

Testing Genetic and Environmental Associations Between Personality Disorders and Cocaine Use: A Population-Based Twin Study

Nathan A. Gillespie,¹ Steven H. Aggen,¹ Amanda E. Gentry,² Michael C. Neale,^{1,3} Gun P. Knudsen,⁴ Robert F. Krueger,⁵ Susan C. South,⁶ Nikolai Czajkowski,^{4,7} Ragnar Nesvåg,^{4,8} Eivind Ystrom,^{4,9,10} Tom H. Rosenström,⁴ Fartein A. Torvik,⁴ Ted Reichborn-Kjennerud,^{4,11} and Kenneth S. Kendler^{1,3}

¹Department of Psychiatry, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA

²Department of Biostatistics, Virginia Commonwealth University, Richmond, VA, USA

³Human and Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA

⁴Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway

⁵Department of Psychology, University of Minnesota, Minneapolis, MN, USA

⁶Department of Psychological Sciences, Purdue University, West Lafayette, IN, USA

⁷Department of Psychology, University of Oslo, Oslo, Norway

⁸Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway

⁹Department of Psychology, Section of Health, Developmental and Personality Psychology, University of Oslo, Oslo, Norway

¹⁰Pharmaco Epidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Oslo, Norway

¹¹Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Until now, data have not been available to elucidate the genetic and environmental sources of comorbidity between all 10 DSM-IV personality disorders (PDs) and cocaine use. Our aim was to determine which PD traits are linked phenotypically and genetically to cocaine use. Cross-sectional data were obtained in a face-to-face interview between 1999 and 2004. Subjects were 1,419 twins ($\mu_{\text{age}} = 28.2$ years, range = 19–36) from the Norwegian Institute of Public Health Twin Panel, with complete lifetime cocaine use and criteria for all 10 DSM-IV PDs. Stepwise multiple and Least Absolute Shrinkage and Selection Operator (LASSO) regressions were used to identify PDs related to cocaine use. Twin models were fitted to estimate genetic and environmental associations between the PD traits and cocaine use. In the multiple regression, antisocial ($OR = 4.24$, 95% CI [2.66, 6.86]) and borderline ($OR = 2.19$, 95% CI [1.35, 3.57]) PD traits were significant predictors of cocaine use. In the LASSO regression, antisocial, borderline, and histrionic were significant predictors of cocaine use. Antisocial and borderline PD traits each explained 72% and 25% of the total genetic risks in cocaine use, respectively. Genetic risks in histrionic PD were not significantly related to cocaine use. Importantly, after removing criteria referencing substance use, antisocial PD explained 65% of the total genetic variance in cocaine use, whereas borderline explained only 4%. Among PD traits, antisocial is the strongest correlate of cocaine use, for which the association is driven largely by common genetic risks.

■ **Keywords:** cocaine use, antisocial, personality disorder traits, LASSO, twin, genes, environment

In 2013, 601,000 persons in the United States reported using cocaine for the first time within the previous 12 months (Substance Abuse and Mental Health Services Administration, 2014). Although the economic, physiological, and psychiatric consequences of cocaine use and misuse are well documented (Karila et al., 2012; National Drug Intelligence Center, 2011; Strickland et al., 1998), the psychiatric antecedents are not well understood. Commensurate with research-based prevention programs that target communities and individuals at high risk of substance use, research

has begun linking personality disorders (PDs) to licit and illicit substance use (Bidwell et al., 2015; Few et al., 2013; Hasin et al., 2011; Lejuez et al., 2010; Lopez-Quintero et al.,

RECEIVED 29 November 2017; ACCEPTED 7 December 2017

ADDRESS FOR CORRESPONDENCE: Nathan A. Gillespie, PhD, Virginia Institute for Psychiatric and Behavioral Genetics, 800 East Leigh St, Suite 101, Richmond, Virginia 23219, USA. E-mail: nathan.gillespie@vcuhealth.org

2011; Peters et al., 2014; Verdejo-Garcia et al., 2008; Wu et al., 2011). Approximately, 13–15% of adults have at least one PD (Grant et al., 2004; Torgersen et al., 2001). However, a comprehensive investigation of the genetic and environmental pathways linking pathological personality to lifetime cocaine use has never been reported.

Among the 10 DSM-IV PDs (American Psychiatric Association, 1994) consistently linked to cocaine use, borderline and antisocial have received the strongest attention and empirical support (Albein-Urios et al., 2014; Bornovalova et al., 2008; Carpenter et al., 2016; Chahua et al., 2015; Chen et al., 2011; Compton et al., 2005; Narvaez et al., 2014). Both of these PDs are associated with increased prevalence of substance use disorders (Hasin et al., 2011; Lopez-Quintero et al., 2011; Peters et al., 2014; Wu et al., 2011). While twin studies provide compelling evidence that PDs and cocaine use are heritable (Distel et al., 2009; Kendler et al., 2008; Kendler, Aggen et al., 2012; Kendler, Chen et al., 2012; Kendler et al., 2007; Livesley et al., 1993; Torgersen et al., 2012), genetically informative data have not been available until now to elucidate the genetic and environmental sources of comorbidity between all 10 PDs and cocaine use.

To our knowledge, no study to date has modeled the association between all 10 DSM-IV (American Psychiatric Association, 1994) Axis-II PD traits and cocaine use. It is plausible that within a more integrated model, a number of PD traits may correlate with the liability to cocaine use. We address these gaps by focusing on two aims. The first aim will identify which DSM-IV PD traits best predict the liability to cocaine use. The second aim is to use genetically informative models to identify and obtain estimates of the genetic and environmental factors that influence the relationship between PD traits and cocaine use.

Materials and Methods

Sample

Participants came from the Norwegian National Institute of Public Health Twin Panel (Harris et al., 2002) comprising twins born from 1967 to 1979 who were identified through the Norwegian National Medical Birth Registry established in 1967. Data were collected in an interview study between 1999 and 2004, which assessed DSM-IV Axis I and Axis II disorders (American Psychiatric Association, 1994). Of the 3,221 twin pairs eligible for the interview study, there were 1,391 complete pairs (43.2%) and 19 single twins (0.6% pairwise), totaling 2,801 twins who participated (43.4%; 63% female, $\mu_{\text{age}} = 28.2$ years, range = 19–36). All interviewers were advanced psychology students or psychiatric nurses, who received standardized training and were supervised during data collection. Written-informed consent was obtained from all subjects, who received stipends of \$35 for participation. Ethical approval came from The

Norwegian Data Inspectorate and the Regional Ethical Committee.

Measures

Personality disorders. The DSM-IV (American Psychiatric Association, 1994) personality disorders were assessed using a Norwegian version of the Structured Interview for DSM-IV personality disorders (SIDP-IV; Pfohl et al., 1995) comprising: schizotypal (nine criteria), schizoid (seven criteria), paranoid (seven criteria; conduct disorder before age 15 criterion not included), histrionic (eight criteria), borderline (nine criteria), obsessive-compulsive (eight criteria), dependent (eight criteria), avoidant (seven criteria); narcissistic (nine criteria), and antisocial (seven criteria). The SIDP-IV used non-pejorative questions organized into topical sections rather than by individual PD, thereby improving the flow of the interview. The SIDP-IV interview was conducted after the Composite International Diagnostic Interview (CIDI; American Psychiatric Association, 1994; Wittchen & Pfister, 1997) to enable interviewers to distinguish long-standing behaviors from temporary states resulting from Axis I disorders. Each criterion was scored on a four-point scale (*absent*, *subthreshold*, *present*, or *strongly present*), which was then dichotomized (0 = absent, 1 = \geq subthreshold), and summed for each PD. However, because very few subjects endorsed most criteria, each PD sum score was recoded onto a three-point ordinal scale (0 criteria, 1–2 criteria, ≥ 3 criteria; see Table S1 for variable distributions). We have previously tested the validity of this approach by examining the fit of the multiple threshold model in order to determine whether the number of endorsed criteria reflects differences in severity along a single, normally distributed continuum of liability. In brief, this was done using the twin data and testing the fit of the bivariate normal distribution. This assumption is supported for all 10 PDs examined (Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2008).

Cocaine use. As part of a Norwegian version of the Composite International Diagnostic Interview (American Psychiatric Association, 1994; Wittchen & Pfister, 1997), all twins were asked ‘Have you ever taken cocaine’ (No = 1,362, Yes = 57). Cocaine use was 5.2% and 3.5% for males and females, respectively, while the average age of most frequent cocaine use was 21.6 years ($SD = 3.2$, range = 15–28).

Complete PD trait scores were available from 2,793 twins. Data on cocaine use were available from 1,419 twins.

Statistical Analyses

Overview. To identify which PD traits best predict lifetime cocaine use, our first aim applies linear regressions in which all 10 DSM-IV PD traits together with sex and age are entered as predictors of cocaine. We next validate this method using a Least Absolute Shrinkage and Selection Operator (LASSO) regression. Any PD traits that are

significantly predictive of cocaine use are then brought forward, and biometrical twin models are fitted to estimate the proportion of genetic and environmental risks shared between the PD traits and cocaine use.

Regressions. We fitted logistic regressions using the generalized linear model `glm()` function in R_{3.1.1} (R Development Core Team, 2008) to determine how well each PD trait predicts cocaine use. Our rationale for presenting univariate results is to illustrate the strength of each predictor when other PDs are not taken into account. This was followed by a multiple regression in which cocaine use was regressed onto all 10 PDs, again using the `glm()` function with forward and backward selection in R_{3.1.1} (R Development Core Team, 2008). We applied this stepwise method to determine which subset of PD traits best predicts cocaine use. All regressions included sex and age as covariates, and in order to account for non-independence introduced by twin data, the standard errors were corrected for clustering.

LASSO regression. Given the widely recognized limitations of stepwise regression (Whittingham et al., 2006), we sought to replicate and validate the findings by fitting a 10-fold, cross-validated LASSO, or penalized regression, using the `cv.glmnet()` function (Friedman et al., 2010) in R_{3.1.1} (R Development Core Team, 2008). This method works by adding an L1-penalization term ($\lambda \|\beta\|_1 = \lambda \sum_{j=1}^p |\beta_j|$) to the regression equation (Tibshirani, 1996), where larger λ values correspond to the shrinking of more regression coefficients to zero. We ran the `cv.glmnet()` function 1,000 times and averaged the error curves. The λ with the smallest binomial error deviance between predicted and actual observations was then fitted to a final penalized regression again using the `glmnet()` function (Friedman et al., 2010) in R_{3.1.1} (R Development Core Team, 2008) to identify the subset of PD traits predictive of cocaine use. When interpreting the results, LASSO bounds the sum of absolute values of the regression coefficients. This has the effect of forcing the coefficients of the worst predictors among the correlated variables to approach zero, which amounts to automatic variable selection and reduces possible estimator instability due to near multicollinearity.

Twin analyses. PD traits found to predict cocaine use were then brought forward into bivariate twin analyses. All twin models were fitted to the raw ordinal data using Full Information Maximum Likelihood (FIML) using the OpenMx_{2.0} software package (Neale et al., 2016) in R_{3.1.1} (R Development Core Team, 2008). This approach assumes that the observed ordinal categories within each variable are an imprecise measure of a latent normal distribution of liability and that this liability distribution has one or more threshold values. Thresholds can be conceived of as cut-points along a standard normal distribution that relate category frequen-

cies to cumulative probabilities indicating increasing levels of risk. All thresholds were adjusted for the fixed effects age and sex.

By exploiting the expected and observed genetic and environmental correlations between monozygotic (MZ) and dizygotic (DZ) twin pairs, standard bivariate biometrical genetic methods (Neale & Cardon, 1992) were used to estimate the size and significance of the genetic and environmental correlations between each significant PD and the CU and CUD outcomes. The classical twin design assumes that covariance between MZ and DZ twin pairs can be decomposed into additive (A) genetic, shared environmental (C), and non-shared or unique (E) environmental components or risks. Because MZ twin pairs are genetically identical, compared to DZ twin pairs who share on average half of their genes, the expected twin pair correlations for the genetic (A) effects are 1.0 and 0.5, respectively. An important assumption is that common environments (C) are equal in MZ and DZ twin pairs, and because non-shared environments (E) are by definition uncorrelated, E must also reflect measurement error. In order to determine the best-fitting model, a fully saturated (A+C+E) model was used as a reference to compare models in which the shared environmental and genetic parameters were dropped to zero.

Computational demands increase with increasing numbers of ordinal variables. Therefore, only bivariate predictors that explained significant genetic or environmental covariance with cocaine use were included in the multivariate twin analyses. As illustrated in Figure 1, a popular multivariate analysis is the Cholesky triangular decomposition (Neale & Cardon, 1992). We specified a decomposition for each source of latent risk (A, C, and E) as part of a fully saturated A+C+E Cholesky. This was used as a reference to compare submodels in which the C and A parameters were fixed to zero. In both the bivariate and multivariate twin analyses, model comparisons were evaluated using the Akaike Information Criterion (Akaike, 1987), which provides a balance between model complexity and model or data misfit.

Results

Regressions

With the exception of schizoid and obsessive compulsive, all PD traits in the univariate logistic regressions had significant partial odd ratios greater than one for cocaine use (see Table 1). In the multiple regression with forward and backward selection, the partial regression coefficients and corresponding odds ratios for antisocial and borderline PD traits were significantly and positively predictive of cocaine use. Age was significant such that younger subjects reported more frequent cocaine use. Standard errors corrected for family clustering in the multiple regression are shown in Table S2.

TABLE 1
Univariate, Multiple Stepwise¹, and Least Absolute Shrinkage and Selection Operator (LASSO) Regression Coefficients

	Cocaine use				
	Logistic regressions		Multiple regression ¹		LASSO ²
	OR	(95% CI)	OR	(95% CI)	
Sex			–	–	–
Age at interview			0.89	[0.82, 0.97]	–
DSM-IV PD traits:					
Paranoid	1.88	[1.25, 2.78]	–	–	–
Schizoid	1.10	[0.59, 1.93]	0.58	[0.29, 1.06]	–
Schizotypal	1.69	[1.02, 2.69]	–	–	–
Antisocial	6.05	[3.95, 9.45]	4.24	[2.66, 6.86]	0.08
Borderline	3.73	[2.49, 5.71]	2.19	[1.35, 3.57]	0.02
Histrionic	2.50	[1.69, 3.73]	–	–	0.01
Narcissistic	1.84	[1.23, 2.75]	–	–	–
Avoidant	1.29	[1.87, 1.89]	–	–	–
Dependent	1.67	[1.09, 2.51]	–	–	–
Obsessive compulsive	1.25	[0.83, 1.89]	–	–	–

Note: Univariate and multiple stepwise linear regression coefficients (including odds ratio and 95% confidence interval) represent the amount of change in the measures of cocaine use for every one unit of change in the ordinal personality disorder trait scores. ¹Predictors in the multiple stepwise linear regression are based on the best-fitting solution with forward and backward selection. Significant predictors are in bold type. ² $\lambda = 0.006$.

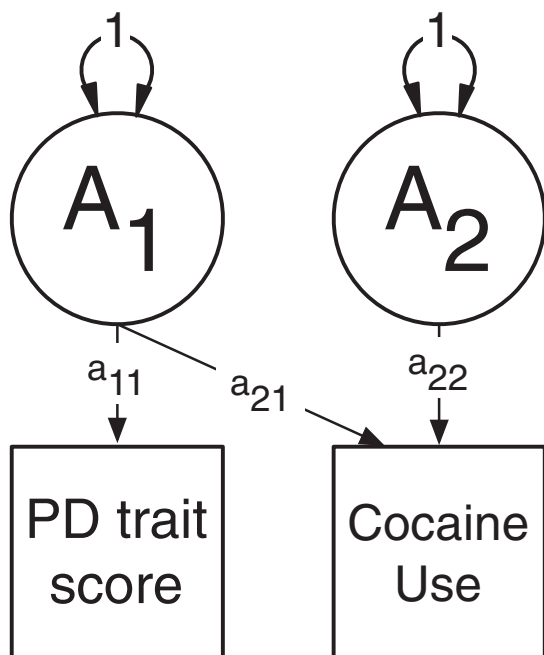


FIGURE 1
Pathway diagram illustrating a bivariate Cholesky decomposition for decomposing the genetic and environmental variance-covariance between a personality disorder trait and cocaine use. A_1 and A_2 denote the unobserved or latent additive genetic risk factors responsible for variation in the observed personality disorder trait and cocaine use, respectively. The model assumes an underlying multivariate normal liability, with latent factor means of zero (not shown) and variances of 1 (double-headed arrows). The latent factor contributions are estimated via the pathway coefficients (a_{11} – a_{33}). Latent shared (C_{1-3}) and non-shared (E_{1-3}) environmental sources of variance are not shown.

LASSO

As shown in Table 1, LASSO identified three PD traits significantly predictive of cocaine use: antisocial, borderline, and histrionic PD traits.

Bivariate Twin Analyses

The three PDs that were significant predictors in the multiple linear regression or LASSO were then examined in separate bivariate twin analyses. In each instance, an additive genetic model in which the shared environmental risks were removed provided the most parsimonious fit to the data. See Table S3 for all model comparisons.

As shown in Table 2, the phenotypic (r_P) correlations between the three PD traits and cocaine use ranged from moderate (+0.33) to large (+0.63). Unlike the genetic (r_A) and environmental (r_E) correlations between borderline and cocaine use, which approximated the level of phenotypic association, the r_A between antisocial PD and cocaine use was very high (+0.83). Among the three PD traits, the phenotypic correlation between histrionic and cocaine was the smallest, with a slightly higher genetic correlation.

The histrionic, borderline, and antisocial PD traits explained 10%, 13%, and 52% of the total variance in cocaine use, respectively. Effectively, 72% (41/[41+16]) of the total genetic risks in cocaine use were shared with the antisocial PD trait. In comparison, 25% (13/[13+38]) of the total genetic risks in cocaine use are shared with the borderline PD trait. Confidence intervals surrounding these genetic covariance estimates were significant for antisocial PD, and only marginally significant for the borderline PD trait. For the histrionic PD trait, despite modest genetic and environmental correlations, the confidence intervals on both

TABLE 2

Phenotypic (r_P), Additive Genetic (r_A), and Environmental (r_E) Correlations Between Each of the Significant Personality Disorder Traits and Cocaine Use, Along With Standardized Proportions of Genetic and Environmental Variance in Cocaine Use (Including 95% CIs) Explained By Each Trait

DSM-IV PD traits	Correlations			Proportions of variance in cocaine use							
				Genetic variance				Environmental variance			
	r_P	r_A	r_E	Shared		Unique		Shared		Unique	
Antisocial	0.63	0.85	0.43	41%	[15, 73]	16%	[00, 43]	8%	[03, 25]	35%	[15, 62]
Borderline	0.50	0.51	0.50	13%	[01, 39]	38%	[09, 61]	12%	[01, 33]	36%	[15, 66]
Histrionic	0.33	0.44	0.27	10%	[00, 36]	40%	[05, 67]	4%	[00, 16]	47%	[23, 79]
Antisocial (trimmed)	0.51	0.82	0.26	36%	[11, 70]	18%	[00, 48]	3%	[00, 17]	43%	[20, 71]
Borderline (trimmed)	0.32	0.22	0.40	2%	[00, 20]	47%	[15, 71]	8%	[00, 27]	43%	[19, 75]

Note: Results based on the most parsimonious additive genetic (A) + unique environment (E) bivariate model; trimmed = Borderline trait excluded 'Failure to conform to social norms with respect to lawful behavior as indicated by repeatedly performing acts that are grounds for arrest', Antisocial trait excluded 'Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating)'.

TABLE 3

Multivariate Model Fit Comparisons Based on a Cholesky Decomposition to Identify the Sources of Variance-Covariance Between Borderline and Antisocial PD Criteria and Cocaine Use

Model	Parameters		-2LL	df	Δ -2LL	Δ df	p	AIC
A	C	E	29	9016.24	6,985			-4953.76
A		E	23	9019.35	6,991	3.11	.79	-4962.65
	C	E	23	9028.41	6,991	12.16	.06	-4953.59

Note: A, C, and E = additive genetic, shared, and non-shared environmental latent risk factors respectively; -2LL = $-2 \times \log$ likelihood; Δ -2LL = change in -2LL; AIC = Akaike Information Criterion.

the genetic and environmental variance components shared with cocaine use spanned zero.

The antisocial and borderline PD trait scores each included criteria referencing substance use or substance use-related problems. Therefore, the bivariate analyses were repeated after removing the 'Failure to conform to social norms with respect to lawful behavior as indicated by repeatedly performing acts that are grounds for arrest' and 'Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating)' criteria from antisocial and borderline, respectively (see Table S1 for variable distributions). There were reductions in the phenotypic, genetic, and environmental correlations between 'drug-free' antisocial and borderline PD traits and cocaine use (see Table 2). Correspondingly, antisocial PD explained 67% (36/[36+18]) of the total genetic variance in cocaine use and remained significant. In contrast, the proportion of total genetic variance in cocaine use explained by the borderline PD trait dropped to 4% (2/[2+47]) and was no longer significant.

Multivariate Twin Analyses

The antisocial and borderline PD traits (with substance use criteria retained) were next entered into a multivariate Cholesky decomposition to predict cocaine use (see Figure S1). There was no evidence that shared environmental (C) risk factors were responsible for any covariance between these measures. These C factors could, therefore, be dropped from the model without any significant change in the $-2 \times \log$ -likelihood (see Table 3). Consequently, addi-

TABLE 4

Additive Genetic (Below Diagonal) and Non-Shared Environmental (Above Diagonal) Correlations Between the Latent Factors for Antisocial and Borderline Personality Disorder Traits and Cocaine Use

	1.	2.	3.
1. Antisocial	1	0.46	0.45
2. Borderline	0.72	1	0.47
3. Cocaine	0.83	0.48	1

tive genetic (A) risk factors best explained the familial aggregation between all three variables. Moreover, additive genetic risk factors unique to cocaine use (see a_{33} Figure S1) could be dropped from the model without any significant deterioration in model fit (Δ -2LL = 0.66, Δ df = 1, $p = .42$).

As shown in Table 4, the genetic correlation between antisocial and borderline PD traits was high, whereas the non-shared environmental correlation was more modest. The genetic correlation between antisocial PD trait and cocaine use was also significantly higher than the borderline cocaine correlation; a model in which the PD-cocaine genetic correlations were constrained to equal ($r_A = 0.73$) produced an albeit marginal significant deterioration in fit (Δ -2LL = 3.94, Δ df = 1, $p < .047$). In terms of the non-shared environmental risk factor correlations, the antisocial and borderline PD traits were each modestly and comparably associated with cocaine use. As a final check, the variable order was reversed before refitting the Cholesky decomposition. We obtained an identical pattern of results, including the

same pattern of additive genetic and non-shared environmental correlations.

Discussion

To our knowledge, this is the first study integrating all 10 DSM-IV personality disorder traits within a genetically informative design to predict cocaine use. Multiple regression, LASSO, and twin analyses revealed that antisocial followed by borderline PD traits were the strongest phenotypic and genetic correlates of cocaine use. The multivariate twin analysis further illustrated that the risk of cocaine use is significantly linked to correlated genetic risk factors mostly through antisocial followed by borderline PD traits. Although a proportion of the shared genetic risks were driven by PD criteria referencing substance use, when these criteria were excluded, antisocial still explained two-thirds of the genetic risks in cocaine use. Non-shared environmental risks in antisocial and borderline PD were only modestly linked to cocaine use.

Antisocial (Compton et al., 2007) and borderline (Carpenter et al., 2016) PDs have been linked to cocaine use disorder. Our findings are commensurate with results based on the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) data showing an approximately three-fold increase in the number of cocaine users who have a diagnosed PD, for whom the probability of transitioning to cocaine dependence is very high (Lopez-Quintero et al., 2011). The strength of our findings is (1) the demonstration of the relative importance of Antisocial PD vis-à-vis all other PD traits, even after removing criteria referencing drug use; and (2) the very high genetic and modest non-shared environmental correlations between antisocial and borderline PD traits and lifetime cocaine use.

Recently, we have shown that antisocial and borderline PD traits also predict the phenotypic and genetic risks in alcohol and cannabis use and misuse (CUD) criteria (Gillespie et al., 2017; Long et al., 2017). Indeed, the correlations between these two PDs are best explained by common and longitudinally stable genetic risk factors (Reichborn-Kjennerud et al., 2015). Despite cannabis and cocaine having very distinct pharmacological properties, including routes of administration, we speculate that the genetic and environmental risks in antisocial and borderline PD traits are indexing the sequelae of behavioral and psychological processes linked to the initiation and maintenance of substance use and misuse in general. This is consistent with PDs as significant indicators of the spectrum of externalizing disorders, which is highly heritable (Krueger et al., 2002) and characterized by conduct disorder, licit and illicit substance use, and misuse (Dick et al., 2008; Markon et al., 2005), as well as antisocial and borderline PDs (Eaton et al., 2011; Iacono et al., 2003; Markon & Krueger, 2005). Borderline PD also predicts, at least phenotypically, the liability to facets within the spectrum of internalizing disorders

(Eaton et al., 2011). In summary, not only do antisocial and borderline PD criteria predict cocaine use, but the same criteria also index the broader genetic liability to substance use and other correlated psychiatric disorders. Although our modeling is consistent with correlated, non-causal mechanisms underpinning associations between PD traits and cocaine use, we emphasize that we have not tested alternative, causal hypotheses, which may otherwise have direct clinical implications. Such analyses were beyond the scope of this manuscript.

Limitations

Our results should be interpreted in the context of four potential limitations.

First, there was some sample attrition from the original birth registry through to the interview study. In longitudinal studies, attrition reduces statistical power, but will only introduce bias if it is non-random with respect to critical-dependent variables (Tambs et al., 2009). Multiple lines of evidence have indicated that the sample is broadly representative with respect to the key areas of interest whereby demographic and not psychiatric and substance use measures significantly predicted cooperation across assessment waves (Tambs et al., 2009). No psychiatric variables predicted cooperation assessed during an earlier study in 1998. Instead, the strongest predictors of participation were sex, zygosity, and education. Based on examination of 45 variables potentially predictive of cooperation from a richer 1998 survey, including 22 indicators of mental health, only 2 of 45 variables — age and zygosity — significantly predicted cooperation at the interview study (1999–2004), whereas none of the psychiatric variables predicted cooperation. Using the 1998 data, we also fitted standard twin models to 25 variables (including proxies for all 10 PDs, five Axis I psychiatric disorders, and alcohol abuse) to determine whether results differed between non-subjects and subjects in the interview study. None of the parameters differed significantly. So while some attrition bias remains possible, our use of FIML is robust to missing data when missingness is random or predicted by other variables in the analyses (Little & Rubin, 1987), which means that attrition was unlikely to have biased our results.

Second, there were 91 complete and 164 incomplete (singletons) opposite-sex DZ twin pairs with cocaine use data. Consequently, the lack of statistical power precluded investigating sex differences in the additive genetic risk factors (Neale & Cardon, 1992).

Third, the study relied on Norwegian adults. Consequently, variation and replication of our results are required to determine whether they generalize to different age groups and sample populations.

Finally, administration of the substance use items was contingent upon the response to 'Are you prepared to speak openly about this subject?' Substance use was higher among cooperative twins whose co-twin was unprepared to speak

openly about his/her history of substance use. The anti-social and borderline bivariate analyses were therefore re-run, wherein cocaine use was contingent upon 'speaking openly' (see Figure S2). There were declines in the phenotypic (+0.63 to +0.44) and genetic (+0.85 to +0.73) correlations between antisocial PD criteria and cocaine use. For borderline PD criteria, the phenotypic correlation declined (+0.50 to +0.45), whereas the genetic correlation (+0.51 to +0.54) increased marginally. We therefore conclude that this contingency had minimal impact on the results.

Conclusion

Among the 10 DSM-IV PDs, antisocial followed by borderline PD traits are the strongest phenotypic and genetic correlates with lifetime cocaine use. Associations between these PD traits and cocaine use are driven largely by common genetic risk factors. Future twin analyses will test the direction of causation between these PD traits and cocaine use.

Acknowledgments

We acknowledge funding from the US National Institutes of Health and National Institute on Drug Abuse (1R01DA037558-01A1 and 12R01DA018673), the Norwegian Research Council, the Norwegian Foundation for Health and Rehabilitation, the Norwegian Council for Mental Health, and the European Commission under the program 'Quality of Life and Management of the Living Resources' of the Fifth Framework Program (QLG2-CT-2002-01254). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosure of Interests

None.

Details of Ethical Approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Supplementary Material

To view supplementary material for this article, please visit <https://doi.org/10.1017/thg.2017.73>.

References

Akaike, H. (1987). Factor analysis and AIC. *Psychometrika*, *52*, 317–332.

- Albein-Urios, N., Martinez-Gonzalez, J. M., Lozano, O., & Verdejo-Garcia, A. (2014). Monetary delay discounting in gambling and cocaine dependence with personality comorbidities. *Addictive Behaviors*, *39*, 1658–1662.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed., DSM-IV). Washington DC: Author.
- Bidwell, L. C., Knopik, V. S., Audrain-McGovern, J., Glynn, T. R., Spillane, N. S., Ray, L. A., ... Leventhal, A. M. (2015). Novelty seeking as a phenotypic marker of adolescent substance use. *Substance Abuse*, *9*(Suppl. 1), 1–10.
- Bornoalova, M. A., Gratz, K. L., Daughters, S. B., Nick, B., Delany-Brumsey, A., Lynch, T. R., ... Lejuez, C. W. (2008). A multimodal assessment of the relationship between emotion dysregulation and borderline personality disorder among inner-city substance users in residential treatment. *Journal of Psychiatric Research*, *42*, 717–726.
- Carpenter, R. W., Wood, P. K., & Trull, T. J. (2016). Comorbidity of borderline personality disorder and lifetime substance use disorders in a nationally representative sample. *Journal of Personality Disorders*, *30*, 336–350.
- Chahua, M., Sanchez-Niubo, A., Torrens, M., Sordo, L., Bravo, M. J., Brugal, M. T., & Domingo-Salvany, A. (2015). Quality of life in a community sample of young cocaine and/or heroin users: The role of mental disorders. *Quality of Life Research*, *24*, 2129–2137.
- Chen, K. W., Banducci, A. N., Guller, L., Macatee, R. J., Lavelle, A., Daughters, S. B., & Lejuez, C. W. (2011). An examination of psychiatric comorbidities as a function of gender and substance type within an inpatient substance use treatment program. *Drug and Alcohol Dependence*, *118*, 92–99.
- Compton, W. M., Conway, K. P., Stinson, F. S., Colliver, J. D., & Grant, B. F. (2005). Prevalence, correlates, and comorbidity of DSM-IV antisocial personality syndromes and alcohol and specific drug use disorders in the United States: Results from the national epidemiologic survey on alcohol and related conditions. *Journal of Clinical Psychiatry*, *66*, 677–685.
- Compton, W. M., Thomas, Y. F., Stinson, F. S., & Grant, B. F. (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: Results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry*, *64*, 566–576.
- Dick, D. M., Aliev, F., Wang, J. C., Grucza, R. A., Schuckit, M., Kuperman, S., ... Goate, A. (2008). Using dimensional models of externalizing psychopathology to aid in gene identification. *Archives of General Psychiatry*, *65*, 310–318.
- Distel, M. A., Trull, T. J., Willemsen, G., Vink, J. M., Derom, C. A., Lynskey, M., ... Boomsma, D. I. (2009). The five-factor model of personality and borderline personality disorder: A genetic analysis of comorbidity. *Biological Psychiatry*, *66*, 1131–1138.
- Eaton, N. R., Krueger, R. F., Keyes, K. M., Skodol, A. E., Markon, K. E., Grant, B. F., & Hasin, D. S. (2011). Borderline personality disorder co-morbidity: Relationship to the internalizing-externalizing structure of common mental disorders. *Psychological Medicine*, *41*, 1041–1050.

- Few, L. R., Miller, J. D., Rothbaum, A. O., Meller, S., Maples, J., Terry, D. P., ... MacKillop, J. (2013). Examination of the Section III DSM-5 diagnostic system for personality disorders in an outpatient clinical sample. *Journal of Abnormal Psychology, 122*, 1057–1069.
- Friedman, J., Hastie, T., & Tibshirani, R. (2010). Regularization paths for generalized linear models via coordinate descent. *Journal of Statistical Software, 33*, 1–22.
- Gillespie, N. A., Aggen, S. H., Neale, M. C., Knudsen, G. P., Krueger, R. F., South, S. C., ... Reichborn-Kjennerud, T. (2017). *Associations between personality disorders and cannabis use and cannabis use disorder: A population-based twin study*. Manuscript submitted for publication.
- Grant, B. F., Hasin, D. S., Stinson, F. S., Dawson, D. A., Chou, S. P., Ruan, W. J., & Pickering, R. P. (2004). Prevalence, correlates, and disability of personality disorders in the United States: Results from the national epidemiologic survey on alcohol and related conditions. *Journal of Clinical Psychiatry, 65*, 948–958.
- Harris, J. R., Magnus, P., & Tambs, K. (2002). The Norwegian Institute of Public Health Twin Panel: A description of the sample and program of research. *Twin Research, 5*, 415–423.
- Hasin, D., Fenton, M. C., Skodol, A., Krueger, R., Keyes, K., Geier, T., ... Grant, B. (2011). Personality disorders and the 3-year course of alcohol, drug, and nicotine use disorders. *Archives of General Psychiatry, 68*, 1158–1167.
- Iacono, W. G., Malone, S. M., & McGue, M. (2003). Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude. *International Journal of Psychophysiology, 48*, 147–178.
- Karila, L., Petit, A., Lowenstein, W., & Reynaud, M. (2012). Diagnosis and consequences of cocaine addiction. *Current Medicinal Chemistry, 19*, 5612–5618.
- Kendler, K. S., Aggen, S. H., & Patrick, C. J. (2012). A multivariate twin study of the DSM-IV criteria for antisocial personality disorder. *Biological Psychiatry, 71*, 247–253.
- Kendler, K. S., Aggen, S. H., Czajkowski, N., Roysamb, E., Tambs, K., Torgersen, S., ... Reichborn-Kjennerud, T. (2008). The structure of genetic and environmental risk factors for DSM-IV personality disorders: A multivariate twin study. *Archives of General Psychiatry, 65*, 1438–1446.
- Kendler, K. S., Chen, X., Dick, D., Maes, H., Gillespie, N., Neale, M. C., & Riley, B. (2012). Recent advances in the genetic epidemiology and molecular genetics of substance use disorders. *Nature Neuroscience, 15*, 181–189.
- Kendler, K. S., Czajkowski, N., Tambs, K., Torgersen, S., Aggen, S. H., Neale, M. C., & Reichborn-Kjennerud, T. (2006). Dimensional representations of DSM-IV cluster A personality disorders in a population-based sample of Norwegian twins: A multivariate study. *Psychological Medicine, 36*, 1583–1591.
- Kendler, K. S., Myers, J., Torgersen, S., Neale, M. C., & Reichborn-Kjennerud, T. (2007). The heritability of cluster: A personality disorders assessed by both personal interview and questionnaire. *Psychological Medicine, 37*, 655–665.
- Krueger, R. F., Hicks, B. M., Patrick, C. J., Carlson, S. R., Iacono, W. G., & McGue, M. (2002). Etiologic connections among substance dependence, antisocial behavior, and personality: Modeling the externalizing spectrum. *Journal of Abnormal Psychology, 111*, 411–424.
- Lejuez, C. W., Magidson, J. F., Mitchell, S. H., Sinha, R., Stevens, M. C., & de Wit, H. (2010). Behavioral and biological indicators of impulsivity in the development of alcohol use, problems, and disorders. *Alcoholism: Clinical and Experimental Research, 34*, 1334–1345.
- Little, R. J., & Rubin, D. B. (1987). *Statistical analysis with missing data*. New York: Wiley & Sons.
- Livesley, W. J., Jang, K. L., Jackson, D. N., & Vernon, P. A. (1993). Genetic and environmental contributions to dimensions of personality disorder. *American Journal of Psychiatry, 150*, 1826–1831.
- Long, E. C., Aggen, S. H., Neale, M. C., Knudsen, G. P., Krueger, R. F., South, S. C., ... Reichborn-Kjennerud, T. (2017). The association between personality disorders with alcohol use and misuse: A population-based twin study. *Drug and Alcohol Dependence, 174*, 171–180.
- Lopez-Quintero, C., Perez de los Cobos, J., Hasin, D. S., Okuda, M., Wang, S., Grant, B. F., & Blanco, C. (2011). Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the national epidemiologic survey on alcohol and related conditions (NESARC). *Drug and Alcohol Dependence, 115*, 120–130.
- Markon, K. E., & Krueger, R. F. (2005). Categorical and continuous models of liability to externalizing disorders: A direct comparison in NESARC. *Archives of General Psychiatry, 62*, 1352–1359.
- Markon, K. E., Krueger, R. F., & Watson, D. (2005). Delineating the structure of normal and abnormal personality: An integrative hierarchical approach. *Journal of Personality and Social Psychology, 88*, 139–157.
- Narvaez, J. C., Jansen, K., Pinheiro, R. T., Kapczynski, F., Silva, R. A., Pechansky, F., & Magalhaes, P. V. (2014). Psychiatric and substance-use comorbidities associated with lifetime crack cocaine use in young adults in the general population. *Comprehensive Psychiatry, 55*, 1369–1376.
- National Drug Intelligence Center. (2011). *The economic impact of illicit drug use on American society*. Washington DC: United States Department of Justice.
- Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families* (1st ed.). Dordrecht: Kluwer Academic Publishers.
- Neale, M. C., Hunter, M. D., Pritikin, J. N., Zahery, M., Brick, T. R., Kirkpatrick, R. M., ... Boker, S. M. (2016). OpenMx 2.0: Extended structural equation and statistical modeling. *Psychometrika, 81*(2), 535–549.
- Peters, E. N., Schwartz, R. P., Wang, S., O'Grady, K. E., & Blanco, C. (2014). Psychiatric, psychosocial, and physical health correlates of co-occurring cannabis use disorders and nicotine dependence. *Drug and Alcohol Dependence, 134*, 228–234.
- Pfohl, B., Blum, N., & Zimmerman, M. (1995). *Structured interview for DSM-IV personality (SIDP-IV)*. Iowa City: University of Iowa, Department of Psychiatry.

- R Development Core Team. (2008). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from <http://www.r-project.org/>.
- Reichborn-Kjennerud, T., Czajkowski, N., Neale, M. C., Orstavik, R. E., Torgersen, S., Tambs, K., ... Kendler, K. S. (2007). Genetic and environmental influences on dimensional representations of DSM-IV cluster C personality disorders: A population-based multivariate twin study. *Psychological Medicine*, 37, 645–653.
- Reichborn-Kjennerud, T., Czajkowski, N., Ystrom, E., Orstavik, R., Aggen, S. H., Tambs, K., ... Kendler, K. S. (2015). A longitudinal twin study of borderline and antisocial personality disorder traits in early to middle adulthood. *Psychological Medicine*, 45(14), 3121–3131.
- Strickland, T. L., Miller, B. L., Kowell, A., & Stein, R. (1998). Neurobiology of cocaine-induced organic brain impairment: Contributions from functional neuroimaging. *Neuropsychology Review*, 8, 1–9.
- Substance Abuse and Mental Health Services Administration. (2014). Results from the 2013 national survey on drug use and health: Summary of national findings. Rockville, MD: NSDUH Series H-46, HHS Publication No. (SMA) 13–4795.
- Tambs, K., Ronning, T., Prescott, C. A., Kendler, K. S., Reichborn-Kjennerud, T., Torgersen, S., & Harris, J. R. (2009). The Norwegian Institute of Public Health Twin Study of Mental Health: Examining recruitment and attrition bias. *Twin Research and Human Genetics*, 12, 158–168.
- Tibshirani, R. (1996). Regression shrinkage and selection via the Lasso. *Journal of the Royal Statistical Society, Series B*, 58, 267–288.
- Torgersen, S., Czajkowski, N., Jacobson, K., Reichborn-Kjennerud, T., Roysamb, E., Neale, M. C., & Kendler, K. S. (2008). Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of Norwegian twins: A multivariate study. *Psychological Medicine*, 38, 1617–1625.
- Torgersen, S., Kringlen, E., & Cramer, V. (2001). The prevalence of personality disorders in a community sample. *Archives of General Psychiatry*, 58, 590–596.
- Torgersen, S., Myers, J., Reichborn-Kjennerud, T., Roysamb, E., Kubarych, T. S., & Kendler, K. S. (2012). The heritability of cluster B personality disorders assessed both by personal interview and questionnaire. *Journal of Personality Disorders*, 26, 848–866.
- Verdejo-Garcia, A., Lawrence, A. J., & Clark, L. (2008). Impulsivity as a vulnerability marker for substance-use disorders: Review of findings from high-risk research, problem gamblers and genetic association studies. *Neuroscience and Biobehavioral Reviews*, 32, 777–810.
- Whittingham, M. J., Stephens, P. A., Bradbury, R. B., & Freckleton, R. P. (2006). Why do we still use stepwise modelling in ecology and behaviour? *Journal of Animal Ecology*, 75, 1182–1189.
- Wittchen, H.-U., & Pfister, H. (1997). *DIA-X Interviews (M-CIDI): Manual fur screening-verfahren und interview*. Frankfurt, Germany: Swets & Zeitlinger.
- Wu, L. T., Gersing, K., Burchett, B., Woody, G. E., & Blazer, D. G. (2011). Substance use disorders and comorbid Axis I and II psychiatric disorders among young psychiatric patients: Findings from a large electronic health records database. *Journal of Psychiatric Research*, 45, 1453–1462.