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A population-based Swedish Twin and Sibling Study of cannabis, stimulant and sedative abuse in men

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Abstract

Background—Prior studies, utilizing interview-based assessments, suggest that most of the genetic risk factors for drug abuse (DA) are non-specific with a minority acting specifically on risk for abuse of particular psychoactive substance classes. We seek to replicate these findings using objective national registry data.

Methods—We examined abuse of cannabis, stimulants (including cocaine) and sedatives ascertained from national Swedish registers in male–male monozygotic (1720 pairs) and dizygotic twins (1219 pairs) combined with near-age full siblings (76,457 pairs) to provide sufficient power. Modeling was performed using Mx.

Results—A common pathway model fitted better than an independent pathway model. The latent liability to DA was highly heritable but also influenced by shared environment. Cannabis, stimulant and sedative abuse all loaded strongly on the common factor. Estimates for the total heritability for the three forms of substance abuse ranged from 64 to 70%. Between 75 and 90% of

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Contributors

Drs. Kendler and Ohlsson designed the study. Drs. Jan and Kristina Sundquist advised on the background to the study and were responsible for the assembly of analyzed data sets. Dr. Ohlsson analyzed the data. Dr. Kendler conducted the background literature search. Drs. Kendler and Ohlsson wrote the initial draft of the manuscript. All authors contributed to the revisions of the manuscript.

Conflict of interest

No conflict declared.

that genetic risk was non-specific, coming from the common factor with the remainder deriving from substance specific genetic risk factors. By contrast, all of the shared environmental effects, which accounted for 18–20% of the variance in liability, were non-specific.

Conclusions—In accord with prior studies based on personal interviews, the large preponderance of genetic risk factors for abuse of specific classes of psychoactive substance are non-specific. These results suggest that genetic variation in the primary sites of action of the psychoactive drugs, which differ widely across most drug classes, play a minor role in human individual differences in risk for DA.

Keywords

Genetics; Drug abuse; Cannabis; Stimulants; Sedatives; Twins

1. Introduction

Drug abuse (DA), a major worldwide public health problem (World Health Organization, 2010), is a highly familial syndrome (Bierut et al., 1998; Merikangas et al., 1998). Therefore, an important research goal has been to understand the nature of these familial risks. Prior twin and adoption studies have consistently shown a substantial etiologic role for genetic factors in the etiology of DA (Kendler et al., 2000, 2012, 2013a; Kendler and Prescott, 1998; Lynskey et al., 2002; Tsuang et al., 1996; van den Bree et al., 1998).

Because drug abusers consume a wide variety of psychoactive substances with substantially different pharmacological properties involving distinct molecular targets in the brain (Koob and Le Moal, 2006), it is of substantial interest to determine the degree to which genetic and environmental risk factors for these substances are specific to individual pharmacological classes or non-specific in predisposing to dependence on a range of psychoactive drugs (Goldman and Bergen, 1998; Tsuang et al., 1998).

Two large population-based twin studies have explored this question for illicit psychoactive substances (Kendler et al., 2003; Tsuang et al., 1998). Tsuang et al. (1998) examined the abuse of 5 classes of illicit drugs (marijuana, sedatives, stimulants, heroin or opiates, and psychedelics) in 3372 male twin pairs from the Vietnam Era register. They found that most genetic and environmental risk factors were shared amongst these substances, although modest amounts of drug specific genetic and environmental influences were also seen (Tsuang et al., 1998). Kendler et al. (2003) examined the abuse or dependence of six illicit psychoactive drug classes (cannabis, sedatives, stimulants, cocaine, opiates, and hallucinogens) in 1196 male–male twin pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD). They found that all the genetic influences on abuse/dependence of these six substance classes were non-specific and shared across substances. In a subsequent confirmatory analysis of abuse/dependence of cannabis, cocaine, alcohol, nicotine, and caffeine in both the male and female twins from VATSPSUD, Kendler et al. (2007) found evidence for highly correlated but separable licit and illicit common factors with modest degrees of substance specific genetic influences.

All these studies required that subjects agree to participate in surveys and relied on their ability to accurately recall and report their drug abuse, an illegal behavior. In this study, we examine official criminal and medical records on cannabis, stimulant (including cocaine) and sedative abuse in twins and full siblings in a Swedish nationwide male sample. We fit multivariate models that permit us to determine the degree to which genetic and environmental risk factors are shared versus specific across abuse of these three major classes of psychoactive substances.

2. Methods

Our study used linked data from multiple Swedish nationwide registries and healthcare data. Linking was achieved via the unique individual Swedish 10-digit personal ID number assigned at birth or immigration to all Swedish residents. Our databases utilized the following registers: the Multi-Generation Registry, providing information on family relations; the Swedish Twin Registry, providing self-reported measures of zygosity validated against biological markers that enable us to differentiate monozygotic and dizygotic twins with 95–99% accuracy (Lichtenstein et al., 2002); the total population registry and the population and housing censuses providing individual household data (individuals sharing the same dwelling are assigned a unique number).

Cannabis, stimulant (including cocaine) and sedative abuse was identified from the Mortality registry, providing cause and contributory cause(s) of death; the Swedish hospital discharge registry, providing all inpatient hospitalizations; and the outpatient hospital care registry, providing all consultations/diagnoses at all Swedish hospitals. Cannabis abuse was defined by ICD10 code F12 (excluding F12.5 and F12.7) and ICD9 codes 3052, 3043. Stimulant abuse was defined by ICD10 codes F14, F15 and ICD9 codes 3056, 3042, 3057, 3044. Sedative abuse was defined by ICD10 code F13 and ICD9 codes 3054, 3041. We also employed the Swedish Crime Registry that includes national data on all convictions, using references to laws covering narcotics (law 1968:64, paragraph 1, point 6) and drug-related driving offences (law 1951:649, paragraph 4, subsection 2 and paragraph 4A, subsection 2). Within those laws cannabis was defined by code 8; stimulant by codes 1, 2, 3, 4, 5, 6, 7; and sedatives by codes 17, 19.

Cannabis, stimulant and sedative abuse were identified for each individual from their 15th birthday until year 2010 (except from the outpatient hospital care registry where we only had information from 2001 to 2010). Thus, those born at the beginning of our cohort (i.e., 1970) were followed until age 40 while those that are born at the end of our cohort (i.e., 1990) were only followed until age 20.

2.1. Sample

Within the population of male individuals born in Sweden between 1970 and 1990 (N = 1270,557) and residing in Sweden at age 15, we identified all MZ (N = 1753) and DZ (N = 1263) twin pairs from the Swedish Twin Registry, and from the Multi-Generation Registry all full sibling pairs (all twin pairs are excluded) with a maximum age difference of 2 years (N = 79,208). Furthermore, we required that the twins/siblings within a pair resided together at least 80% of the time until they turned 18. 33 MZ pairs, 44 DZ pairs and 2751 full sibling

pairs were excluded due to this restriction. In total we investigated 1720 MZ twin pairs, 1219 DZ twin pairs and 76,457 full sibling pairs.

2.2. Statistical analysis

Our model divides the sources of individual differences in liability to three forms of DA into additive genetic (A), shared environment (C), and unique environment (E). The model assumes that MZ twins share all their genes while DZ twins and full siblings share on average half of their genes identical by descent, and that the shared environment, reflecting family and community experiences, is the same within each twin/sibling pair. Unique environment includes random developmental effects, environmental experiences not shared by siblings, and random error. The aim of the models was to investigate to what extent genetic and environmental factors are the same for the three phenotypes. In the first model, an independent pathway model, we assume that each of the three variance components (A, C and E) consists of two parts: one that is common to all three phenotypes (denoted A_c, C_c, and E_c) and one that is specific to each one of them (A_s, C_s, and E_s). In the second model, a common pathway model, we assume that the common variance components (A_c, C_c, and E_c) are mediated by a latent phenotype represented by a common factor (called “vulnerability to drug abuse” in Fig. 1). The common pathway model is nested within the independent pathway model. This latent phenotype mediates the common genetic and environmental effects, as the paths from A_c, C_c, and E_c run via the latent phenotype. Although our sample size is considerable, the models include relatively rare phenotypes and have limited statistical power. We therefore follow the recommendations based on simulations which show that in such situations, parameter estimates from the full model are typically more accurate than those from submodels even if the latter provide a better model fit (Sullivan and Eaves, 2002). Models were fit in the OpenMx software (Boker et al., 2011).

3. Results

3.1. Descriptive findings

The prevalence of registration for cannabis, stimulant and sedative abuse in our entire sample of Swedish males born 1970–1990 (N = 1270,557), and in members of MZ and DZ twins, and near-age siblings are seen in Table 1. Cannabis abuse was most common followed by stimulant abuse and sedative abuse. The prevalences of all three of these forms of drug abuse were considerably lower in the two twin groups than in the general population or siblings, likely because the twins were screened for cooperativeness in having to return questionnaires about zygosity.

The tetrachoric correlations between and within relative pairs for the three forms of drug abuse in MZ twins, DZ twins and near-aged siblings are seen in, respectively, Tables 2a–2c. Four patterns of findings are noteworthy. First, within individuals, registration for cannabis, stimulant and sedative abuse are highly intercorrelated with most correlations ranging from +0.70 to +0.90. Second, due to the rarity of our phenotypes and the resulting low numbers of concordant pairs, we could obtain only two stable cross-twin correlations in the DZ twins for cannabis abuse, and between cannabis abuse in twin1 and stimulant abuse in twin2. However, both these values (+0.53 and +0.46, respectively) were very similar to the parallel

findings for the near-aged siblings (+0.52 and +0.46, respectively). Third, the correlations between twins for the same individual substance and for different substances were substantially higher in MZ twins than those seen in DZ twins and siblings suggesting an important role for genetic factors. Fourth, in the MZ and near-aged siblings, the cross-twin correlations within substances were consistently higher than across substances although the cross-substance correlations were substantial. This pattern is consistent with some familial influences on DA being general and acting across substances, and others being substance-specific in their effect.

3.2. Model fitting and results

We first fitted an independent pathway model which resulted in a log likelihood and AIC of 55,831.52 and −896,878.5, respectively. The common pathway model, which included five fewer parameters, had the following log likelihood and AIC: Likelihood: 55,838.0; estimated parameters 17; AIC: −896,880.0. So by a modest margin, the AIC of the common pathway model was superior.

The parameter estimates for the best-fitting common pathway model are seen in Fig. 1. The estimated total contributions of additive genetic, shared and unique environmental effects on the three forms of DA, and the proportion of each that is common versus substance class specific in its effect is seen in Table 3. Six results are particularly worthy of comment. First, all three forms of DA loaded quite strongly on the common factor, with the loading for stimulant abuse (+0.94) being slightly higher than that seen for sedatives (+0.90) and cannabis abuse (+0.89). Second, the latent liability to DA was highly heritable ($a^2 = 0.67$) but also appreciably influenced by shared environmental effects ($c^2 = 0.22$). Third, estimates for the total heritability for the three forms of substance abuse were similar and high, ranging from 64% for stimulant and sedative abuse to 70% for cannabis abuse. Fourth, estimates for total shared environmental contributions to the three classes of DA were more modest and quite similar: 20% for stimulant abuse and 18% for both cannabis and sedative abuse. Fifth, substance specific gene effects were seen for all three classes of substances. Such effects were largest for cannabis – accounting for 24% of total genetic influences – and smallest for stimulants where the parallel figure was 8%. Finally, in contrast to the pattern for genetic effects, no substance specific shared environmental effects were detected. All of the shared environmental influences on cannabis, stimulant and sedative abuse were, in this model, estimated to derive from the common latent factor.

Because of its nearness in fit to the common pathway model, we also examined the parameter estimates of the independent pathway model. For cannabis and stimulants, the overall estimates of a^2, c^2 and e^2 were very similar and cannabis continued to have by far the largest contribution from substance-specific genetic effects. For sedatives, however, the estimate of total a^2 was lower (0.40 (0.35; 0.50)) and c^2 higher 0.32 (0.30; 0.35) than that seen in the independent pathway model.

4. Discussion

4.1. Compare to univariate results for DA

One plausible hypothesis about the nature of the genetic variation in humans that influences risk for drug abuse is that it should arise largely from genes that code for the primary sites of action of the psychoactive drugs themselves (e.g., Guindalini et al., 2006). If this were the case, we would expect most of the genetic variation to be substance specific as current evidence suggests that the principal receptor sites for the major drug classes such as cannabis, stimulants and sedatives, are largely distinct (Koob and Le Moal, 2006). However, prior twin studies based on personal interviews have found that a large proportion of the genetic influences on the abuse of specific classes of illicit substances were non-specific (Kendler et al., 2003, 2007; Tsuang et al., 1998). The main goal of this report was to determine whether we could replicate this pattern of results using a quite different methodological approach based on objective nation-wide data on DA from medical, mortality and criminal registries.

Our results were consistent with many of the critical findings from the previous personal interview-based twin studies of multiple forms of DA. Most importantly, in accord with the previous findings from the Vietnam Era and VATSPSUD studies (Kendler et al., 2003, 2007; Tsuang et al., 1998), we found that the large majority of genetic variation to DA of individual substance classes was non-specific. In some instances, the results were strikingly similar. For example, in the VATSPSUD study with both males and females (Kendler et al., 2007), the total heritability of cannabis abuse/dependence was estimated at 71% (versus 70% in this report) and the proportion of genetic variance that was substance-specific was estimated at 17% (versus 24%) in this report. The Vietnam era study estimated that the proportion of genetic variance which was substance specific for cannabis, stimulants and sedative abuse, was respectively, 33%, 27% and 19% (Tsuang et al., 1998). These estimates were all moderately higher than our parallel figures of 24%, 8% and 16%.

Our results were also congruent with two other aspects of the analyses of the Vietnam Era Twin Registry (Tsuang et al., 1998). Both studies formally tested independent and common pathway models for multiple classes of DA and found the common pathway model to have a superior fit. In both studies, the large majority of shared environmental influences on various classes of DA were non-specific.

Our findings can be usefully compared to prior estimates for all forms of DA that we previously reported in a Swedish national sample of MZ and DZ twins and all full siblings (Kendler et al., 2013a). In that study, heritability of DA in males was estimated to equal 55% with 23% of the variance in liability resulting from common environmental influences.

We have replicated across different countries, cultures and ascertainment methods the key observation from multivariate twin analyses that a substantial majority of the genetic risk for DA is shared across different substance classes. This provides, we suggest, convincing evidence that genetic variation in the genes that code for the primary sites of action of the psychoactive drugs themselves play a minor role in human individual differences in risk for DA. Instead, these consistent set of findings suggest that the genetic variants that influence

human DA are likely to include psychological traits and/or brain systems which impact responses to a diversity of substance classes. These likely include personality and personality-like traits that impact on risk for experimentation with most psychoactive compounds (Krueger et al., 2002; Zuckerman, 1972), frontal inhibitory systems that modulate impulsive reward-related behaviors (Dick et al., 2010; Koob and LeMoal, 2006), and brain systems that subserve the hedonic response to a most substances of abuse (Koob and LeMoal, 2006).

4.2. Limitations

These results should be interpreted in the context of four potentially important methodological limitations. First, we detected subjects with DA from medical, legal and mortality records, a method that does not rely on accurate respondent recall. However, such data likely contains both false negative and false positive diagnoses, the frequency of which we cannot estimate. An epidemiological study of DA conducted in neighboring Norway, which has similar rates of drug use and abuse (Hibell et al., 2007; Kraus et al., 2003), found lifetime prevalence rates of DSM-III-R (American Psychiatric Association, 1987) DA quite similar to those found using our registry based methods (Kringlen et al., 2001). Thus, under-ascertainment of at least the more severe forms of DA is unlikely.

Second, we have previously shown evidence for increased rates of DA in Sweden over the time period of our study (Giordano et al., 2013). We therefore explored whether incorporating these effects into our structural models would impact our parameter estimates. They did not as nearly all estimates in the model remained the same to two significant places.

Third, we were unable to study resemblance for cannabis, stimulant and sedative abuse in female–female pairs because the prevalence rates were too low to provide stable statistical estimates.

Fourth, given the relative rarity of our outcome measures, we had an insufficient number of DZ twins to obtain useful estimates of key parameters. Therefore, we added to the sample near-aged sibling pairs who have the same genetic relationship to one another as do DZ twins and, like DZ twins, closely share their rearing environment. There is a possibility that resemblance in these pairs might be lower for than for DZ pairs (because their level of environmental sharing may be slightly less—they do not share the same womb at the same time) although that is not supported by a comparison of the results available to use (see Tables 2b and 2c). If this is the case, then this would result in some over-estimate of genetic effects and a likely underestimate of shared environmental effects. A major bias in parameter estimates is unlikely because when we examined all forms of DA in both twins and all full siblings, we estimated the “special twin environment” – which would cause excess resemblance DZ pairs compared to all siblings – to account for only 3% of the variance in liability (Kendler et al., 2013a). Prior evidence for analyses of DA in Swedish siblings suggests that this effect would be still smaller in siblings quite close to one another in age (Kendler et al., 2013a, 2013b).

Fourth, as typical for twin studies, we were only able to include same-sex twins whose zygosity was known as a result of at least one member responding to a mailed questionnaire. (This was not needed for full sibling pairs). As expected, DA was associated with a reduced probability of returning questionnaires so the rate of DA was lower in pairs with known zygosity. This is a form of "concordance-dependent" ascertainment where the probability of known zygosity will be lowest in pairs concordant for DA, intermediate in those discordant for DA and highest in those where neither twin has DA (Kendler and Eaves, 1989). Simulations suggest that with the level of differential ascertainment expected in our data given the observed prevalence differences, biases in parameter estimates are unlikely to be very large and most probably would result in underestimation of genetic and shared environmental effects and overestimation of the individual-specific environment (Kendler and Eaves, 1989).

4.3. Conclusion

We examined abuse of cannabis, stimulants (including cocaine) and sedatives in national Swedish registers in male–male monozygotic and dizygotic twins and near-age full siblings. Model-fitting indicated that these data were best explained by a common pathway model in which the latent liability to DA was highly heritable but also influenced by shared environment. Cannabis, stimulant and sedative abuse all loaded strongly on this common factor with estimates of the total heritability ranging from 64 to 70%. The large preponderance of the genetic risk was non-specific, coming from the common factor as were all of the shared environmental effects. Consistent with prior studies based utilizing personal interviews, most of the genetic risk for abuse of specific classes of psychoactive substance are non-specific. These results suggest that genetic variation in primary sites of action of the psychoactive drugs, which differ substantially across most drug classes, likely play a minor role in human individual differences in risk for DA.

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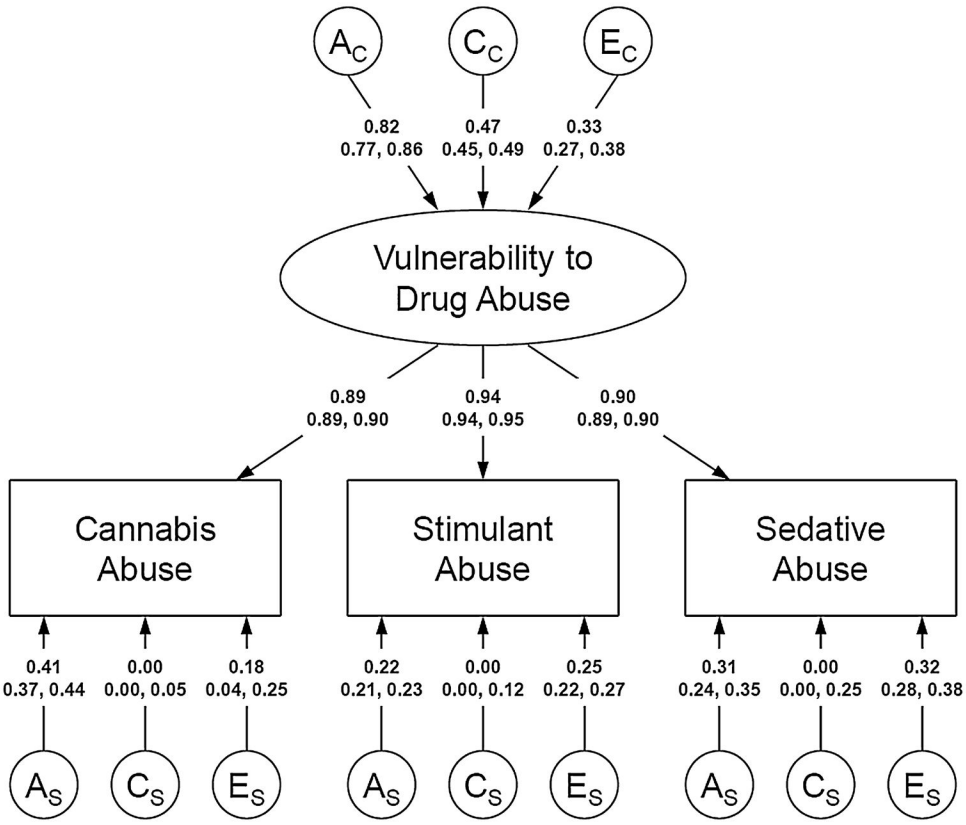

Fig. 1.

Parameter estimates from the best-fitting common pathway model for cannabis, stimulant and sedative abuse in Swedish male–male twin and near-aged sibling pairs. (A, C and E) refer, respectively, to additive genetic, shared environmental, and unique environmental risk factors. The subscript “c” refers to risk factors on the common latent factor, here labeled “vulnerability to drug abuse.” The subscript “s” refers to risk factors specific to the abuse of individual substance classes. The paths from the common latent factor to the individual forms of drug abuse reflect the degree to which those forms of drug abuse index the liability to the latent factor.

Table 1

The prevalence of registration for cannabis, stimulants and sedative abuse in the general population, MZ and DZ twins and near.

	General population (%)	MZ twin (%)	DZ twins (%)	Siblings (%)
Cannabis	2.2	1.0	1.2	1.9
Stimulants	1.7	0.7	0.6	1.4
Sedatives	1.0	0.5	0.5	0.9

Table 2a

Tetrachoric correlations (and 95% confidence intervals) in MZ male–male twin pairs within and between cannabis, stimulant and sedative abuse (N = 1720).

Male MZ pairs	Twin 1 cannabis	Twin 1 stimulant	Twin 1 sedatives	Twin 2 cannabis	Twin 2 stimulants
Twin 1 stimulant	0.73 (0.54; 0.92)				
Twin 1 sedatives	0.92 (0.83; 1.00)	0.82 (0.66; 0.98)			
Twin 2 cannabis	0.92 (0.83; 1.00)	0.62 (0.36; 0.88)	0.67 (0.42; 0.92)		
Twin 2 stimulants	0.52 (0.21; 0.83)	0.90 (0.79; 1.00)	0.61 (0.31; 0.92)	0.80 (0.67; 0.92)	
Twin 2 sedatives	0.81 (0.63; 1.00)	0.66 (0.36; 0.95)	0.81 (0.60; 1.00)	0.90 (0.77; 1.00)	0.80 (0.58; 1.00)

Table 2b

Tetrachoric correlations (and 95% confidence intervals) in DZ male–male twin pairs within and between cannabis, stimulant and sedative abuse (*N* = 1219).

Male DZ pairs	Twin 1 cannabis	Twin 1 stimulant	Twin 1 sedatives	Twin 2 cannabis	Twin 2 stimulants
Twin 1 stimulant	0.90 (0.76; 1.00)				
Twin 1 sedatives	0.82 (0.61; 1.00)	0.90 (0.74; 1.00)			
Twin 2 cannabis	0.53 (0.21; 0.86)	–	–		
Twin 2 stimulants	0.46 (0.03; 0.89)	–	–	0.77 (0.57; 0.97)	
Twin 2 sedatives	–	–	–	0.50 (0.07; 0.93)	0.88 (0.70; 1.00)

Table 2c

Tetrachoric correlations (and 95% confidence intervals) in male–male near-age sibling pairs within and between cannabis, stimulant and sedative abuse (*N* = 76,457).

Male near-age sibling pairs	Twin 1 cannabis	Twin 1 stimulant	Twin 1 sedatives	Twin 2 cannabis	Twin 2 stimulants
Twin 1 stimulant	0.85 (0.84; 0.87)				
Twin 1 sedatives	0.80 (0.78; 0.82)	0.84 (0.82; 0.86)			
Twin 2 cannabis	0.52 (0.49; 0.55)	0.47 (0.43; 0.50)	0.47 (0.42; 0.51)		
Twin 2 stimulants	0.46 (0.43; 0.50)	0.51 (0.47; 0.54)	0.48 (0.43; 0.52)	0.83 (0.82; 0.85)	
Twin 2 sedatives	0.46 (0.42; 0.51)	0.50 (0.46; 0.54)	0.53 (0.48; 0.57)	0.79 (0.77; 0.81)	0.85 (0.83; 0.86)

Table 3

Estimates of the total contributions of additive genetic, shared and unique environmental effects to cannabis, stimulant and sedative abuse and the proportion of each that is common versus substance class specific in its effect.

Substance class	Additive genetic effects			Shared environmental effects			Unique environmental effects		
	Total	% Common	% Specific	Total	% Common	% Specific	Total	% Common	% Specific
Cannabis	0.70	76	24	0.18	100	0	0.12	72	28
Stimulants	0.64	92	8	0.20	100	0	0.16	60	40
Sedatives	0.64	84	16	0.18	100	0	0.18	48	52