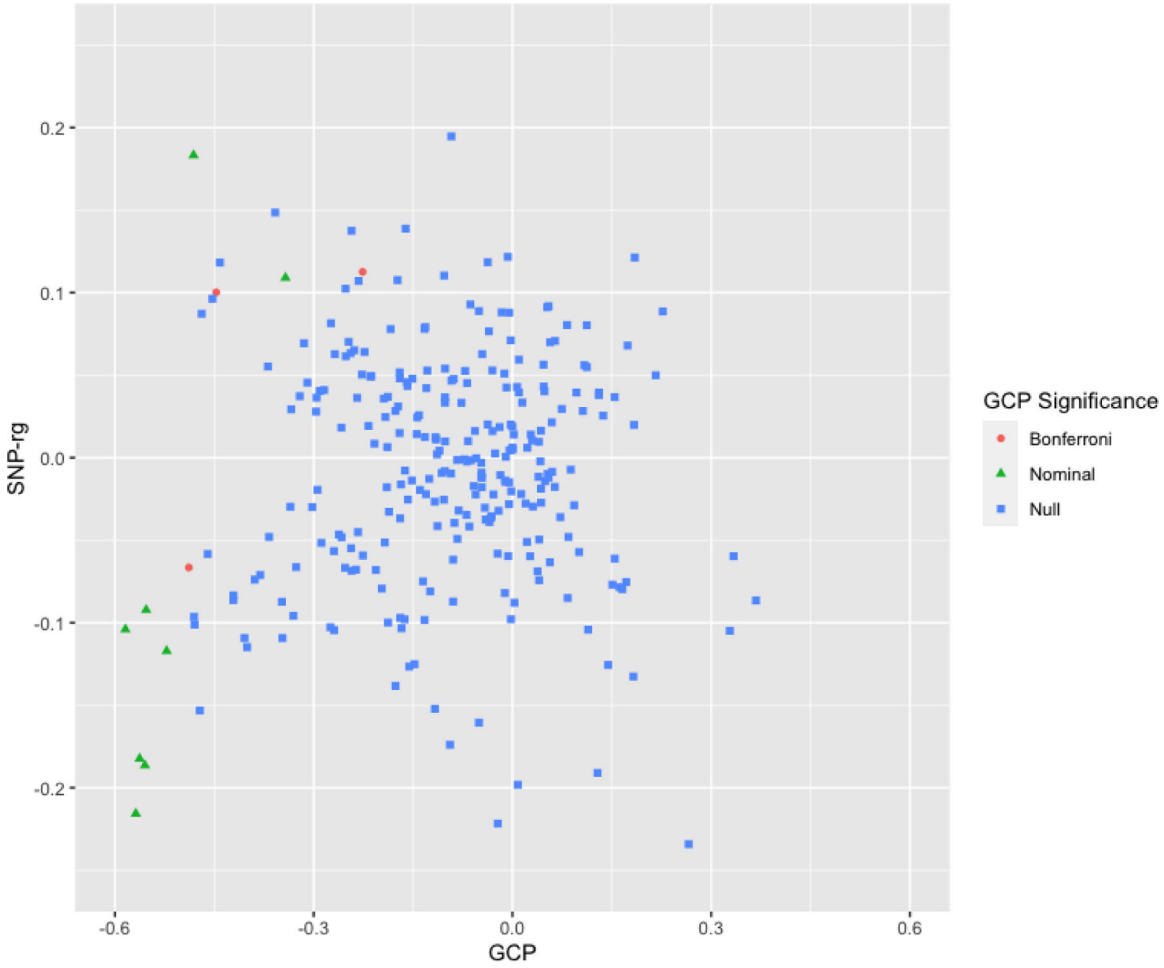

Figure 1. Latent Causal Variable Estimates and Genetic Correlations Between Brain Structure Phenotypes and Problematic Alcohol Use (n=278)

Latent causal variable estimates for brain structure phenotypes (n=278) and problematic alcohol use plotted by Genetic Causality Proportion (GCP; X axis) and Genetic Correlation (SNP-rg Y Axis). Coloration and shape represent GCP significance; blue squares represent non-significant GCPs, green triangles represent nominally-significant GCPs ($p < .05$), orange squares represent significant GCPs following Bonferroni correction (correction within modality). All Bonferroni and nominally significant GCPs were negative and the spread of the scatter plot is greater on the negative side. This is suggestive of genetic liability for brain structure putatively causing liability for problematic alcohol use.

Table 1.

Bonferroni Corrected and Nominally Significant Results from Latent Causal Variable Analyses of Brain Structure and Problematic Alcohol Use

Modality	Region	GCP	GCP SE	GCP P	SNP-rg	h^2
Cortical Volume	**Left Pars Opercularis**	**−0.643**	**0.173**	**0.00019**	**0.062**	**0.172**
Cortical Thickness	**Cuneus**	**−0.226**	**0.066**	**0.00059**	**0.113**	**0.103**
Subcortical Volume	**Left Basal Forebrain**	**−0.489**	**0.144**	**0.00067**	**-0.067**	**0.103**
Cortical Thickness	Precuneus	−0.447	0.162	0.00584	0.100	0.124
Cortical Volume	Right Pars Triangularis	−0.584	0.243	0.01613	−0.104	0.147
Cortical Thickness	Pericalcarine Gyrus	−0.343	0.143	0.01641	0.109	0.061
Cortical Thickness	Postcentral Gyrus	−0.600	0.260	0.02116	0.103	0.101
Cortical Volume	Right Superior Frontal Gyrus	−0.555	0.250	0.02629	−0.186	0.333
Subcortical Volume	Right Vessel	−0.563	0.259	0.02977	−0.182	0.233
Cortical Volume	Right Lateral Occipital Gyrus	−0.553	0.258	0.03227	−0.092	0.242
Cortical Thickness	Lingual Gyrus	−0.481	0.227	0.03380	0.183	0.101
Cortical Thickness	Mean Thickness	−0.567	0.270	0.03553	−0.216	0.260
Cortical Thickness	Medial Orbitofrontal Cortex	−0.522	0.264	0.04790	−0.117	0.029

Note: Nominal significance was determined by GCP estimates with P < .05 before multiple correction. GCP=genetic causality proportion, SE = Standard error of GCP, GCP P = GCP p-value, SNP-rg = genetic correlation, h^2 = SNP heritability (calculated by the original study). Bold represents phenotypes that are significant after Bonferroni correction. For ENGIMA cortical surface phenotypes, only mean across hemispheres was available. All results from the UKBiobank (gray and white matter volume) use bilateral parcellations. The h^2 is from the original study for each phenotype.