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Genetic and Environmental Risk Factors for Illicit Substance Use and Use Disorders: Joint Analysis of Self and Co-twin Ratings

Eivind Ystrom,

Department of Genetics, Environment and Mental Health, Norwegian Institute of Public Health, Nydalen, P.O. Box 4404, 0403 Oslo, Norway

Ted Reichborn-Kjennerud,

Department of Genetics, Environment and Mental Health, Norwegian Institute of Public Health, Nydalen, P.O. Box 4404, 0403 Oslo, Norway

Michael C. Neale, and

Virginia Institute for Psychiatric and Behavioral Genetics, Department of Human and Molecular Genetics, Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

Kenneth S. Kendler

Virginia Institute for Psychiatric and Behavioral Genetics, Department of Human and Molecular Genetics, Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

Eivind Ystrom: eivind.ystrom@fhi.no

Abstract

The specificity of genetic and environmental risk factors for illicit substance use and substance use disorders (SUD) was investigated by utilizing self and co-twin reports in 1,791 male twins. There was a high rate of comorbidity between both use of, and SUD from, different classes of illicit substances. For substance use, the model that included one common genetic, one shared environmental, and one individual-specific (i.e., unique) environmental factor, along with substance-specific effects that were attributed entirely to genetic factors fit the data best. For illicit SUD, one common genetic and one common unique environmental risk factor, and substance specific shared environmental and unique environmental risk factors were identified. Risk factors for illicit substance use and SUD are mainly non-specific to substance class. Co-twin rating of illicit substance use and SUD was a reliable source of information, and by taking account of random and systematic measurement error, environmental exposures unique to the individual were of lesser importance than found in earlier studies.

Keywords

Illicit drugs; Substance use; Substance abuse; Comorbidity; Rater bias; Co-twin report

Introduction

Relatives of probands with substance use disorder (SUD) have increased risk of SUD (Agrawal and Lynskey 2008; Merikangas et al. 1998). Twin studies indicate that familial

transmission of illicit substance use is due to both genetic and environmental risk factors shared by family members, whereas familial transmission of illicit SUD appears to arise largely from genetic effects (Kendler and Prescott 1998; Kendler et al. 2003). Results from twin studies also suggest that illicit substance use and illicit SUD is mostly caused by genetic and environmental risk factors common to multiple substances, and to a lesser extent by risk factors specific to a substance class (Kendler et al. 2003, 2007; Tsuang et al. 1998).

Structured interviews for the assessment of illicit substance use and SUD were used to generate data for these studies. Although this is considered to be the best method of assessment, both random and systematic measurement error can influence the results in different ways. Unreliability due to random measurement error causes a downward bias in the estimates of genetic and familial environmental risk factors. This is for example caused by inaccurate responses about prior or current consumption of illicit substances and related problems creating false positive or false negative cases (Andrews et al. 2007). Using multiple sources of information about illicit substance use and illicit SUD, e.g. proband and reports from family members, could reduce random error and improve reliability (Kendler et al. 2002).

Systematic rater bias related to information source (e.g. self-report) and interview context is another type of measurement error that could artifactually increase comorbidity. For example, a tendency to admit to multiple drug uses to impress the interviewer would create a systematic bias and artifactually increase comorbidity. Conversely, when asking about illegal behaviors, such as illicit substance use, self-report might be subjected to under-reporting. Such under-reporting would lead to artifactually decreased comorbidity. Artifactually increased or decreased comorbidity emerging from the data collection in itself, would, when using a single data source, be attributed to environmental risk factors unique to the individual, but common to use, abuse, or dependence of multiple illicit substance classes.

One way of addressing these methodological limitations in the previous literature is to utilize information from both members of twin pairs. By using more than one source of information on several phenotypes it is possible to estimate random measurement error and systematic measurement error, or rating bias, common to several phenotypes. In this study we use data from a large population-based sample of male–male twin pairs, including both self and co-twin reports, to correct for both random and systematic measurement error. We estimate the relative influence of genetic and environmental factors on use and use disorders for a number of illicit substances, as well as investigate the extent to which these risk factors are shared in common or are specific for each substance.

Method

Sample and study population

For the current study, we utilized data from the third wave of interviews in white, adult, male twins born between 1940 and 1974 from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD) (Kendler and Prescott 2006). The subjects for the VATSPSUD were ascertained from the Virginia Twin Registry, a population based register formed from a systematic review of birth certificates in the Commonwealth of Virginia. Of the 9,417 eligible twins, 6,814 (72.4 %) completed the first wave of interviews (1993–1996). At least 1 year later, those who had completed the first interview were contacted again for a follow-up. The second interview (1994–1998) was completed by 5,629 (82.6 %) of those who had completed the first interview.

The third interview wave (1998–2004), restricted to members of male–male twin pairs, was completed by 1,791 twins who had participated in the second interview representing 75.1 %

of the entire sample and 77.8 % of those eligible (excluding those who died and were lost to follow-up). Subjects were 24–62 years old (mean age = 40.3 years, SD = 9.0). This sample included both members of 467 monozygotic (MZ) and 282 dizygotic (DZ) pairs, and 293 singletons (153 MZ; 140 DZ).

Most subjects were interviewed by telephone. Subject were informed about the goals of the study and provided informed consent before interviews. This project was approved by the Virginia Commonwealth University institutional review board. The two members of a twin pair were always interviewed by different interviewers blind to information about the co-twin. Zygosity was assigned by a combination of self-report measures, photographs, and DNA polymorphisms (Kendler and Prescott 2006).

Assessment procedures

The participants were asked if they or their co-twin had ever in their lifetime used: cannabis (marijuana or hashish), stimulants (amphetamine, dexandrine, methadrine, ritalin, or ecstasy), cocaine (intranasal, injected, freebase, or crack), hallucinogens (LSD, mescaline, peyote, psilocybin, STP, mushrooms, or PCP/angel dust), and illicitly acquired sedatives (quaaludes, seconal, valium, xanax, librium, barbiturates, ativan, dalmane, or halcion). The self-report question was: “In your life, have you ever used [the drug in question]”. The co-twin report question was: “Has your twin ever used [the drug in question]”.

Self and co-twin report of lifetime use disorders of three classes of illicit substances was also elicited (cannabis, stimulants, and cocaine). For self-reported use disorders, twins who met our screening criterion (used 15 or more times in a month or six or more times lifetime plus admitted at least one abuse criteria), were asked, individually about all the DSM-IV criteria for both abuse and dependence (American Psychiatric Association 2000). A person was categorized as having a SUD by being diagnosed with either substance abuse or substance dependence or both disorders. Each twin was also asked about drug use in their cotwins. For those who answered positively, they were asked all the relevant questions from the Family History Research-Diagnostic Criteria (FH-RDC) (Endicott et al. 1975). The FH-RDC specifies that a case needs to (A) have a problem with substance use not limited to isolated incidents, and (B) have at least one substance-related problem in the following areas: (1) Legal problems, (2) health problems, (3) marital or family problems, (4) work problems, (5) treatment for use of the relevant substance, or (6) social problems. These criteria were then used to assign a cotwin reported diagnosis of SUD.

Statistical methods

The approach we use to multivariate twin data is reviewed elsewhere (Kendler et al. 1992b; Neale and Maes 2004). We assumed a liability-threshold model. The strengths and limitations of this model have been outlined previously (Kendler et al. 1992a; Neale and Maes 2004). In factor analysis, one seeks to explain the covariation between a number of variables, e.g. comorbidity between several psychiatric disorders, using a smaller number of underlying factors. In all biometric models utilized in the current study, individual differences in liability to substance use and use disorders are assumed to originate from three different sources: additive genetic (A) comprising all additive genetic effects that contribute to similarity between twins; shared environment (C), comprising all environmental exposures that contribute to similarity between twins; and unique environmental (E) factors, comprising all non-shared environmental factors not contributing to similarity in twins.

The E risk factors are confounded with random measurement error when only using one source of information. This is because random measurement error, such as a false positive

diagnosis, makes the twins appear more dissimilar than they really are. To increase reliability, we used both self and co-twin reports of illicit substance use and use disorders in a biometric model (Fig. 1) (Neale and Maes 2004; Neale and Stevenson 1989). When reliability goes up, it is at the cost of the estimated E effects (Kendler et al. 2002). That is, we were able to detect ‘true’ E effects as opposed to the part of E effects that reflect random error. To model systematic measurement error, or artifactually increased comorbidity (Neale and Kendler 1995), i.e. covariation across measured phenotypes only related to the rater and the rating situation, we used a single rater bias factor (Fig. 1). By modeling systematic measurement error, we were able to discriminate ‘true’ common E effects (E_c) from the part of E effects that reflect systematic error across phenotypes. In preliminary univariate analyses we tested for rating bias as a function of the latent phenotype (i.e. substance use leads to over or under reporting of substance use in the co-twin) (Kendler et al. 2002). Although we did find evidence that ever cannabis and cocaine use led to over report of the co-twin (standardized factor loading of 0.23 for both substance classes), due to modeling difficulties these paths were not included in the current multivariate approach comprising ten observed variables of illicit substance use. Both the observed self and co-twin reports and the latent illicit substance use or SUD phenotypes were constrained to have a variance of unity.

If co-twin report is a measure of the same unobserved liability measured by self-rating there can be no specific causes to co-twin report. We tested the assumption that the A and C factors specific to co-twin report would be estimated to zero using a bivariate Cholesky model (Fig. 2). We could not test this assumption on E effects because of confounding with measurement error.

To estimate common and specific risk factors for illicit substance use and use disorders, we utilized an ‘independent pathway model’ (Fig. 3). This is a multivariate model where both A, C, and E factors common to all phenotypes (A_c , C_c , and E_c), and A, C, and E factors specific to each phenotype (A_{sp} , C_{sp} , and E_{sp}) are modeled (Neale and Maes 2004). First, the full model for use of the five classes of illicit substances contained the maximum number A_c , C_c , and E_c factors (i.e. two factors for A, C and E, respectively) and A_{sp} , C_{sp} , and E_{sp} (five for A, C, and E, respectively). Second, the full model for SUD contained, in addition to the substance-specific factors, one A_c , C_c , and E_c factor, respectively.

We then sought to simplify the full model, first by reducing the number of common factors and then by eliminating the substance-specific factors. Corresponding to the principle of parsimony, models with fewer parameters are preferable if they do not result in a significant deterioration of fit. A useful index of parsimony and fit is Akaike's information criterion (i.e. $\Delta\chi^2 - 2\Delta df$) (Akaike 1987), which we used for model selection.

We used the software package Mx (Neale et al. 2006) to fit the biometric models to the data. Using full information maximum likelihood it is possible to estimate missing data. We were therefore able to use data from twin pairs with only one respondent.

Results

Prevalences, rater agreement, and comorbidity

Both self and cotwin prevalences of illicit substance use and use disorders are shown in Table 1. Cannabis use and use disorders were most common and sedative use and use disorders were the least common. The prevalence of self-report substance use is, across all substances, moderately higher by self-report than by cotwin report. By contrast, rates of self-report SUD are much higher by self-report than by cotwin report.

The level of agreement across self and co-twin rating for illicit substance use ranged from moderate for sedative use (tetrachoric = 0.68) to high for cannabis and cocaine use (tetrachoric = 0.86) (Table 1). The agreements between self and co-twin rating for SUD were moderate (tetrachoric from 0.65 to 0.74).

In Table 2, we show the comorbidity between the different classes of illicit substance use and SUD, as represented by the correlations between the latent phenotypes (i.e. joint analysis of self and co-twin rating). Above the diagonal are the phenotypic correlations for use of five classes of illicit substances, and below the diagonal the phenotypic correlations for use disorders of three classes of illicit substances. The correlations are all substantial, ranging from 0.83 (cannabis-sedatives; sedatives-hallucinogens) to 0.89 (cannabis-cocaine) for use, and from 0.76 (cannabis-cocaine) to 0.81 (cannabis-stimulants) for SUD.

Genetic and environmental risk factors for substance use and SUDs

Bivariate twin analyses—To test for A and C risk specific to co-twin report, we ran bivariate Cholesky models for each substance class across use and use disorders (Fig. 1). The A and C risk factors specific to co-twin report were estimated to zero for use and use disorders of all substances (Table 3). The one exception was a minor specific A influence for cocaine use disorders, but this factor loading could be set to zero without a reduction of model fit. Except for stimulant use disorders, the impact of A and C effects was for all substance classes comparable for self and co-twin report.

Illicit substance use

Model fitting: illicit substance use—Table 4 shows the details for model fitting for use of five classes of illicit substances. Model I contains two A_c , C_c , and E_c factors, respectively, and A_{sp} , C_{sp} , and E_{sp} factors for each substance. This model is denoted the 2-2-2; as-cs-es model; where the first three digits represent the number of A_c , C_c , and E_c factors, respectively, and as-cs-es, represents A_{sp} , C_{sp} , and E_{sp} factors. We first aimed at reducing the number of common factors, and thereafter setting substance-specific factors to zero.

In model II through IV, the number of A_c , C_c , and E_c factors was sequentially reduced by one factor. In this first step, the best fitting model, model IV, included only one E_c factor in addition to two A_c and C_c factors.

In step two, we continued from model IV and, as in step one, reduced the number of A_c , C_c , and E_c factors by one factor (model V through VII). In this, second step, the best fitting model, model V, only included one A_c factor.

In step three, we simplified model V, and the best fitting model, model IX, only included one A_c , C_c , and E_c factor, respectively.

In step four, we attempted to improve model IX by reducing by one common factor, but none of the tested models gave an improved fit to the data (model XI through XIII).

In step five, we started to eliminate the substance-specific factors by running three models, each without one form of A_{sp} , C_{sp} , or E_{sp} factors. The best fitting model in this fifth step proved to be the one without C_{sp} factors (model XV).

In step six, working on from model XV, we ran two models where we removed A_{sp} and E_{sp} factors (model XVII and XVIII). The best fitting model in this sixth step was the one with only A_{sp} factors (model XVIII).

In step seven, we tried to remove the last type of A_{sp} effects, but the model (model IXX) had a worse fit than the previous one (model XVIII) according to AIC.

The model that fitted the data best (model XVIII in Table 4) included one A_c , C_c , and E_c factor, respectively, and only A_{sp} factors.

Parameter estimates: illicit substance use—The parameter estimates for the best fitting model are shown in Fig. 3a and in the top part of Table 5. Although usages of all classes of illicit substances were related to the A_c factor, there were some differences to what extent they were related. While the loading of cannabis use on the A_c factor was 0.48, the loadings for the other forms of usages ranged from 0.59 (cocaine) to 0.75 (stimulants). These loadings were higher than the loadings of the A_{sp} factors, which ranged from 0.28 for stimulants to 0.38 for sedatives. An average of 77 % of the genetic variance came from the common factor, with a range from 73 % for cannabis to 88 % for stimulants. The total heritability ranged from 31 % for cannabis use to 62 % for sedative use, and is presented in Table 5.

The individual substances were all substantially influenced by the C_c factor. While sedatives had the lowest factor loading, 0.51, cannabis was the form of substance use most influenced by the C_c factor (factor loading 0.75).

All the classes of substances had similar loadings on the E_c factor, with a range from 0.29 for stimulants and hallucinogens to 0.34 for cannabis and sedatives.

Causes of true and artifactually increased comorbidity: illicit substance use

When modeling several variables in twin models, it is possible to split the sources of comorbidity between phenotypes into parts attributable to A, C, and E sources. In Fig. 4 we present the correlations between the latent variables of illicit substance use. While it appears that liability to use two forms of illicit substances can be about equally divided into A and C sources, it seems that E factors are of little importance in explaining correlation between use of different illicit substances. For example, cannabis and cocaine use is correlated 0.89. However, this correlation can be decomposed into 0.28, 0.50, and 0.11 due to A, C, and E contributions, respectively.

Illicit SUDs

Model fitting: illicit SUDs—The model fitting for illicit SUD followed the same procedure as described for illicit substance use, and is shown in Table 6. We started out with the full model, model I, and reduced it, first, by the C_c factor (model III). Second, we attempted to do further reductions (model V–VI), without any improvement in fit to the data. In the third step, we started setting A_{sp} , C_{sp} , or E_{sp} factors to zero, where the A_{sp} factors could be eliminated (model VII). We then, as a fourth step, removed C_{sp} and E_{sp} factors, respectively, but no further improvements could be made to the model (model X–XI). Model VII fitted the data for SUD best; it included A_c and E_c factors, and C_{sp} and E_{sp} factors.

Parameter estimates: illicit SUDs—The best fitting model is depicted in Fig. 3b. The loadings for the A_c factor were all high, ranging from 0.74 for cocaine to 0.88 for cannabis, leading to total heritabilities of 79, 54, and 68 % for cannabis, cocaine, and stimulant SUD, respectively.

C risk factors were all substance-specific, and of varying size. While cocaine and stimulant use disorders were the phenotypes most influenced by their C_{sp} factor with factor loadings of 0.40 and 0.44 respectively, cannabis use disorders did not prove to be substantially influenced by a C_{sp} factor.

While cocaine use disorder was the phenotype most influenced by the E_c factor, with a factor loading of 0.47, stimulant and cannabis use disorders had respective factor loadings of 0.36 and 0.23. With the exception of cannabis use disorder, the E_c factor loadings were all higher than the E_{sp} factor loadings. While only 27 % of the E variance in cannabis use disorder could be attributed to the E_c factor, the same figure was 75 and 100 % for cocaine and stimulant use disorders (Table 5, lower part).

Causes of true and artifactually increased comorbidity: illicit SUDs—In the right side of Fig. 4 we present the sources of correlation between latent variables of use disorders of three different classes of illicit substances. Comorbidity between use disorders of different illicit substances can be explained by A_c factors. For example, cannabis and cocaine use disorders are correlated 0.76 at the phenotypic level; however this can be divided into 0.65 due to A contributions, and 0.11 due to E contributions.

Co-twin rating: reliability and rater bias

Reliability—The associations between the latent factor and observed variables of illicit substance use is indexed by the factor loadings depicted as black one-headed arrows in Fig. 3a. Self-rating and co-twin rating of illicit substance about equally indexed the latent liability to substance use. The factor loadings of self-rating ranged from 0.84 for sedatives to 0.94 for cannabis and cocaine. The factor loadings of co-twin rating ranged from 0.81 for sedatives to 0.92 for cocaine.

Although both forms of SUD ratings were adequate indices of latent liability to SUD, self-rated SUD appeared to better reflect latent liability to SUD than co-twin rated SUD. Factor loadings for self-rating were 0.91, 0.99, and 0.89 for cannabis, cocaine, and stimulant use disorders, respectively (Fig. 3b). Factor loadings for co-twin rating for the same SUD were 0.76, 0.75, and 0.73, respectively.

There was no clear pattern on which source of information, self or co-twin ratings, was the most influenced by random error. For illicit substance use, estimates of random error ranged from 6 (sedatives) to 10 % (hallucinogens) for self-report, and 6 (cannabis) to 30 % (sedatives) for co-twin report. For SUDs, estimates of random error ranged from 0 (cocaine) to 19 % (stimulants) for self-report, and 13 (stimulants) to 26 % (cannabis) for co-twin report.

Rater bias—The rater bias factor, measuring artifactually increased comorbidity related to both the rater and rater situation, had moderate factor loadings on all forms of illicit substance use. Co-twin rating appeared to be marginally more influenced by systematic measurement error, particularly for co-twin rated SUD. The rater bias factor had for self-reported substance use factor loadings ranging from 0.25 (sedatives) to 0.32 (hallucinogens) and for co-twin report 0.25 (cannabis) to 0.55 (sedatives). The rater bias factor loadings ranged from 0.09 (stimulants) to 0.24 (cannabis) for self-reported SUD and 0.41 (cannabis) to 0.58 (stimulant) for co-twin reported SUD.

Discussion

We utilized self and co-twin reports from a population-based sample of male–male twin pairs to investigate the specificity of genetic and environmental risk factors for illicit substance use and SUD. Three results were of particular interest. First, we found that while both A and C factors were about equally important for illicit substance use, C factors were of little importance for illicit SUD. Factors not contributing to similarity in twins, E factors, were of marginal importance. Second, A, C, and E influence was mostly common to use and use disorders of all illicit substances, and to a minor extent specific to substance class, with

the exception of C influence on SUD. Third, although both self and co-twin rating of illicit substance use and SUD were adequate indices of latent liability to SUD, some of the comorbidity observed could be attributed to rater bias. This artifactually increased comorbidity would otherwise, without multiple sources of information, have been attributed to E_c risk factors.

In the following we will (i) compare our results with findings from earlier studies, (ii) evaluate the relative importance of genetic and environmental risk factors for illicit substance use and SUD, (iii) discuss the implications of using multiple sources of information to assess the causes of comorbidity, and, (iv) review potential limitations of the study.

Risk factors for use, abuse and dependence of illicit substances

Earlier studies on common and specific genetic and environmental risk factors for illicit substance use and SUD—In a family study on familial transmission of risk for illicit SUD, relatives of probands with one or more SUD were eight times more likely to have any SUD (Merikangas et al. 1998). The familial aggregation of risk appeared to be more general than substance-specific. However, results from another family study, using data from the Collaborative Study on the Genetics of Alcoholism, indicated that familial transmission of cannabis and cocaine use disorders were largely substance-specific (Bierut et al. 1998). The aforementioned family studies were based on substance abusing or dependent probands recruited from clinics, not population registries; whether these results would be generalizable to community samples is unclear.

An earlier twin study on illicit substance abuse was carried out using data from the Vietnam Era Twin Registry (Tsuang et al. 1998). Looking at the same substances included in our current study, they found that, on average, substance-specific influence accounted for 20 % of the genetic variation in liability to substance abuse. In terms of comparability to our current study, substance abuse can be roughly viewed as an intermediate level between use and dependence (Kendler and Prescott 1998). Although the model without C_{sp} effects had the best fit to the Vietnam Era Registry Data, Tsuang et al. only presented results from the less parsimonious model with all the substance-specific results estimated. Like in Tsuang et al.'s best fitting model on substance abuse, our best fitting model on illicit substance use, had no C_{sp} effects. We found that 23 % of the genetic variance in liability to substance use was substance-specific, a figure that is comparable to the aforementioned study on substance abuse.

In the one prior study investigating common and specific risk factors for both illicit substance use, abuse, or dependence using an earlier assessment of the male–male twin pairs from the Virginia Twin registry the results were similar to our current finding (Kendler et al. 2003). The best fit model on substance use required, in addition to A_{sp} and E_{sp} factors, one A_c and C_c factor, respectively, and two E_c factors. Subsuming the same five substances used in our current study, 11 % of the genetic variance in liability to substance use was substance-specific. Our results on illicit substance use elaborate this model by separating true E_{sp} from substance-specific measurement error, and finding that true E_{sp} risk to substance use is not significant (Table 4; model XV compared to model XVIII; χ^2 9.6, 5df, $p = 0.09$). Furthermore, we elaborate the model on illicit substance use by having only one E_c , but also having a rater-bias factor comprising non-shared factors common to all substances. We modeled this unique, or non-shared, common influence as systematic measurement error contributing to artifactually increased comorbidity. Rater bias could be due to inaccurate memory, but it could also be due to deliberate non-response because of the socially undesirable nature of illicit substance use (Andrews et al. 2007).

The previous multivariate study by Kendler et al. included twice as many SUDs, and both the A_c factor, and the E_c factor gave increased risk for abuse or dependence of all substance classes. This is in line with our current findings. However, the best fitting model in the previous, six-variate, study included a C_c factor, but no C_{sp} factors. The C_c factor previously found gave an increased risk for hallucinogen use disorders, negative risk for sedative and stimulant use disorders, and a marginal increase in risk for cannabis and cocaine use disorders. This implies that the C_c factor identified earlier does not substantially contribute to covariation between the three SUDs included in the current study. We would therefore not expect to identify the C_c factor without also including hallucinogen and sedative use disorders. However, given that SUD is contingent on use, and that use of all illicit substances was influenced by a C_c factor, it is puzzling that we did not find a C_c factor for SUD. Agrawal et al. (2005) found use and SUD of any illicit drug to be correlated 0.67 in males (Agrawal et al. 2005). This implicates that the C_c factor for illicit substance use would in average explain 18 % of the variance in SUD. Conversely, we found SUD to in average be 21 % influenced by C_{sp} factors. It could be that we lacked the statistical power to detect a putative C_c factor.

Since E_{sp} factors for SUD were also significant in the current study (Table 6; model VII compared to model XI; χ^2 9.7, 3df, $p = 0.02$), where we removed random measurement error, it seems that the E_{sp} factors previously found to a great extent represent true environmental risk factors for SUD, and not error of measurement. Since true E_{sp} risk was of non-significant importance for substance use, this finding implicates that non-familial environmental exposures on the path between ever using a drug and abusing or getting addicted to that drug are of substantial importance. A pathway to more severe illicit drug use could be that once a person starts using one drug, he is likely to be exposed to other drugs through friends, dealers, and other drug-related environments,

Genetic risk factors for illicit substance use and use disorders

We found that for use of illicit substances only 23 % of the genetic risk was substance-specific, and, that the genetic risk for cannabis, cocaine, and stimulant SUD could be viewed as entirely common to all classes of substances. That is, a person who is dependent on cocaine would be expected to have the same high genetic risk of becoming dependent of stimulants. This is in accordance with previous research (Kendler et al. 2003), and has important implications for genetic studies on use, abuse, and dependence of illicit substances (Meyers and Dick 2010).

Environmental risk factors for illicit substance use and use disorders

Shared environmental experiences has also earlier been found to increase the liability of illicit substance use in twins (Agrawal and Lynskey 2006; Kendler et al. 2000; van den Bree et al. 1998), and these experiences have been found to be general across substance classes (Kendler et al. 2003). We did not find any evidence that shared experiences gave any substance-specific risk, and therefore corroborate earlier conclusions on the same matter (Kendler et al. 2003). Initiation of substance use does not seem to be primarily caused by imitation and social learning (Akers 2009) or directly by the availability of a specific substance. Our findings points at more general contextual factors as important for illicit substance use. This information is important when understanding social risk factors for, and the prevention of, illicit substance use.

We found that C risk factors for illicit SUD to be substance-specific. Only cocaine and stimulant use disorders were substantially influenced by shared environment, and only 1 % of the phenotypic variance in cannabis use disorders was explained by this source of risk. There has earlier been mixed findings on the importance of C risk factors for cocaine and

stimulant use disorders (Agrawal and Lynskey 2006; Kendler et al. 2000; Lynskey et al. 2003; Tsuang et al. 1998; van den Bree et al. 1998). Kendler et al. (2003) found in their previous study on common and specific risk factors shared environmental risk to be common to several substances. The common risk factor explained about 1 % of the variance in cannabis and cocaine use disorders, but was a substantial predictor of stimulant use disorders. In the current study, we found cocaine use disorders to be substantially influenced by C_{sp} risk factors. While cocaine and stimulant use disorders are highly phenotypically correlated, mostly because of common genetic etiology, it could be that the use of and exposure to the two drugs are related to different social strata, and therefore form independent C risk factors.

As in earlier studies, we found that there are environmental risk factors unique to the individual, but common to abuse or dependence of different substances. The estimates of E_{sp} risk factors have in earlier studies to an unknown degree been confounded with error of measurement. However, we were here able to estimate the size of these risk factors, by jointly using two sources of information and removing random and systematic measurement error. There appeared to be true E_{sp} risk factors of substantial size for cannabis and cocaine use disorders, but not for stimulant use disorders.

Unique environment and artifactually increased comorbidity: implications of jointly analyzing information from multiple sources

Reliability—There are two main implications of utilizing several sources of information in twin models. First, E factors comprise all factors not contributing to making MZ twins similar. If factors that only contribute to apparently making twins dissimilar, i.e. random measurement error, is accounted for, the relative contribution of A and C increases as the diagnostic uncertainty decreases. For all analyses on illicit substance use and SUD, we removed random and systematic error of measurement by using both self and co-twin ratings, and therefore to a greater extent estimated the true size of common and substance-specific factors. To the best of our knowledge, we are the first to separate error of measurement from true E influence by using several sources of information in a statistical genetic study on illicit substance use, and therefore the first to test the substance-specificity of E factors. We found that while the E risk factors for illicit substance use was common to all classes of substances, and the substance-specific risk could be removed entirely, 74, 25, and 0 % of E risk for illicit SUD were substance-specific for cannabis, cocaine, and stimulants, respectively.

The use of several sources of information can for moderately reliable phenotypes substantially increase the heritability. By using two psychiatric interviews, (Ystrom et al. 2011) recently found the heritability of alcohol dependence to increase from 54 to 71 %. However, use of several sources of information can have a large impact on the heritability of phenotypes with low reliability. In an earlier study using self and co-twin report to estimate genetic and environmental risk factors for several mental disorders (Kendler et al. 2002) found the heritability of life-time major depression to almost double from 31 to 59 %.

The random measurement errors are assumed to be normally distributed, which implies that people are just as likely to over-report as to underreport substance use and symptoms of SUD, something not likely to be true (Andrews et al. 2007). Andrews et al. (2007) found that it was very unlikely to underreport a SUD when the co-twin reported a SUD. This implies that if a person tells his brother about a SUD, then he is likely to also tell the interviewer. The substantial difference in self and co-twin reported SUD could on the other hand be due to the fact that the co-twin is not informed about his brother's symptoms of SUD. It could also be due to that the instruments used for self and co-twin ratings of SUD

were not identical in structure. However, with these limitations in mind, future twin studies should to a greater extent consider collecting data from multiple sources.

Rater bias—The most widely used source of information in psychiatric genetics is some form of self-report. By jointly using several sources of information we were, for the observed self-report measure, able to divide the E influence into true E variance, systematic measurement error due to rater bias, and random measurement error. On average, the relative sizes of these three forms of influence were 30, 30, and 40 % for substance use, and 58, 9, 33 % for SUD. This means that while less than a third of what would otherwise be attributed to E factors for illicit substance use were here deemed to be true, the same etiology for self-reported SUD reflects true variance more than measurement error. This corresponds to findings of Kendler et al. (2002), where they estimated the true environmental impact on use disorder of any illicit drug and found that the true environmentality of abuse/dependence of any illicit substance class to be 21 %. The remaining 79 % was explained by additive genetics.

In the current study, the common variance in substance use accounted for by the rater bias factor, comprising systematic measurement error creating artifactually increased comorbidity, would, when only utilizing a single source of information, be explained by a E_c factor with an average factor loading of 0.28. The artifactually increased comorbidity modeled by the rater bias factor besides representing bias originating from the interview situation, could also represent true E risk factors for illicit substance use and SUD (Kendler et al. 2002). If so, a share of the artifactually increased comorbidity due to the rater bias factor is true comorbidity. The rater bias could in addition to be a measure of true E factors also comprise clinically useful and valid information (Carey and Gottesman 1978), like poor communication with the interviewer, failing memory, distracting events that happened that day, or fear of condemnation or criminal persecution.

Limitations to the study

The results should be interpreted in the light of four limitations. First, the sample comprises only natively born male Virginians of Caucasian origin. Generalization to other populations, or to females, should therefore be done with caution. Second, although the effect was small, drinking problems predict non-participation in the current study (Kendler and Prescott 2006). We are under the “missing at random assumption” able to estimate some of the missing data caused by this effect by including incomplete pairs with co-twin report in the analyses. Third, the sample was of quite variable age at assessment, and historical prevalence rates of illicit substance use are substantially different across these cohorts (Kendler et al. 2005). However, there is in the current sample no evidence for any difference in the relative contribution of genetic and environmental factors for psychoactive substance use (Kendler et al. 2005). Fourth, we were not able to provide reliable standard errors or confidence intervals for the estimates in the models. However, statistical significance for sets of parameters (e.g. specific E_{sp}) can be inferred by comparing the model fit. Fifth, while the rate of co-twin rating of illicit substance use was comparable to the rate of self-reported illicit substance use, the rate of co-twin reported SUD was substantially lower than self-reported SUD. This could be because different instruments were used to measure self and co-twin reported SUD. It could also be because SUD more often than substance use occurs after adolescence and is less known to the co-twin or because core features of SUD are subjective experiences of tolerance, craving, or withdrawal not evident to an observer.

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Fig. 1.

Squares represent observed variables and *circles* represent latent variables. *Colors* denote different parts of the model. *Black* measurement model; *grey* random measurement error; *yellow* systematic measurement error; *dark red* common additive genetic effects; *dark green* (Color figure online)

Fig. 2.

A bivariate twin model for selfreport and co-twin report. This model was used to find out whether the same genetic (denoted by the letter A), shared environmental (C), and unique environmental risk factors (E) influence self and co-twin report. The model contains two set of factors: those that are common for self and co-twin report (in *red* denoted by subscript s), and those that are unique to co-twin report (in *grey* denoted by u). We did not assume self and co-twin report to be equally reliable measures of illicit substance use, so the loadings of the common factors were allowed to differ (denoted by a 'prime' symbol) (Color figure online)

Fig. 3.

a Best-fit model for liability to lifetime use of five illicit substances by 1,791 male twins from a population based registry. *Black circles* represent latent factors of phenotypic liability, and *squares* represent observed liability to illicit substance use—all which have a variance of unity. The path coefficients represent standardized regression coefficient. The *square* of the product of coefficients from the upstream variables to the downstream variables is the explained variance in observed illicit substance use. **b** Best-fit model for liability to lifetime use disorder of cannabis, cocaine, and stimulants by 1,791 male twins from a population based registry. *Black circles* represent latent factors of phenotypic liability, and *squares* represent observed liability to illicit substance use—all which have a

variance of unity. The path coefficients represent standardized regression coefficient. The *square* of the product of coefficients from the upstream variables to the downstream variables is the explained variance in observed illicit substance use

Fig. 4. Sources of phenotypic correlation predicted by best fit model for lifetime use disorders of these classes of illicit substances

Table 1
Lifetime prevalence of illicit substance use and use disorders by rater, and level of agreement between raters, in 1,791 male twins from a population-based registry

Behavior and substance	Prevalence (%)		Level of agreement Tetrachoric
	Self rating	Co-twin rating	
Use			
Cannabis	60.3	44.4	0.86
Stimulants	22.1	13.8	0.77
Cocaine	21.5	15.4	0.86
Hallucinogens	17.9	11.9	0.81
Sedatives	13.3	8.2	0.68
Use disorders			
Cannabis	20.6	4.7	0.69
Stimulants	8.2	1.4	0.74
Cocaine	5.8	1.4	0.65

Table 2
Correlations between latent phenotypic variables indicated by self and co-twin ratings of lifetime illicit substance use and use disorders in 1,791 twins from a population-based registry

	Cannabis	Stimulants	Cocaine	Hallucinogens	Sedatives
Cannabis	1.00	0.85	0.89	0.88	0.83
Stimulants	0.81	1.00	0.88	0.86	0.88
Cocaine	0.76	0.77	1.00	0.87	0.85
Hallucinogens	<i>a</i>	<i>a</i>	<i>a</i>	1.00	0.83
Sedatives	<i>a</i>	<i>a</i>	<i>a</i>	<i>a</i>	1.00

Note Correlations for substance use are shown above the diagonal; correlations for substance use disorders are shown below the diagonal

a Hallucinogen and sedative use disorders were not measured

Table 3
Parameter estimates for fitting of bivariate Cholesky model for self-report and co-twin report of illicit substance use and substance use disorders

	Common to self and co-twin					Unique to co-twin report				
	Self-report					Co-twin report				
	a _s	c _s	e _s	a _s	c _s	e _s	a _u	c _u	e _u	
Cannabis use	0.45	0.77	0.46	0.42	0.77	0.14	0.00	0.00	0.45	
Cocaine use	0.62	0.66	0.42	0.63	0.69	0.03	0.00	0.00	0.35	
Hallucinogen use	0.57	0.68	0.47	0.59	0.73	-0.02	0.00	0.00	0.34	
Sedative use	0.66	0.45	0.60	0.73	0.51	-0.08	0.00	0.00	0.44	
Stimulant use	0.73	0.43	0.53	0.77	0.50	-0.09	0.00	0.00	0.38	
Cannabis use disorder	0.76	0.23	0.61	0.85	0.17	-0.01	0.00	0.00	0.50	
Cocaine use disorder	0.64	0.52	0.56	0.61	0.36	0.34	0.14	0.00	0.61	
Stimulant use disorder	0.83	0.24	0.50	0.48	0.72	0.15	0.00	0.00	0.48	

Note We used a bivariate Cholesky model to determine to what extent the same additive genetic effects (a); shared environmental effects (c); and unique environmental effects (e) influence self and co-twin report of illicit substance use and substance use disorders. While subscript s denotes effects common to self and co-twin report, subscript u denotes effects unique to co-twin report. A 'prime' symbol denotes common effects related to co-twin report

Table 4
Results of multivariate fitting for self and co-twin report of lifetime use of five illicit substance classes by 1,791 twins from a population based twin registry

Model, model fitting test step, and description					Likelihood ratio Chi Square Test ^a		Akaike's information criterion
		-2 Log likelihood	df	χ^2	df		
I	Full model with all common factors (two additive genetic, two shared environmental, and two unique environmental common factors) and all substance-specific factors (additive genetic, shared environmental, and unique environmental substance specific factors) (2-2-2; as-cs-es model).	9,853.804	16,344				
Step 1 (test against model I)							
II	1-2-2; as-cs-es model	9,854.682	16,349	0.878	5	-9.122	
III	2-1-2; as-cs-es model	9,860.352	16,349	6.548	5	-3.452	
IV	2-2-1; as-cs-es model	9,854.267	16,349	0.463	5	-9.537	
Step 2 (test against model IV)							
V	1-2-1; as-cs-es model	9,857.310	16,354	3.506	10	-16.494	
VI	2-1-1; as-cs-es model	9,859.572	16,354	5.768	10	-14.232	
VII	2-2-0; as-cs-es model	9,981.776	16,354	127.972	10	107.972	
Step 3 (test against model V)							
VIII	0-2-1; as-cs-es model	9,919.969	16,359	66.165	15	36.165	
IX	1-1-1; as-cs-es model	9,861.542	16,359	7.738	15	-22.262	
X	1-2-0; as-cs-es model	9,983.387	16,359	129.583	15	99.583	
Step 4 (test against model IX)							
XI	0-1-1; as-cs-es model	9,944.754	16,364	90.950	20	60.072	
XII	1-0-1; as-cs-es model	9,903.988	16,364	50.184	20	13.636	
XIII	1-1-0; as-cs-es model	9,988.154	16,364	134.350	20	103.887	
Step 5 (test against model IX)							
XIV	1-1-1; cs-es model	9,866.901	16,364	13.097	20	-26.903	
XV	1-1-1; as-es model	9,864.630	16,364	10.826	20	-29.174	
XVI	1-1-1; as-cs model	9,868.178	16,364	14.374	20	-25.626	
Step 6 (test against model XV)							
XVII	1-1-1; es model	9,951.988	16,369	98.184	25	48.184	
XVIII	1-1-1; as model	9,865.007	16,369	11.203	25	-38.797	

Model, model fitting test step, and description		-2 Log likelihood	df	Likelihood ratio Chi Square Test ^a		Akaike's information criterion
				χ^2	df	
Step 7 (test against model XVIII)						
IXX	1-1-1	9,990.667	16,374	136.863	30	76.863

^a Against model I

^b Best-fit model over best-fit model in previous step

^c Final best-fit model

Table 5
Proportions of variance explained in the latent illicit substance use and illicit substance use disorder phenotypes according to the best-fit model

Behavior and substance	Proportion of variance									
			Additive genetic factors		Shared environmental factors		Unique environmental factors			
	Common	Substance-specific	Common	Substance-specific	Common	Substance-specific	Common	Substance-specific	Common	Substance-specific
Use										
Cannabis	0.23	0.08	0.31	0.56	0.00	0.00	0.12	0.00	0.12	0.12
Stimulants	0.56	0.08	0.64	0.27	0.00	0.00	0.27	0.08	0.00	0.08
Cocaine	0.35	0.11	0.46	0.44	0.00	0.00	0.44	0.11	0.00	0.11
Hallucinogens	0.31	0.14	0.45	0.46	0.00	0.00	0.46	0.08	0.00	0.08
Sedatives	0.48	0.14	0.62	0.26	0.00	0.00	0.26	0.12	0.00	0.12
Use disorder										
Cannabis	0.79	0.00	0.79	0.00	0.01	0.01	0.01	0.05	0.15	0.20
Cocaine	0.54	0.00	0.54	0.00	0.16	0.16	0.16	0.22	0.07	0.30
Stimulants	0.68	0.00	0.68	0.00	0.20	0.20	0.20	0.13	0.00	0.13

N = 1,791 twins from a population-based registry

Table 6
Results of multivariate fitting for self and co-twin report of lifetime use disorders of three illicit substance classes by 1,791 twins from a population based twin registry

Model, model fitting test step, and description	–2 Log likelihood	Likelihood ratio Chi Square Test ^d		Akaike's information criterion	
		df	χ^2	df	
I Full model with all common factors (one additive genetic, one shared environmental, and one unique environmental common factor) and all substance-specific factors (additive genetic, shared environmental, and unique environmental substance specific factors) (1-1-1; as-cs-es model).	3,750.846	9,821			
Step 1 (test against model I)					
II 0-1-1; as-cs-es model	3,763.488	9,824	12.642	3	6.642
III 1-0-1; as-cs-es model	3,751.549	9,824	0.703	3	–5.297
IV 1-1-0; as-cs-es model	3,763.161	9,824	12.315	3	6.315
Step 2 (test against model III)					
V 0-0-1; as-cs-es model	3,857.874	9,827	107.028	6	95.028
VI 1-0-0; as-cs-es model	3,763.885	9,827	13.039	6	1.039
Step 3 (test against model III)					
VII 1-0-1; cs-es model	3,751.934	9,827	1.088	6	–10.912
VIII 1-0-1; as-es model	3,752.655	9,827	1.809	6	–10.191
IX 1-0-1; as-cs model	3,754.166	9,827	3.320	6	–8.680
Step 4 (test against model)					
X 1-0-1; es model	3,766.514	9,830	15.668	9	–2.332
XI 1-0-1; cs model	3,761.634	9,830	10.788	9	–7.212

^a Against model I

^b Best-fit model over best-fit model in previous step

^c Final best-fit model