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Short communication

Genetic correlation of antisocial behaviour with alcohol, nicotine, and cannabis use

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ABSTRACT

Background: There is high comorbidity between antisocial behaviour (ASB) and substance use, and twin studies have shown that part of the covariation is due to overlapping genetic influences. Here we used measured genetic effects to estimate the genetic correlations of ASB with nicotine, alcohol, and cannabis use.

Methods: We meta-analysed data from two genome-wide association studies for ASB and used existing summary statistics from the largest genome-wide association studies into substance use (ever smoking, cigarettes smoked per day, weekly alcohol consumption, and lifetime cannabis use). We performed cross-trait LD-score regression to estimate genetic correlations between ASB and substance use phenotypes explained by all single nucleotide polymorphisms (SNPs). When significant, we tested whether the signs of the regression coefficients of SNPs from the ASB and substance use phenotypes were in the same direction across multiple p-value thresholds and examined enrichment in overlap of the strongest associated SNPs.

Results: We found nominally significant genetic correlations of ASB with lifetime cannabis use ($r_g = 0.69$, $p = .016$) and cigarettes per day ($r_g = 0.59$, $p = 0.036$) but not with weekly alcohol consumption or ever smoking. Sign-tests revealed consistent directions of effect of SNPs for ASB and cannabis use for all p-value thresholds except the most stringent one, whereas for ASB with cigarettes per day no consistent evidence was found. We found no evidence of enrichment in overlap of the most associated SNPs across these traits.

Conclusion: Using measured genetic variants, we found preliminary support for a genetic correlation of ASB with lifetime cannabis use and cigarettes per day.

1. Introduction

Antisocial behaviours (ASBs, including conduct problems and antisocial personality) are characterised by irresponsible, impulsive, aggressive, and dishonest behaviours and pose a major burden on affected individuals and their families as well as on society as a whole (Foster and Jones, 2005; McCollister et al., 2010). The consequences of ASB—particularly violent behaviour—are severe and can be long lasting.

ASBs show substantial comorbidity with other psychiatric syndromes and maladaptive behaviours (Abram et al., 2015). Previous studies have shown that individuals with antisocial personality or conduct problems are at increased risk for substance (ab)use, including nicotine, alcohol, and cannabis use (e.g., Compton et al., 2005; Elkins et al., 2007; Fergusson et al., 2007; Goldstein et al., 2017; Palmer et al., 2013). In a 25-year longitudinal study, Fergusson et al. (2007) found that conduct problems during childhood and adolescence are related to later nicotine, alcohol, cannabis, and illicit drug use, abuse, and dependence (with the exception of alcohol *use*, probably as a result of the high rate of alcohol use in the cohort). The effects remained even after controlling for attentional problems and confounding social, family, and related factors (individual characteristics and behaviours).

Twin and family studies have shown that antisocial behaviours and substance use are heritable traits. Heritability estimates for conduct symptoms and conduct disorder generally range between 40% and 60% (Gelhorn et al., 2005; Miles et al., 2002; Polderman et al., 2015; Rhee

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and Waldman, 2002; Verweij et al., 2016), and a meta-analysis of behavioural genetic studies of antisocial behaviour indicates that genetic factors explain 56% of the variance in antisocial personality and behaviour (Ferguson, 2010). For alcohol consumption, heritability estimates are approximately 40–60% (Heath and Martin, 1994; Kendler et al., 2008; Verweij et al., 2016). A meta-analysis of twin studies estimated the heritability of smoking initiation to be 37% for males and 55% for females and the heritability of smoking persistence to be 59% for males and 46% for females (Li et al., 2003). A meta-analysis of twin studies into lifetime cannabis use estimated the heritability at 48% for males and 40% for females (Verweij et al., 2010).

Results from twin studies further show that the relationship between ASB and substance use is in part due to overlapping genetic influences (Grant et al., 2015; Malone et al., 2004; Miles et al., 2002; Shelton et al., 2007; Verweij et al., 2016), suggesting there may be common biological mechanisms underlying these behaviours. Neuroscientific studies have indeed shown the presence of brain impairments related to cognitive control, impulsivity, and reward sensitivity in both ASB and substance abuse disorders, suggesting common etiological pathways underlying these traits (Hyde et al., 2013; Iacono et al., 2008; Raine, 2008; US DHHS, 2016).

With methodological advances in molecular genetics and increased sample sizes in genome-wide association studies (GWASs), it has become viable to use measured genetic variation among individuals to examine the genetic relationship between antisocial behaviour and substance use. Here, we estimated the genome-wide genetic correlation between antisocial behaviour and substance use phenotypes.

2. Methods

We employed (cross-trait) LD-score regression (Bulik-Sullivan et al., 2015) to estimate the SNP heritability and the genetic correlation between ASB and substance use phenotypes that could be explained by all SNPs. Briefly, LD-score regression is based on the fact that an estimated SNP effect-size incorporates effects of all SNPs in LD with that SNP. SNPs that tag more genetic variation will have a higher probability of tagging a causal variant; therefore, SNPs with higher LD have on average a higher χ^2 statistic than SNPs with lower LD. When regressing the χ^2 statistics as obtained from a GWAS against the LD score for each SNP, the slope of the corresponding regression line provides an estimate of the proportion of trait variance accounted for by all genotyped SNPs (Bulik-Sullivan et al., 2015). Cross-trait LD-score regression is an extension in which the genetic covariation between traits is estimated using GWAS summary statistics of these traits (Bulik-Sullivan et al., 2015). The genetic covariance is estimated using the slope from the regression of the product of z-scores from the GWASs on the LD score. The estimate represents the genetic correlation between the two traits based on all polygenic effects captured by all SNPs.

Here, we estimated the genetic correlation of ASB with alcohol, nicotine, and cannabis use by capitalizing on large GWAS meta-analyses available. For substance use, summary statistics were obtained for four phenotypes from the three largest published GWASs to date (see Supplementary Table 1): ever smoking (≥100 cigarettes) and cigarettes per day (Tobacco and Genetics Consortium, 2010), weekly alcohol consumption (Clarke et al., 2017), and lifetime cannabis use (Stringer et al., 2016).

For ASB we performed a GWAS meta-analysis in order to obtain a larger GWAS sample. We meta-analysed summary data from the publicly available EAGLE consortium (N = 18,988, Pappa et al., 2016) with those from non-overlapping samples of the Broad Antisocial Behavior Consortium (Tielbeek et al., 2017), totalling 31,968 participants. To maximize sample size, we included studies with a broad range of antisocial measures, including both aggressive and non-aggressive domains of antisocial behaviour, and utilized study-specific scales in different age groups (details are provided elsewhere, see Pappa et al., 2016; Tielbeek et al., 2017). The meta-analysis was run using a fixed-effects model with z-scores weighted by sample size as implemented in the software METAL (Willer et al., 2010). We only utilized the results of polymorphisms with a combined sample size greater than 20,000.

From the cannabis, alcohol, and nicotine GWAS summary statistics, only SNPs present in all contributing cohorts were included. Furthermore, we only included HapMap-3 SNPs (as recommended by Bulik-Sullivan et al., 2015), resulting in 968,384, 911,020 and 967,376 SNPs for nicotine, alcohol, and cannabis use, respectively. Analyses were performed with the LDSC software package using pre-calculated LD scores (Finucane et al., 2015).

We performed additional (follow-up) analyses for those substance use traits for which we found a nominally significant ($p < 0.05$) genetic correlation with ASB. We clumped the SNPs in PLINK to identify a smaller set of independent SNPs (using 1000 Genomes V3 for Europeans as reference panel, 0.1 as LD r^2 threshold, and 500 KB as physical distance threshold). First, we tested whether the signs of the regression coefficients of the SNPs for ASB and the substance use phenotypes were, more often than expected by chance, in the same direction using a binomial test to verify whether the proportion of SNPs with concordant sign was higher or lower than expected by chance (0.5). Secondly, we tested whether there was significant overlap in associated SNPs for ASB and substance use phenotypes for different p-value bins using Fisher exact tests. Briefly, we computed 2 × 2 contingency tables and then tested for homogeneity of proportion by computing an odds ratio through comparison of the binomial probabilities of enrichment of low p-values in same SNPs versus no enrichment.

3. Results

First, the SNP-based heritability estimates of and the genetic correlations between ASB and the substance use phenotypes were calculated (see Table 1). The estimated proportion of the phenotypic variance in ASB explained by all SNPs was 2.9% with a standard error of 1.5% ($p = .0.06$), which is very low. We found nominally significant ($\alpha < 0.05$) genetic correlations of ASB with lifetime cannabis use ($r_g = 0.69$, $p = 0.016$) and with cigarettes smoked per day ($r_g = 0.59$, $p = .036$) but not with alcohol consumption or ever smoking ($r_g = -0.06$, $p = .047$; $r_g = 0.24$, $p = .019$, respectively).

3.1. Follow-up analyses

The sign-tests revealed consistent directions of effect for SNPs in ASB and lifetime cannabis use for three p-value thresholds (proportions were 0.53, 0.56, and 0.62 for p-value thresholds 1, 0.05, and 0.001, respectively) but not for the most stringent threshold of 0.0001. These

Table 1
Estimates of the SNP-based heritability and the genetic correlations (r_g) between ASB and four substance use phenotypes.

		SNP-based heritability		Genetic correlation with ASB	
Phenotype	Sample size	h^2_{SNPs} (SE)	P-value	r_g (SE)	P-value
Antisocial Behaviour (ASB)	31,968	0.029 (0.015)	0.060	–	–
Weekly alcohol Consumption	112,117	0.079 (0.006)	< 0.0001	0.26 (0.21)	0.225
Cannabis use (lifetime)	32,330	0.091 (0.016)	< 0.0001	0.69 (0.29)	0.016*
Smoking (ever use)	74,035	0.077 (0.007)	< 0.0001	0.24 (0.19)	0.191
Smoking (cigarettes per day)	38,181	0.057 (0.014)	< 0.0001	0.59 (0.28)	0.036*

* Significant at $\alpha < 0.05$; SNP h^2: narrow-sense heritability based on all SNPs; r_g: genetic correlation with ASB.

Table 2
Sign and Fisher's exact test of SNP effects between 1) ASB and cannabis use and 2) ASB and cigarettes per day for different p-value thresholds.

		Sign-test		Fisher's exact test	
Phenotypes	P Threshold	Proportion**	P-value	Odds Ratio	P-value
ASB – Cannabis*	1	0.53	$< 2.2 \times 10^{-16}$		
ASB – Cannabis*	0.05	0.56	$< 2.2 \times 10^{-16}$	0.91	0.11
ASB – Cannabis*	0.001	0.62	9.7×10^{-7}	0.68	0.13
ASB – Cannabis*	0.0001	0.58	0.13	NA	NA
ASB – CPD*	1	0.50	0.03		
ASB – CPD*	0.05	0.50	0.26	0.97	0.42
ASB – CPD*	0.001	0.50	0.55	NA	NA
ASB – CPD*	0.0001	0.58	0.11	NA	NA

* Clumped SNPs.

** The expected proportion under the null hypothesis is 0.5. CPD = cigarettes per day; NA: too few SNPs were available to perform this test.

results further support the finding of genetic overlap between the two traits. The sign-tests for ASB and cigarettes per day showed no consistent directions of effect (proportions were 0.50, 0.50, 0.50, and 0.58 respectively) for SNPs selected for different p-value thresholds (1, 0.05, 0.001 and 0.0001). Moreover, Fisher exact tests showed no evidence for enrichment of SNPs with low p-values across the genetically overlapping traits, regardless of sign, which indicates that the genetic covariance is not due to SNPs with low p-values in both samples but to more subtle effects of a large sample of SNPs with the same direction of effect (see Table 2 for full results of the follow-up analyses).

4. Discussion

Using measured gene effects, we found nominally significant genetic correlations of ASB with lifetime cannabis use and cigarettes smoked per day but not with alcohol consumption and ever smoking. The genetic correlations of ASB with cannabis use and cigarettes smoked per day were substantial ($r_g = 0.69$, $p = 0.016$ and $r_g = 0.59$, $p = 0.036$, respectively), indicating a considerable overlap in the genetic influences on ASB and those on cannabis use and cigarettes per day. Findings for the genetic correlation between ASB and cannabis use were further supported by the sign test demonstrating the same direction of effect for SNPs in most p-value bins for ASB and cannabis use but not for ASB and cigarettes smoked per day.

The genetic correlations of ASB with alcohol consumption and ever smoking were much lower and not significantly different from zero. A potential explanation for higher correlations of ASB with cannabis use and cigarettes per day compared to ever smoking and alcohol use may be that cannabis use and smoking (many) cigarettes per day are more deviant phenotypes than alcohol consumption (Orlando et al., 2005) (which is generally accepted in Western societies) and ever smoking which includes experimenting only. If these traits represent more deviant behaviours, they may be more strongly (genetically) related to antisocial behaviour. In line with this hypothesis, two previous twin studies reported a weaker relationship between ASB/conduct and alcohol (ab)use than between ASB and nicotine or cannabis use (Fergusson et al., 2007; Verweij et al., 2016). Moreover, in another twin study, Grant et al. (2015) found a lower genetic correlation between conduct disorder and alcohol dependence than between conduct disorder and nicotine or cannabis dependence, whereas the phenotypic correlations were in the same range. On the contrary, Verweij et al. (2016) found in their twin study that the correlation between conduct symptoms and alcohol use was almost completely explained by overlapping genetic influences.

Notwithstanding the high genetic correlations, it is important to realize that the SNP-based heritability estimates, on which these results were based, were rather low and ranged from 2.8% for ASB to 9.1% for cannabis use. In particular, the SNP-based heritability for ASB is very low, indicating that—based on these GWAS results— SNPs can only explain a very small proportion of the individual differences in ASB. As a consequence, although the genetic correlations of ASB with cannabis use and cigarettes per day were substantial, in absolute terms the genetic variance that is overlapping between the two traits is relatively low.

A general limitation of these analyses is that they are heavily dependent upon the size of the GWAS samples; larger samples provide more power to accurately estimate the SNP effect sizes. For ASB and cannabis use, the sample sizes were relatively small for this type of analyses, and both meta-analyses were based on data from very heterogeneous cohorts (see Supplementary Table S1) which could lead to less accurate SNP effects and hence a lower SNP-based heritability. On the other hand, we did find a significant genetic correlation between these two phenotypes, suggesting the power was sufficient to detect such effects. It should also be noted that a genetic correlation does not imply that the same genes underlie both phenotypes (genetic pleiotropy), but rather that it could also be due to a causal relationship between the two phenotypes.

Overall, our study provides some support for a correlation of ASB with lifetime cannabis use and cigarettes per day on a genetic level. Future studies with advanced technologies, novel statistical approaches (such as Mendelian randomisation), and larger sample sizes should aim to determine the nature of the genetic association between ASB and substance use and identify common genes and biological mechanisms that can explain the genetic association.

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Contributors

JJT and KJHV were responsible for the study concept and the design of the study. JJT performed the data analyses, under supervision of KJHV. KJHV and JJT drafted the manuscript. JMV, TJCP, AP, and DP provided critical revision of the manuscript for important intellectual content. All authors contributed to and approved the final version for publication.

Conflict of interest

Nothing declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugalcdep.2018.03.020.

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