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Caffeine Consumption, Toxicity, Tolerance and Withdrawal; Shared Genetic Influences With Normative Personality and Personality Disorder Traits

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Our main aim was to estimate the extent of overlapping etiology between caffeine consumption and response and normative and pathological personality. Linear mixed-effects models were used to identify normative personality domains and personality disorder (PD) traits for inclusion in multivariate twin analyses together with individual caffeine related measures. Data were obtained from Norwegian adult twins in a face-to-face interview conducted in 1999–2004 as part of a population-based study of mental health and through self-report in 2010–2011 and 2015–2017. Personality disorder data was available for

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All authors contributed significantly to the manuscript, and all authors have read and approved the final manuscript. Every measure included in the analyses, as well as all data exclusions are reported in the methods section. None of the authors have any conflicts of interest to declare. None of the ideas or any of the results on to the caffeine measures have previously been presented at conferences, websites, or other outlets. Results from analysis of the personality disorder data have been used in a number of previous publications, and results from analysis of several substance measures—among them nicotine, alcohol, and cannabis—have also been published. Caffeine consumption and response are heritable, and the present study provides evidence that a small to-modest proportion of this genetic etiology is shared with both normative and pathological personality.

Author Contributions: Nikolai Czajkowski served as lead for conceptualization, formal analysis, methodology, and writing–original draft and served in a supporting role for data curation. Kenneth S. Kendler served as lead for funding acquisition and project administration and served in a supporting role for conceptualization, data curation, and writing–review & editing. Fartein Ask Torvik served in a supporting role for methodology and writing–review & editing. Eivind Ystrom served in a supporting role for methodology and writing–review & editing. Tom Rosenström served in a supporting role for methodology and writing–review & editing. Nathan A. Gillespie served in a supporting role for methodology and writing–review & editing. Ted Reichborn-Kjennerud served as lead for data curation, funding acquisition, and project administration and served in a supporting role for writing–review & editing.

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2,793 twins, normative personality for 3,889 twins, and caffeine for 3,862 twins (mean age 43.0 years). Normative personality was assessed using the self-reported Big Five Inventory, PD traits were assessed by the Structured Interview for *DSM–IV* Personality, and caffeine consumption, toxicity, tolerance, and withdrawal were assessed through a self-report questionnaire developed at the Norwegian Institute of Public Health. Caffeine measures were found to be moderately heritable, h^2 = 30.1%-45.0%. All normative personality domains and four PD traits, antisocial, borderline, dependent and paranoid, were significantly associated with at least one caffeine variable. A small proportion of variance in caffeine consumption was attributable to genetic factors shared with normative personality (1.3%) and personality disorders (11.4%). A modest proportion of variance in caffeine tolerance and toxicity was attributable to genetic factors shared with both normative personality (26.9%, 24.8%) and personality disorders (21.0%, 36.0%). The present study found caffeine consumption and response to be heritable and provides evidence that a small to-modest proportion of this genetic etiology is shared with both normative and pathological personality.

Public Health Significance
Both the amount of caffeine people consume and their response to caffeine is heritable. A modest proportion of the genetic influences underlying caffeine use and response is shared with personality and personality disorder traits.

Keywords: caffeine, heritability, personality, personality disorder traits, twin

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Caffeine, a central nervous system stimulant naturally occurring in coffee, tea, and an additive in many soft drinks, is by far the most used psychoactive substance (James, 1997). More than 80% of people in the United States regularly drink coffee or tea (Mitchell, Knight, Hockenberry, Teplansky, & Hartman, 2014), and the effect of caffeine on mood, mental state, and behavior is well established. In low to moderate doses, caffeine is known to increase alertness, reduce fatigue, and improve vigilance (Smith, 2002). In higher doses, caffeine can result in toxic effects, with symptoms including nervousness, restlessness, insomnia, nausea, and anxiety (Daly & Fredholm, 1998).

There are modest phenotypic associations between caffeine use and certain normative personality traits, such as novelty seeking (Gurpegui et al., 2007) and sensation seeking (Jones & Lejuez, 2005). However, few studies have investigated the relationship between caffeine consumption and the five domains of the prevailing model of normative personality. According to the "Big Five" theory, the main features of normative personality can be summarized by scores on the five primary domains of extraversion, agreeableness, conscientiousness, neuroticism and openness to experience (McCrae & John, 1992). The lack of studies investigating the relationship between the Big Five domains and caffeine is in stark contrast to other psychoactive substances such as alcohol (Malouff, Thorsteinsson, Rooke, & Schutte, 2007), nicotine (Terracciano & Costa Jr, 2004), and cannabis (Fridberg, Vollmer, O'Donnell, & Skosnik, 2011). Furthermore, while the literature on Big Five and caffeine is scarce, hardly any studies have explored whether there is an association between caffeine and pathological personality. Of all the 10 personality disorders listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM; Association, 2000, 2013), association with caffeine has only been investigated for antisocial traits (Kendler, Myers, & Gardner, 2006); this despite evidence suggesting that caffeine intake is related to the risk of many clinical disorders, such as depression (Grosso, Micek, Castellano, Pajak, & Galvano, 2016), anxiety and panic disorders (Vilarim, Rocha Araujo, & Nardi, 2011), psychosis (Lara, 2010), eating disorders (Burgalassi et al., 2009), and the high levels of comorbidity known to exist between clinical disorders and personality disorders (Lenzenweger, Lane, Loranger, & Kessler, 2007). The lack of research on personality disorders and caffeine cannot be attributed a low likelihood of shared etiological influences. Indeed, our research group has previously found antisocial and borderline traits to be both phenotypically and etiologically associated with the use of other psychoactive substances, including alcohol (Rosenström et al., 2018), cannabis (Gillespie, Aggen, Neale, et al., 2018), and cocaine (Gillespie, Aggen, Gentry, et al., 2018).

Twin studies have found the heritable influences on caffeine intake to be in the range 30% to 60% (Yang, Palmer, & de Wit, 2010), with some evidence that the heritability of heavy use (daily consumption above 500 mg) might be as high as 77% (Kendler & Prescott, 1999). Symptoms of caffeine tolerance, toxicity, and withdrawal have been subject to less study in genetically informative samples, and the only twin study to investigate these phenotypes reported heritability estimates in the range 35% to 45% (Kendler & Prescott, 1999). Normative personality and personality disorders have also been shown to be influenced by genetic factors, with genetic influences accounting for approximately 40% to 60% of individual differences across the Big 5 domains (Bouchard & McGue, 2003; Vukasović & Bratko, 2015). The heritability of personality disorders as defined by the DSM criteria are similar in magnitude to normative personality (Livesley & Jang, 2008; Reichborn-Kjennerud, 2010).

While the literature suggests that familial factors predispose to caffeine intake, the extent to which genetic and environmental influences are shared with both normative and disordered personality is largely unexplored. To the extent that the same personality domains, both normative and pathological, are associated with caffeine use as with other substances, genetically informative studies can provide insight into the mechanisms of the association. If the association is largely genetic, it could inform future genetic

association studies or alternatively motivate the search for mediating environmental factors.

In this paper we present results from analyses of several caffeine related measures collected from a large cohort of Norwegian twins. Our first aim is to estimate the heritability of caffeine consumption, tolerance, toxicity, and withdrawal. Our second aim is to determine whether any domains of normative personality or personality disorder traits are associated with these caffeine measures and to what extent this association is attributable to shared or distinct etiological factors.

Method

Participants

Data for the study were provided by twins recruited from the population-based Norwegian Twin Registry. The Norwegian Institute of Public Health self-report questionnaire (NIPH-SR) was distributed to $N = 6{,}308$ eligible twins in the period from November 2015 to June of 2017. The invited twins consisted of two subsets. The first set of twins had previously participated in two waves of psychiatric interviews (the first 2001–2004 and the second 2010–2011), hereafter referred to as the AIAII study and the AIAII-follow up study respectively. From the first subsample, valid responses were gathered from $N = 1{,}916$ twins (mean (*SD*) age = 43.1 (3.8), range = 36–50). From the second group of twins, who had agreed to be registered in the official Norway twin registry and were participating for the first time, responses were returned from $N = 1{,}946$ individuals (age = 42.9 (3.7) range = 36–49). In total, caffeine measures were available from $N = 3{,}862$ twins. The study was approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics, and written informed consent was obtained from all participants.

Questionnaire and Interview Data

The following caffeine related measures were included in the NIPH-SR. Current caffeine use was assessed by the question: "During the past year, how many cups of coffee/tea or bottles/cans (0.33–0.5litres) of caffeinated beverages did you usually drink per day?"

Heavy use was defined as consuming five or more caffeinated beverages per day, corresponding approximately to a daily consumption of caffeine greater than 500 mg. Five cups of coffee has been used as a threshold for heavy caffeine use in previous twin studies (Kendler et al., 2006). Caffeine tolerance was indicated by an affirmative response to either of the following two questions: (a) "When you drank caffeinated beverages the most, did you need to drink significantly more caffeinated beverages in this period than you did when you first drank in order to get the desired effect?", or (b) "When you drank these in the same amounts as previously, did you experience less effect?" Caffeine toxicity was defined as an affirmative response to the question; "Did you ever feel unwell, shaky or restless after having drunk caffeinated beverages?" Finally, caffeine withdrawal was indicated with a positive response to either of the two questions (a) "Some people suffer from withdrawal symptoms when they reduce their intake of caffeinated beverages. Did you have headaches when you cut out/reduced your intake of caffeinated drinks?" or (b) "Did you experience nausea and/or vomiting when you stopped/cut down on your intake of caffeinated drinks?"

Normative personality was assessed using the Big Five Inventory (BFI; John & Srivastava, 1999), a self-report instrument consisting of 44 items each scored on a 5-point scale. Extraversion is represented by eight items ($\alpha = .86$), agreeableness by nine items ($\alpha = .72$), conscientiousness by nine items ($\alpha = .75$), neuroticism by eight items ($\alpha = .84$), and openness by 10 items ($\alpha = .78$). The responses to the BFI items were summed for each of the five domains, resulting in variables that were approximately normally distributed, and in all subsequent analyses, personality variables were treated as continuous. Twins who participated in the AIAII study completed the BFI instrument at wave 2, while twins who did not participate in AIAII received a longer version of the NIPH-SR that also included the BFI instrument. Complete BFI data was available on 3,889 twins.

At wave 1 in the AIAII study, all 10 *DSM–IV* personality disorders were assessed using the comprehensive Structured Interview for *DSM–IV* Personality (SIDP-IV; Pfohl, Blum, & Zimmerman, 1997). 2,793 twins had valid data for *DSM–IV* personality disorders. The endorsement rates for the individual personality disorder criteria were too low for twin models to be fitted to DSM-derived categorical personality disorder diagnostic status. In the twin models, we therefore analyzed the counts of personality disorder criteria endorsed either at the clinical or subclinical level (SIDP score >0). Finally, to ensure that model estimation was not adversely affected by empty cells in the twin contingency tables, symptom counts above 3 for each of the personality disorder variables were collapsed. The final measure for each personality disorder trait was thus an ordinal variable ranging from 0 to 3.

All but 231 (8.3%) of the SIDP interviews were conducted face-to-face, and the remainder were conducted by telephone. Interviewers were mainly senior clinical psychology graduate students or experienced psychiatric nurses, although some were clinical psychologists. Each twin in a pair was interviewed by a different interviewer.

Statistical Analyses

We assessed the phenotypic association between caffeine consumption and normative personality and personality disorder traits by calculating the Pearson correlation coefficient or the polyserial/polychoric correlations when one or both variable was ordinal or binary. Polyserial and polychoric correlations are less prone than Pearson correlations to bias the association between variables when one of them has few response categories (Olsson, Drasgow, & Dorans, 1982).

Univariate twin models were fitted to each individual caffeine phenotype. These models permit the variance of an observed measure to be partitioned into proportions attributable to three separate sources. Additive genetic influences (A) can be inferred when the correlation between monozygotic twins is twice as large as the correlation between dizygotic twins. The proportion of the total variance of the trait that can be attributed additive genetic influences is referred to as the heritability of the trait. The influence of shared environmental effects (C) can be inferred when the correlation between dizygotic twins is more than half that of monozygotic twins. Any remaining variance in the phenotypes that

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cannot be accounted for by A or C is attributed to unique environmental influences (E). The E factor thus represent the sum of influences that make individuals within both monozygotic and dizygotic twin pairs dissimilar, and this includes measurement error. When all three sources of variance are present in the model, it is referred to as an ACE model.

We then investigated the extent of genetic and environmental overlap between each caffeine measure and personality. This was done separately for normative personality and personality disorders. Shared etiology was investigated by fitting a series of multivariate Cholesky models (Neale & Cardon, 1992). See Figure 1 for an illustration of the structure of the Cholesky decomposition. Since multivariate twin modeling on ordinal variables can be extremely computationally demanding as the number of variables increases, we limited the number of personality variables included in the twin models only to those that were found to be significantly associated with at least one caffeine measure. This subset was determined through a series of initial multiple mixed (multilevel) models, a class of models well suited when observations are not independent (Hox, 1998), as is the case for individual twins within a pair.

The five caffeine measures were used as dependent variables in five separate mixed models. In all models, age and sex were included as control variables. If not controlled for, age and sex could bias the estimates of the genetic variance shared between personality and caffeine. There are strong sex differences in the prevalence of personality disorders (Paris, 2004) and patterns of normative personality (Schmitt, Realo, Voracek, & Allik, 2008). Furthermore, both the amount of caffeine consumed and the response to caffeine consumption are associated with sex (Nehlig, 2018). A similar argument, though perhaps for somewhat weaker associations, can be made for age (McCrae et al., 1999; Nehlig, 2018). Nonindependence caused by within twin-pair similarity was handled by the inclusion of a twin-pair specific random intercept.

Analogous to the way in which the variance in a phenotype can be partitioned into A, C, and E, multivariate Cholesky twin models allow the covariance between variables to be partitioned into the same sources. This decomposition, in turn, can be used to calculate the genetic and environmental correlation between any two variables in the model. Note that there can be significant genetic correlations despite lack of phenotypic correlations when environmental correlations work to cancel the phenotypic one, and vice versa.

Because of the large number of twin pairs required to estimate sex-specific effects, path coefficients were constrained to be equal across sex, but separate thresholds and means were estimated for male twins and female twins to account for mean-level sex differences.

All statistical analyses were performed in R, Version 3.6.1 (Team, 2019). We fitted the mixed models using the mle4 package (Bates, Maechler, Bolker, & Walker, 2014), and twin models using the R-based OpenMx structural equation modeling package (Neale et al., 2016). Model parameters in the twin analyses were estimated by means of full information maximum likelihood, an approach that makes use of all observed data. Competing twin models were compared using Akaike's information criterion (AIC), a fit statistic that jointly expresses the parsimony and explanatory power of a model (Akaike, 1987).

Results

Descriptive Results

Altogether 93.5% of participants reported drinking caffeinated beverages such as coffee, tea, Coca Cola or Pepsi Max, either every day or several times a week. The average number of beverages consumed daily was 3.4 (sd = 2.0), with males reporting higher levels than females (3.7 vs. 3.1). Individuals who reported

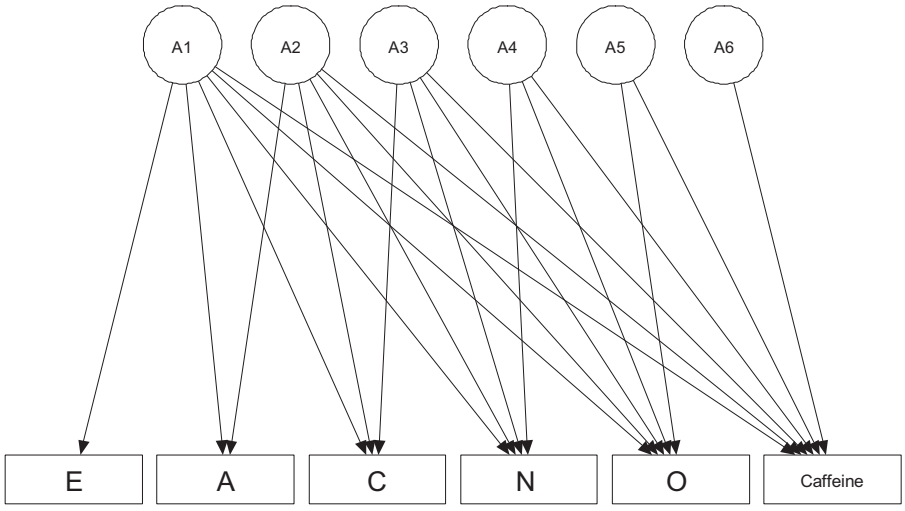

Figure 1. The latent variables (circles) in the Cholesky model represent the additive genetic effects influencing scores on the Big 5 personality domains (extraversion (E), agreeableness (A), conscientiousness (C), neuroticism (*N*) and openness to experience (O)) and caffeine use. The first genetic factor (A1) is shared by all six variables, the second (A2) is shared by the rightmost five, and so on. The genetic influence represented by A6 is unique to caffeine, and the variance in caffeine it causes is not shared with normative personality.

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Table 1
Results From Univariate Twin Models

Caffeine measure	Twin correlations[a]		Univariate model fit (AIC)[b]			Univariate model estimates[c]		
	Correlation MZ pairs (95% CI)[a]	Correlation DZ pairs (95% CI)[a]	ACE	AE	CE	A	C	E
Daily consumption	.46 (.39, .52)	.19 (.10, .27)	8134.675	**8132.675**	8160.523	45 (.33, .51)	.00 (.00, .09)	.55 (.49, .61)
Heavy consumption	.43 (.29, .56)	.15 (.00, .30)	−3440.395	**-3442.491**	−3436.055	.41 (.12, .53)	.00 (.00, .22)	.59 (.47, .72)
Toxicity	.45 (.32, .57)	.24 (.10, .38)	−2785.095	**-2787.075**	−2782.287	.42 (.04, .57)	.03 (.00, .33)	.55 (.43, .68)
Withdrawal	.31 (.07, .52)	.13 (-.08, .32)	−4592.862	**-4594.862**	−4593.548	.30 (.00, .49)	.00 (.00, .32)	.70 (.52, .92)
Tolerance	.34 (.06, .58)	.01 (-.21, .24)	−4897.136	**-4899.136**	−4897.303	.26 (.00, .48)	.00 (.00, .27)	.74 (.52, 1.00)

[a] Pearson correlation is reported for "daily consumption", polychoric correlation is reported for the remaining four caffeine measures. [b] Akaike information criteria for univariate ACE, AE, and CE twin models, with the best fitting model indicated in bold. [c] Parameter estimates from the full univariate ace model.

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drinking at least 5 units per day were classified as heavy users, a subgroup that constituted 24.7% of the sample ($N = 937$). Furthermore, 10.3% ($N = 396$) met the criteria for caffeine tolerance, 32.3% ($N = 1,196$) for toxicity and 12.8% ($N = 473$) for withdrawal.

Univariate Analyses of Caffeine

Results from univariate twin models on the caffeine variables are given in Table 1. Twin correlations for the caffeine measures were substantial, and the pattern was suggestive of a largely genetic etiology, with MZ correlations being approximately twice as large as DZ correlations. In line with this, according to AIC, the AE model, with shared environmental effects set to zero, was the best fitting for all five caffeine related measures. The highest heritabilities were observed for daily use ($h^2 = 0.45$, 95% CI [0.33, 0.51]), heavy use ($h^2 = 0.41$, 95% CI [0.12, 0.53]), and toxicity ($h^2 = 0.42$, 95% CI [0.04, 0.57]). Marginally lower additive genetic influence were observed for withdrawal ($h^2 = 0.31$, 95% CI [0.00, 0.49]) and tolerance ($h^2 = 0.34$, 95% CI [0.00, 0.48]).

Mixed Models

Results from the mixed models for normative personality and personality disorder traits are given Table 2 and Table 3 respectively. All Big Five domains were significantly associated with at least one caffeine measures, and all were therefore included in the subsequent Cholesky twin models. We observed modest associations between normative personality and daily caffeine use, while associations were more pronounced for tolerance and withdrawal.

Four personality disorder traits were significantly associated with at least one caffeine variable in the multiple mixed models; antisocial, borderline, dependent, and paranoid. While only a single PD trait was significant in most models on the caffeine measures, after controlling for sex and age, toxicity was significantly associated with three (paranoid, antisocial, and borderline).

Multivariate Twin Analyses

As a result of the personality domains found to be significant in the multilevel models, six-variate Cholesky models were run for the Big Five domains and five-variate models for the personality disorder traits. As no shared environmental effects were implicated in the univariate analyses on caffeine, and since none was reported in previous publications on normative personality and personality disorder traits, only AE versions of the multivariate twin models were run. Table 4 and 5 list the phenotypic, genetic, and environmental correlation between normative and disordered personality, and the caffeine measures, as well as the proportion of genetic variance shared with personality. Across the different caffeine measures, more of the variance was accounted for by personality disorder measures than normative personality. For both normative and disordered personality, the least amount of genetic overlap was observed with daily caffeine consumption. Both normative personality and personality disorder traits shared a substantial proportion of genetic variance with caffeine tolerance and toxicity. The estimates of genetic liability for caffeine were largely identical in the univariate and multivariate models,

Table 2
Estimates From Linear Mixed Models With Big Five Personality Domains as Independent Variables

Normative personality trait	Daily cups[a]	Heavy use[b]	Tolerance[b]	Toxicity[b]	Withdrawal[b]
Extraversion	**0.03 (0.01, 0.04)**	**1.03 (1.01, 1.05)**	**1.22 (1.11, 1.33)**	1.00 (0.98, 1.02)	**1.09 (1.08, 1.10)**
Agreeableness	0.00 (−0.02, 0.02)	0.99 (0.96, 1.01)	1.06 (0.95, 1.18)	1.01 (0.98, 1.03)	**0.94 (0.93, 0.94)**
Conscientiousness	**−0.03 (−0.04, −0.01)**	0.99 (0.97, 1.01)	**0.82 (0.74, 0.91)**	**0.97 (0.95, 1.00)**	**0.80 (0.79, 0.80)**
Neuroticism	**0.01 (0.00, 0.03)**	1.01 (0.99, 1.03)	**1.19 (1.09, 1.31)**	**1.08 (1.06, 1.10)**	**1.08 (1.07, 1.10)**
Openness	−0.01 (−0.02, 0.00)	0.99 (0.97, 1.00)	0.99 (0.91, 1.07)	**1.07 (1.05, 1.09)**	**0.85 (0.85, 0.86)**

Note. Coefficients with associated p values less than 0.05 are marked in bold. All estimates are controlled for age and sex.
[a] Beta coefficients. [b] Odds-ratios, and their associated 95% confidence intervals from linear mixed models with normative personality domains as independent variables.

Table 3
Estimates From Linear Mixed Models With Personality Disorder Traits as Independent Variables

Personality disorder trait	Daily cups[a]	Heavy use[b]	Tolerance[b]	Toxicity[b]	Withdrawal[b]
Paranoid	0.00 (−0.12, 0.11)	1.08 (0.92, 1.28)	0.96 (0.78, 1.17)	**1.16 (1.00, 1.34)**	**1.39 (1.10, 1.76)**
Schizoid	0.00 (−0.15, 0.15)	1.01 (0.81, 1.24)	1.20 (0.94, 1.53)	1.14 (0.95, 1.38)	1.10 (0.81, 1.48)
Schizotypal	−0.02 (−0.17, 0.14)	0.96 (0.77, 1.20)	1.01 (0.78, 1.32)	1.03 (0.85, 1.26)	0.85 (0.61, 1.17)
Antisocial	**0.17 (0.04, 0.30)**	1.12 (0.94, 1.34)	0.99 (0.80, 1.22)	**1.24 (1.05, 1.45)**	1.12 (0.87, 1.45)
Borderline	0.04 (−0.06, 0.15)	1.05 (0.91, 1.23)	**1.48 (1.23, 1.78)**	**1.25 (1.09, 1.43)**	1.17 (0.94, 1.45)
Histrionic	0.02 (−0.08, 0.12)	0.95 (0.82, 1.09)	0.91 (0.76, 1.09)	1.04 (0.92, 1.19)	1.00 (0.82, 1.22)
Narcissistic	−0.05 (−0.16, 0.05)	1.02 (0.88, 1.19)	1.06 (0.88, 1.27)	1.01 (0.88, 1.15)	0.91 (0.73, 1.13)
Avoidant	0.05 (−0.05, 0.14)	1.04 (0.90, 1.20)	1.02 (0.85, 1.21)	1.04 (0.92, 1.19)	0.83 (0.67, 1.03)
Dependent	−0.02 (−0.13, 0.09)	**0.84 (0.71, 0.99)**	0.91 (0.74, 1.11)	0.87 (0.75, 1.01)	0.85 (0.67, 1.07)
Obsessive	0.00 (−0.09, 0.08)	1.10 (0.98, 1.25)	1.05 (0.90, 1.23)	0.99 (0.89, 1.11)	1.02 (0.85, 1.21)

Note. All estimates are controlled for age and sex. Coefficients with associated *p* values less than 0.05 are marked in bold.
[a] Beta coefficients. [b] Odds-ratios, and their associated 95% confidence intervals from linear mixed models with personality disorder traits as independent variables.

though marginally higher values estimated for tolerance and toxicity in the multivariate analyses.

Discussion

To our knowledge, this is the first study to investigate to what extent genetic factors can explain the association between caffeine use, tolerance, toxicity and withdrawal, and personality. The five caffeine related measures were found to be moderately heritable, with 26–45% of individual differences attributable to additive genetic influences. Genetic influences underlying daily caffeine use were only weakly shared with normative personality and personality disorders. Conversely, tolerance and toxicity were moderately shared with both normative personality and personality disorder traits. Higher levels of conscientiousness was associated with significantly lower consumption of caffeine, which in turn may account for the reduced levels of tolerance and withdrawal also observed in the linear mixed analyses. The observation that there are both negative genetic and environmental correlations between conscientiousness and caffeine tolerance and withdrawal is also consistent with a causal negative effect of conscientiousness.

Our estimate of the heritability of daily caffeine use (0.45), as measured by the number of caffeinated beverages consumed daily, is squarely in line with results from previous studies. Carmelli, Swan, Robinette, and Fabsitz (1990) found the heritability to be 0.36 in a sample of 4,960 adult twins, though prior to adjusting for occupation and socioeconomic status, their estimates were also 0.45. Two studies have reported heritability estimates for heavy use of caffeine, and both placed the estimates in the upper range of what has been reported for regular use. Kendler and Prescott (1999) found a heritability of 0.77 in a sample of 1,934 twins, using a strict criteria of daily caffeine intake above 625 mg. Swan, Carmelli, and Cardon (1997), based on identical operationalization of "heavy use" as in the present study (500 mg), placed the value at 0.51 in a sample of 4,593 twins.

Like Kendler and Prescott, we also found toxicity to be more heritable than tolerance and withdrawal (Kendler & Prescott, 1999). While their estimates for withdrawal were similar to ours, we observed a somewhat lower heritability for tolerance, although it should be noted that the confidence intervals are largely overlapping.

In our sample, three of the Big Five personality domains were significantly related to daily caffeine intake, but the association was weak and accounted only for 1.3% the genetic variance. Extraversion was found to have the largest genetic correlation with caffeine use. We believe a reasonable interpretation of this can be that extraversion contains the lower level facet of excitement-seeking, a trait found in previous studies to be phenotypically

Table 4
Phenotypic Correlations (rP), Genetic Correlations (rA) and Unique Environmental Correlations (rE) Between Normative Personality and Caffeine Measures

Normative personality trait/genetic variance	Daily cups			Heavy use (>5 units)			Tolerance			Toxicity			Withdrawal		
	rP	rA	rE	rP	rA	rE	rP	rA	rE	rP	rA	rE	rP	rA	rE
Extraversion	0.03	0.09	−0.04	0.04	0.10	−0.01	−0.03	−0.05	−0.03	−0.05	−0.03	−0.08	−0.04	−0.12	−0.01
Agreeableness	−0.04	−0.02	−0.02	−0.07	−0.10	0.01	−0.11	0.07	−0.16	−0.07	−0.11	−0.06	−0.08	0.02	−0.15
Conscientiousness	−0.08	−0.01	−0.08	−0.07	−0.01	−0.04	−0.17	−0.09	−0.20	−0.13	−0.23	−0.05	−0.11	−0.13	−0.14
Neuroticism	0.00	−0.06	0.09	−0.03	−0.02	0.02	0.17	0.34	0.13	0.22	0.36	0.11	0.18	0.18	0.15
Openness	0.00	0.03	−0.08	−0.01	0.02	−0.08	0.09	0.25	−0.01	0.19	0.31	0.06	0.04	0.05	0.04
%Shared[a]	1.3 (0.0, 5.6)			2.8 (0.0, 15.0)			26.9 (13.4, 41.4)			24.8 (13.5, 41.2)			6.0 (0.0, 34.8)		
%Unique[b]	98.7 (94.4, 100)			97.2 (85.0, 100)			73.1 (58.6, 86.6)			75.2 (58.8, 86.5)			94.0 (65.2, 100.0)		
% of total var[c]	45.0			40.8			30.1			47.0			30.5		

[a] Percentage of genetic variance in caffeine shared with normative personality. [b] Percentage of genetic variance in caffeine measures not shared with normative personality. [c] Proportion of total variance in respective caffeine measures that is attributable to additive genetic influences.

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Table 5
Phenotypic Correlations (rP), Genetic Correlations (rA,) and Unique Environmental Correlations (rE) Between Personality Disorder Traits and Caffeine Measures

Personality disorder trait/genetic variance	Daily cups			Heavy use (>5 units)			Tolerance			Toxicity			Withdrawal		
	rP	rA	rE	rP	rA	rE	rP	rA	rE	rP	rA	rE	rP	rA	rE
Antisocial	0.12	0.24	0.04	0.14	0.07	0.10	0.12	0.18	0.07	0.21	0.49	0.02	0.07	0.18	0.08
Borderline	0.05	0.32	−0.05	0.03	0.11	0.02	0.22	0.27	0.22	0.23	0.58	0.00	0.11	0.08	0.15
Dependent	−0.01	0.04	0.07	−0.04	−0.33	0.13	0.04	0.40	−0.08	0.07	0.17	0.03	0.02	−0.05	0.05
Paranoid	0.02	0.22	−0.02	0.09	0.16	−0.02	0.09	−0.17	0.14	0.09	0.36	0.09	0.06	0.18	0.11
%Shared[a]	11.4 (0.00, 23.2)			27.2 (8.1, 43.6)			21.0 (2.0, 40.4)			36.0 (11.8, 60.7)			11.4 (0.0, 60.6)		
%Unique[b]	88.6 (76.8, 100.0)			72.8 (56.4, 91.2)			79.0 (59.6, 98.0)			64.0 (39.3, 88.2)			88.6 (39.4, 100.0)		
% of total var[c]	46.0			40.9			28.0			47.3			30.0		

[a] Percentage of genetic variance in caffeine shared with personality disorder traits. [b] Percentage of genetic variance in caffeine measures not shared with personality disorder traits. [c] Proportion of total variance in respective caffeine measures that is attributable to additive genetic influences.

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related to caffeine use (Jones & Lejuez, 2005). Also for heavy use, the highest genetic correlation was with extraversion. The pattern of genetic correlation was noticeably different for tolerance, toxicity and withdrawal. For all these phenotypes, genetic correlation was highest for neuroticism, and in particularly tolerance and toxicity was found to share etiological factors with normative personality.

The proportion of genetic variance shared with personality disorder traits was higher than for normative personality for all but one caffeine related outcome—tolerance. Two of the PD traits here linked to caffeine, antisocial and borderline, have in previous papers been found to be both phenotypically and etiologically associated with the use of other psychoactive substances, including alcohol (Rosenström et al., 2018), cannabis (Gillespie, Aggen, Neale, et al., 2018), and cocaine (Gillespie, Aggen, Gentry, et al., 2018). Antisocial traits have also been implicated in a cotwin control study (Kendler et al., 2006), where caffeine-associated toxicity and dependence were found to be moderately associated with risk for a wide range of psychiatric and substance use disorders. These results raise the question of whether individuals with antisocial and borderline liability are likely to consume more caffeine and in turn experience more of the adverse effects, or whether they are through their disposition more sensitive to the effects of caffeine or caffeine toxicity and tolerance. Teasing these directions apart would be a valuable contribution of future studies.

Caffeine is the overwhelmingly most used psychoactive substance, and understanding the etiological mechanisms is interesting in its own right. However, we believe that caffeine may also serve as a model for the study of associations between personality and psychoactive substances not influenced by social or societal sanctions. Therefore, while our results pertain to caffeine, we believe they may have implications for research on psychoactive substances in general, and potentially stimulants in particular.

The interpretation of results presented in this study should be considered in the light of several possible limitations. First, due to the low prevalence of endorsed criteria, we were unable to analyze categorical personality disorder diagnoses. In previous publications we have examined whether the personality disorder criterion count variables are in accordance with an underlying continuous liability to increasing levels of endorsements of the personality disorder criteria and found this assumption to be satisfied empirically (Reichborn-Kjennerud et al., 2007). Second, the sample consists of Norwegian twins in a fairly limited age range of adulthood, and the results may therefore not generalize to other populations. Third, more than a decade separates the measurement of the personality disorder traits and caffeine. Also, while normative personality was measured concurrently with report on caffeine for a subset of the twins (N = 1946), the remaining participants (N = 1916) completed the BFI instrument approximately 6 years before the NIPH-SR questionnaire. It is possible that the presence of age specific genetic influences may have attenuated our estimates of the shared etiology between phenotypes assessed at different times. A further limitation follows from only including those personality disorder traits in the twin models that were significantly associated with caffeine in the preliminary mixed models. While this was necessary in order to make the twin models computationally tractable, the approach can potentially lead to an overestimation of the genetic correlations between caffeine and the included subset of personality disorder traits. However, we believe this risk is modest, as the excluded traits were not significantly associated with caffeine. A final limitation concerns the lack of more explicit modeling of sex-differences. Sex-limited twin models of ordinal data require very large samples to attain sufficient power. However, previous twin studies have failed to find either quantitative or qualitative gender differences for *DSM–IV* personality disorders and personality traits (Reichborn-Kjennerud, 2008; Vukasović & Bratko, 2015).

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