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Is there heterogeneity among syndromes of substance use disorder for illicit drugs?

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Abstract

The use of DSM criteria to evaluate liability to substance use disorders (SUDs) and to identify SUD phenotypes may not provide the sensitivity required to identify genes associated with vulnerability to SUDs. The purpose of this study is to evaluate a number of basic aspects of substance use that may be more proximal than full SUDs to risk genes, some of which may thus have greater potential utility as phenotypes in subsequent molecular genetic analyses. In this paper we present results from the first stage of our planned analyses, focusing on how individual symptoms of abuse and dependence may be used to create alternate phenotypes for SUDs. Specifically, we used factor analysis and biometrical modeling on each symptom of illicit substance abuse and dependence within different types of substances, and compared and contrasted factor patterns and heritabilities across the different substances. These analyses were carried out using a population-based sample of 3372 male–male twin pairs from the Vietnam Era Twin Registry who participated in the Harvard Twin Study of Substance Abuse. We obtained

extensive data from these participants on substance use and SUDs via telephone interview in 1992, including data on the illicit substances: opiates, cocaine, cannabis, sedatives, stimulants, and psychedelics. The results indicate that: A) although a one-factor model assuming a single underlying liability for abuse and dependence symptoms and behaviors can be rejected for most substances, there is no uniform support for a two-factor model differentiating between abuse versus dependence; B) patterns of symptoms or behaviors reported by substance users vary across substances; C) not all symptoms or behaviors contribute equally to the presentation of an SUD; and D) the heritability of symptoms or behaviors of substance users varies both within and between substances. These results represent important first steps in facilitating the search for SUD-risk genes in subsequent high- throughput molecular genetic analyses by providing alternate phenotypes that may have both optimal validity and increased heritability.

Keywords

Factor analysis; Heritability; Phenotype; Substance abuse; Substance dependence; Substance use disorders; Twin

1. Introduction

1.1. Limitations of current diagnostic criteria for substance use disorders

Since the publication of the DSM-III (American Psychiatric Association, 1980), the diagnosis of substance use disorders (SUDs) has been based on a single generic set of criteria, which is applied to alcohol and all drug classes. Within any substance category, diagnosis has traditionally also been separated into abuse and dependence. In this system, a diagnosis of abuse is basically reserved for individuals who do not meet the threshold for a diagnosis of dependence but still manifest enough distress or dysfunction to have reached the threshold of a clinically significant disorder. DSM-IV (American Psychiatric Association, 1994) criteria for abuse were more specifically limited to problems in social functions, with cognitive, behavioral, and physiological symptoms more specifically linked to dependence. However, consistent, statistically based evidence supporting this separation of abuse and dependence has been lacking (Muthen, Grant, & Hasin, 1993).

Even if the factor structure of abuse and dependence criteria for different drug classes is resolved or if new factors are discerned, this may still not be sufficient for identifying quantitative traits that will be most useful for molecular genetic studies. Indeed, no matter how central certain symptoms may be to a particular factor (i.e., no matter how high the factor loadings), they will be pointing our molecular genetic efforts in the wrong direction if they are not highly heritable. Thus, there is a need to examine both the individual heritabilities of each symptom, in addition to investigating how well each symptom maps on to liability for SUD. Although there is consistent evidence from a small group of studies for the presence of significant genetic influences on illicit SUDs using diagnoses of dependence and/or abuse (see Jacobson, 2005; Prescott, Maes, & Kendler, 2005 for reviews), some individual symptoms or behaviors may show stronger genetic influences than others. Thus, the current strategy of using aggregate categories of abuse and/or dependence may not provide the best phenotypes from a molecular genetic perspective.

Finally, the use of a single set of diagnostic criteria for all types of substances may be obscuring potentially meaningful differences in genetic and environmental etiology. Drug classes differ in terms of physiological and metabolic effects, behavioral and affective consequences, and cognitive effects. For example, Nelson, Rehm, Uğüstün, Grant, and Chatterji (1999) found that experiencing withdrawal symptoms was more predominant in opiate dependence, whereas development of tolerance was more prominent in cocaine dependence. Social and legal implications can differ substantially as well. For example, it may be considered acceptable for a presidential candidate to have previously smoked marijuana, but public reaction would probably be radically different if a candidate admitted to having injected heroin. Despite the generic diagnostic criteria set for the various SUDs, such differences strongly suggest that useful information can still be gained by examining the patterns of individual criteria to see how they may differ across drug classes. Moreover, it is possible that different symptom patterns could reflect, in part, different genetic architectures for different drug classes.

1.2. Criteria for illicit substance abuse and dependence: single liability or two-factor model?

Although there is relatively consistent evidence among more recent studies for a one-dimensional structure of dependence criteria alone (especially among treatment samples; see Nelson et al., 1999 for brief review), factor-analytic studies of individual symptoms of both illicit drug abuse and illicit drug dependence are less common and have had mixed results. In a large study based predominantly on subjects from treatment settings (80% of sample), Feingold & Rounsaville (1995a) found support for a one-dimensional model of abuse and dependence criteria for alcohol, cocaine, cannabis, and sedatives using DSM-IV criteria assessed with the Composite International Diagnostic Interview (CIDI). However, in another published report using the same sample, CIDI-based criteria for dependence were found to be clearly distinct from five symptoms of abuse consequences as measured by the Addiction Severity Index (Feingold & Rounsaville, 1995b). In an even larger study, based primarily on subjects from the general population, Nelson et al. (1999) initially found support for a one-dimensional structure of past-year abuse and dependence symptoms for cannabis, cocaine, and opiates, based on the subset of the sample ($N = 215$ to 519) who met the threshold for lifetime use (i.e., six or more times). However, they did find a two-factor solution consistent with separate abuse and dependence factors when they further restricted their sample to the subset of individuals with only low-to-moderate symptom levels. Finally, Gillespie and colleagues used both factor analysis and Item Response Theory (IRT) to investigate the structure of lifetime DSM-IV criteria for abuse and dependence, using a population-based sample of 1196 male–male twin pairs from the Virginia Twin Registry (Gillespie, Neale, Prescott, Aggen, & Kendler, submitted for publication). Although results suggested a one-factor, single liability model for all illicit substances (cannabis, cocaine, hallucinogens, opiates, sedatives, and stimulants), the IRT analysis revealed that the individual symptoms assessed different mean levels of SUD liability across the different substance classes, and also varied substantially across substances in terms of their ability to discriminate among low and high levels of liability. Thus, there are clearly still uncertainties with regard to the factor structure of drug abuse and dependence for different types of illicit substances.

1.3. Genetic influences on illicit substance use, abuse, and dependence

Liability to illicit SUDs clearly aggregates in families, suggesting the importance of genetic and/or shared environmental factors (Bierut et al., 1998; Croughan, 1985; Dinwiddie & Reich, 1993; Merikangas et al., 1998; Mirin, Weiss, Sollogub, & Michael, 1984; Rounsaville et al., 1991). Studies based on twin (e.g., Grove et al., 1990; Kendler, Karkowski, Corey, Prescott, & Neale, 1999; Kendler, Karkowski, Neale, & Prescott, 2000; Tsuang et al., 1996; van den Bree, Johnson, Neale, & Pickens, 1998) and adoptive (e.g., Cadoret, Winokur et al., 1996; Cadoret, Yates, Troughton, Woodworth, & Stewart, 1996; Yates, Cadoret, Troughton, & Stewart, 1996) samples have confirmed that while shared environmental factors may play a role in the initiation of substance use, genetic factors are the primary source of familial resemblance for illicit SUDs such as dependence, abuse, or a combination of abuse/dependence. Univariate estimates of the heritability of illicit substance abuse and dependence did vary across substance, ranging from 25% to 79%, with most in the 55–75% range.

To our knowledge, only two published studies have used multivariate behavioral genetic models to examine whether genetic liability to use and abuse of illicit substances is shared across substance classes or is substance-specific. The first, using data from the present sample, found that the majority of genetic influence on individual substances operated through a single underlying factor, indicating a shared genetic vulnerability to all illicit SUDs (Tsuang et al., 1998). There were significant substance-specific familial effects as well; however, there was not enough power to determine whether these effects were due to shared genes, shared environments, or both. The second study, using data from the Virginia Twin Registry, found nearly identical results (Kendler, Jacobson, Prescott, & Neale, 2003), although this study could not find any evidence for substance-specific genetic or environmental factors.

Comparing the magnitudes and sources of genetic influence across substance classes while using aggregate measures of substance abuse and/or dependence may over-simplify the role of genetic factors in the development of an SUD. Furthermore, although the heritabilities of individual symptoms of alcohol abuse and dependence have been examined previously (Johnson, van den Bree, & Pickens, 1996; Slutske et al., 1999), such parameters have rarely been estimated for other drugs of abuse; when they have been studied (e.g., Johnson, van den Bree, Uhl, & Pickens, 1996), the small size of the samples ($N = 38$ monozygotic (MZ) and 35 dizygotic (DZ) twin-pairs) suggests that the obtained estimates of genetic and environmental contributions to these symptoms are neither very precise nor robust. Larger samples are needed to provide ample power to investigate the underlying genetic and environmental etiologies for symptoms with low prevalence rates. Our prior work in this sample examining antisocial traits at the item level showed that shared environmental influences explained about six times more variance in juvenile antisocial traits than in adult traits, whereas genetic factors explained about six times more variance in adult traits than in juvenile traits (Lyons et al., 1995). One implication of such differences could be that they suggest different treatment or intervention strategies. Moreover, this work suggests that item-level data can produce useful results, even for low base-rate phenomena such as antisocial personality disorder or illicit SUD.

1.4. The present study

The present study adds to existing research by examining patterns of endorsement and heritability of individual symptoms of abuse and dependence across a variety of different illicit substances, using a large, population-based sample of male twins. First, we investigated the underlying factor structure of abuse and dependence symptoms and behaviors within each substance class. We were particularly interested in testing whether a single factor representing general liability to SUDs is a better fit to our data than a two-factor model, which may represent distinctions between abuse and dependence symptoms. Second, we estimated the heritabilities of each individual symptom, looking for patterns of symptoms that may be more or less “bgenetically loaded”. Finally, we compared and contrasted these results across the different illicit substance classes to investigate whether patterns are consistent across substance classes.

We focused primarily on illicit substances and not nicotine or alcohol for the following three reasons: 1) symptoms of nicotine dependence do not map on to current DSM-IV symptomatology for alcohol or illicit substance abuse and dependence, making comparisons of nicotine with these other substances difficult; 2) using this sample, we have previously published results of univariate biometrical analyses of alcohol symptoms (Slutske et al., 1999); and 3) although there is evidence that alcohol, nicotine, and illicit substance use and misuse may share some common genetic vulnerabilities, the same studies also provide convincing evidence for specific genetic factors that influence illicit SUDs that are separate from those that influence the more common substances of nicotine and alcohol (e.g., Fu et al., 2002; Hettema, Corey, & Kendler, 1999; Kendler, Prescott, Myers, & Neale, 2003; True, Heath et al., 1999; True, Xian et al., 1999). Nevertheless, we have data from six separate types of illicit substances, which allows us to make some substantive comparisons across substance type, and we report factor analytic results of these illicit substances as well as alcohol.

In summary, the purpose of this first phase of our study of Alternate Phenotypes of Substance Abuse is to investigate whether patterns of individual symptoms of illicit SUDs can be used in the development of alternative phenotypes for SUDs that may provide a greater genetic “signal” in molecular genetic studies. Future goals will be to: 1) extend these analyses through the use of multivariate behavioral genetic models; 2) investigate the utility of developing alternative phenotypes for SUDs using other methods, such as examining comorbidity of SUDs with other psychiatric disorders, or looking for heterogeneity in genetic and environmental pathways to SUD; and 3) use the most informative and heritable alternate phenotypes to test for genetic linkage and association with DNA markers in an attempt to isolate chromosomal loci and, ultimately, the individual genes that influence risk for substance use, abuse, dependence, and related behaviors.

2. Methods

2.1. Sample

Data for this report come from a sample of male–male twins born between 1939 and 1957 who are part of the Vietnam Era Twin (VET) Registry. Twins were recruited to the Registry

after being identified in the late 1980s through a search of the Department of Defense computer files of discharged servicemen. Both siblings had to have served on active military duty during the Vietnam era, lasting from May 1965 to August 1975. Servicemen were selected as potential twins if they had the same last name and same birthdate. Of 5.5 million veterans, 15,711 potential twin pairs were identified and twinship was confirmed using military records. Zygosity was confirmed using questions on similarity and limited blood-group typing.

Information on drug and alcohol use was collected by telephone interview in 1992, as part of the Harvard Twin Study of Substance Abuse. Information obtained during this interview included basic demographic data, life-time histories of drug and alcohol use and misuse, and lifetime history of other psychiatric disorders. Of the 10,253 individuals who were eligible for the study, data was successfully collected from 8169 individuals for a response rate of 79.7%. The present study is restricted to twins in which both members of the pair participated ($N = 1874$ MZ and $N = 1498$ DZ pairs), resulting in a final total sample size of 6744.

The study population of the VET Registry has been described elsewhere (Eisen, True, Goldberg, Henderson, & Robinette, 1987); participants in the Harvard Twin Study of Substance Abuse were similar in composition to the full VET Registry sample. Briefly, participants were 90% non-Hispanic white, 4.9% African-American, 2.7% Hispanic, 1.3% Native American, and 0.7% other ethnicity. They had a mean age of 44.6 years (S.D. 2.8; range 36–55); 33.3% had a high school education, 15.8% attended a vocational school, 38.6% were college graduates, and 10.6% obtained graduate training and/or a graduate degree. At the time of the interview, 92.6% were employed full-time, 1.8% part-time, and 5.6% were not employed. 75% were married and 11% were never married. Study participants came from all 50 states of the United States.

2.2. Assessment

Telephone interviews were conducted by trained interviewers at the Institute for Survey Research at Temple University. The Diagnostic Interview Schedule, Version III, Revised (DIS-III-R; Robins, Helzer, Cottler, & Goldring, 1988) was employed to obtain information on abuse of and dependence on different licit and illicit substances. The DIS-III-R is a structured interview based on DSM-III-R criteria for substance abuse and dependence, and is commonly used in large-scale studies, including the NIMH Epidemiologic Catchment Area Survey (Bourdon, Rae, Locke, Narrow, & Regier, 1992). This instrument was designed specifically to be administered by lay interviewers and it has demonstrated reliability and validity (Helzer et al., 1985).

Information on six different classes of illicit substance use was obtained: 1) cannabis, 2) sedatives, 3) opiates, 4) hallucinogens, 5) stimulants, and 6) cocaine. Cannabis included the use of marijuana, hashish, ganja, or bhang. The category sedatives included barbiturates, sleeping pills, Valium, Seconal, Librium, tranquilizers, Quaaludes, and Xanax. Opiates included heroin, opium, morphine, codeine, Demerol, Percodan, Methadone, Darvon, and Dilaudid. Hallucinogens were assessed as the use of PCP, LSD, mescaline, peyote, psilocybin, and DMT.

Respondents who reported using any of these classes of illicit drugs at least five times in their lifetime were asked additional questions regarding 11 specific symptoms of abuse and dependence. Four of these questions corresponded to traditional symptoms of abuse: 1) continuing to use drugs despite health problems; 2) continuing to use the drug despite social or legal problems; 3) continuing to use the drug despite emotional problems; and 4) using the drug in situations where it increased the likelihood of getting hurt (hazardous use). The remaining seven questions tapped into traditional symptoms of physical dependence, including: 1) spending a lot of time using the drug; 2) giving up important activities to use the drug; 3) being high or using the drug while at work or taking care of children; 4) using more drug than intended; 5) developing a tolerance; 6) feeling dependent; and 7) being unable to stop using the drug.

Alcohol abuse and dependence symptoms were ascertained in a similar manner, with the following two differences. First, five separate alcohol questions were asked concerning specific social/legal problem symptoms, compared to only one question for illicit drugs. In order to make the factor analysis of alcohol comparable with the other illicit substances, a score of “1” was given for that symptom if the respondent endorsed any of the five different questions. Similarly, the symptom of feeling dependent on alcohol was created from four separate questions about having withdrawal symptoms, drinking upon waking, and drinking to reduce a hangover or shakes. Again, responses were combined across individual questions using an “either/or” rule to make results comparable to those of illicit SUDs.

For all substance classes, if a respondent reported that he had never experienced a given symptom, follow-up questions for specific substance classes were not asked. The use of “stem questions” to assess individual symptoms resulted in the following patterns of missing data. First, subjects who had never used the substance or had used it less than five times were given missing values for all responses for all individual symptoms for that particular substance class, because the underlying liability to each symptom is unknown. Second, if a subject failed to respond to the stem questions regarding frequency of use for a given substance class, he was also assigned missing values for all symptoms for that particular substance class. Finally, if a subject was missing data for a stem question for a particular symptom due to non-response, he was also given missing values for that symptom for all substance classes. It should be noted that the majority of missing data is due to the non-use of a particular substance (the first scenario above), indicating that the underlying liability to endorsing specific symptoms of abuse or dependence is unknown or has not been measured. Few subjects had “true” missing data due to non-response.

If a subject had used a specific substance class five or more times in his lifetime, but had never experienced a given symptom, he was given a score of 0 for that particular symptom for the given substance class. If a subject indicated that he had used a particular substance five or more times *and* indicated that he had experienced a given symptom, his score for that symptom for that particular substance class was based on his response to the follow-up question regarding that specific substance. Responses in this instance could therefore be yes (1) or no (0). Thus, in summary, each individual symptom had a possible value of missing, 0, or 1, for each substance class. Only non-missing data are counted as valid in the analyses,

so individual *N*s vary across substance class, although the analyses themselves were conducted using all cases with any non-missing data.

2.3. Statistical analyses

All analyses were conducted using the software package Mx (Neale, Boker, Xie, & Maes, 2003). Models were fit to the raw data, which allows for the inclusion of subjects with some missing data. Because the data were binary (i.e., symptoms were either present or absent), threshold models were used where the thresholds (*z*-scores) were estimated based on the assumption that there is a continuous variable of liability to response, which is normally distributed in the population. The response categories of no and yes are given according to whether the subject is below or above an abrupt threshold. Variance of each binary symptom was constrained to unity, as were variances of all latent variables.

For the factor analysis of individual symptoms, models were fit to data from each individual twin, and all twins with non-missing data were included. For the biometrical analyses of individual symptoms, models were fit to data at the twin-pair level (i.e., both twins within a given pair are analyzed as a single unit). Twin pairs were included in these analyses even if one twin had missing data, as the exclusion of cases with missing data can lead to bias in parameter estimates.

2.3.1. Factor analysis—For the factor analysis of individual symptoms, a marginal maximum likelihood (MML) approach in Mx was used (Neale, Aggen, Maes, Kubarych, & Schmitt, 2006). MML is a simple procedure to speed up the analysis of binary and ordinal data when the factor structure of the model is relatively simple. By integrating across the factor space, the likelihood of the vector of $2m$ observed item responses (m from each twin) can be computed as the product of m integrals of the bivariate normal distribution. This simpler calculation is carried out repeatedly in order to integrate across the factor space. For large numbers of items, MML may be practical, whereas direct integration of the $2m$ dimensional normal distribution is not. MML produces parameter estimates which are equivalent to, and which share the advantageous properties of, maximum likelihood estimates in general. It is also suitable when there is a considerable amount of missing data (such as this case, when missing data occur through the non-endorsement of the use of a particular substance class).

We tested the fit of both one-factor and two-factor models. One of the factor loadings in the two-factor models was set to zero, in order to identify the two-factor solution. Parameter estimates were then rotated using the orthogonal Varimax rotation option in SAS to obtain the factor loadings. Fitting each factor model to observed data generates a fit function in the form of a -2 log-likelihood ($-2LL$), with corresponding degrees of freedom (df) calculated as the number of observed statistics minus the number of estimated parameters. The one-factor model is a nested submodel of the two-factor model, so models can be compared by subtracting the $-2LL$ of the more parsimonious model (i.e., the one-factor model) from the $-2LL$ of the less constrained model (i.e., the two-factor model). Given certain regularity conditions (Lehmann, 1998), the resulting difference in log likelihood is distributed as a chi-square statistic with df equal to the difference in number of parameters estimated between

the two models. This log likelihood ratio test was used to determine whether the one-factor model fit the data significantly more poorly than the two-factor model.

2.3.2. Biometrical models—The heritability of each of the 11 symptoms was estimated using the standard univariate ACE model for analyzing twin data. This model, shown in Fig. 1, assumes that variation in a given behavior or trait is due to additive genetic (A), shared environmental (C), and non-shared environmental (E) factors. Additive genetic factors are correlated 1.0 among MZ twin pairs, because MZ twins share 100% of their genes. In contrast, additive genetic factors correlate 0.5 among DZ twins, because on average, DZ twins share 50% of their genes identical-by-descent (IBD). By definition, shared environmental influences are factors that are shared across twins within a family and that vary across families, such as parental education level, family socioeconomic status, or shared peer groups. These factors are assumed to have the same effect on each twin, regardless of zygosity. Thus, the correlation of shared environmental factors is 1.0 for both MZ and DZ twins. Conversely, non-shared environment refers to any environmental influences that serve to make individuals dissimilar, and are uncorrelated across twin pairs. Non-shared environmental influences can occur if exposure to the environment is not shared by twins, such as effects due to birth order (e.g., differences in birth weight across twins), accidents, and different peer group experiences. Likewise, objectively “shared” environmental factors that have different influences on behavior for individuals in the same family, regardless of their level of genetic similarity, would be estimated as part of the non-shared environmental variance. Errors of measurement are also non-shared environmental influences, as errors are assumed to be uncorrelated across individuals. For these analyses, Mx fits the models to raw data, using full information maximum likelihood (FIML). The resulting estimated genetic, shared environmental, and non-shared environmental parameters can be used to determine the proportion of phenotypic variation due to these factors. The proportion of the variance that is due to additive genetic factors is known as the narrow heritability (h^2).

3. Results

3.1. Prevalence of SUDs

Approximately 10% of the sample had a lifetime diagnoses of abuse of or dependence on at least one illicit substance. The rate of any drug dependence was 9.5%. This rate is similar to that found for lifetime history of substance dependence among male participants in the National Comorbidity Survey (Kessler et al., 1997). Table 1 contains frequencies of endorsements of ever using each drug and using each drug more than five times. Using a drug more than five times is the threshold that leads respondents to be administered questions assessing the symptoms of substance abuse and dependence in the DIS-III-R interview. Marijuana was the most commonly used drug (47.3%) and opiates the most infrequently used category of drug (7.4%). Approximately half of respondents who had ever used a given substance reported using the drug on five or more occasions.

Fig. 2 presents the proportion of respondents who endorsed each of the 11 DSM-III-R abuse and dependence symptoms for marijuana, cocaine, opiates, sedatives, stimulants, and

hallucinogens among subjects who reported using each drug more than five times. A number of patterns are visible in the figure. For example, over one-third of all responders reported using substances in situations which increased their chances of being hurt, with marijuana users reporting the highest frequencies (44%). In contrast, reports of health problems were rare (b 7% of responders), and were similarly endorsed by users of all substances. Cocaine and opiate users generally reported higher frequencies of each symptom compared to users of other substances. This pattern was most pronounced for symptoms referring to possible physical addiction, such as using more than intended, feeling dependent, having difficulty stopping use, and having an increased tolerance. Cocaine users were also more likely to endorse symptoms reflecting adverse consequences of use, such as emotional or social/legal problems. Finally, sedative and hallucinogen users were least likely to report using the substance while working or taking care of children.

3.2. The underlying factor structure of SUD symptoms

In the first stage of our analysis, the symptoms for each substance were subjected to factor analysis. For marijuana, cocaine, opiates, sedatives, stimulants and alcohol, switching from a two-factor solution to a one-factor solution resulted in a statistically significant reduction in the goodness of fit of the model (Table 2). Therefore, for these six substances a two-factor solution was selected. For hallucinogens, the fit of a one-factor model was not significantly worse than that of a two-factor model, indicating that symptoms of hallucinogen abuse and dependence may represent a single underlying liability to SUD, although the low base-rates of hallucinogen use suggest that caution should be exercised when interpreting these results.

Table 3 displays the rotated factor loadings from the factor analyses of marijuana, cocaine, opiates, sedatives, stimulants, and alcohol (hallucinogens were not included because only one factor was identified). What is immediately clear from this table is that patterns of factor loadings do not map cleanly onto distinctions between abuse and dependence symptoms for any of the six illicit substance classes, or for alcohol. Moreover, if we assume meaningful factor loadings are those >0.50 , patterns of factor loadings also vary across substance classes. For marijuana, the first factor seems to reflect patterns and consequences of use (e.g., spend time using marijuana and give up important activities to use marijuana) while the second factor primarily reflects physical addiction (feels dependent, experiences tolerance, and can't stop using). For cocaine, the first factor seems to primarily reflect problematic consequences of cocaine use (e.g., health, social, legal, and emotional problems) while using more cocaine than intended and spending a lot of time using load primarily on the second factor. The first factor for opiates seems to reflect manifestations of physical addiction, while the second factor seems to reflect negative consequences of use. Feeling dependent, feeling unable to stop use, and experiencing tolerance primarily define the first factor for sedatives. Giving up important activities in order to use sedatives and using the drug when in hazardous situations load highest on the second factor. For stimulants, the first factor primarily reflects consequences of stimulant use, while the second factor has the highest loadings for feeling dependent and being unable to stop using. The first factor for alcohol is a combination of dependency and adverse consequences of use while the second factor primarily reflects over-consumption.

3.3. Genetic influences on individual symptoms of SUD

Table 4 shows the heritability of each of the symptoms for each illicit drug class, estimated from the full univariate ACE model (the heritabilities of individual symptoms of alcohol abuse and dependence have been previously published by Slutske et al., 1999, so are not presented here). It should be noted that nearly all of the 95% confidence intervals surrounding these estimates include zero, suggesting that although our sample size was relatively large, low base-rates of some illicit drug use symptoms yielded reduced power to find statistically significant genetic influences. Nevertheless, although we may not be able to determine the statistical significance of the genetic factors, the pattern of results suggests the following general conclusions when focusing on non-zero estimates of heritability.

First, none of the 11 symptoms show consistent, non-zero heritability estimates across all substance classes, indicating that whether or not there are genetic influences on symptoms or behaviors depends, in part, on the type of substance. Similarly, the magnitudes of the heritability estimates differ substantially across different drug classes, ranging from 0 to 0.93. Although the large confidence intervals surrounding each heritability estimate suggest that comparing absolute magnitudes across substances may be difficult, the fact that there is such a wide range of heritability estimates again suggests that the amount of variance accounted for by genetic factors varies across substance class. However, most of the non-zero heritability estimates are estimated between 0.20 and 0.45, indicating that overall, genetic influences on individual symptoms are likely to be relatively modest.

Second, there is also a notable lack of consistency in the patterning of heritabilities for individual symptoms across different substance classes. This is particularly true among the four symptoms that traditionally index abuse. Only cannabis showed non-zero estimates of heritability for all four symptoms. Using the substance despite adverse emotional consequences was estimated as non-zero for all substances but hallucinogens. In contrast, using the drug despite experiencing physical health problems also had non-zero heritability estimates only for cannabis and hallucinogens (although note from Fig. 2 that this symptom had the lowest endorsement rate overall). Using the drug despite problems with family, friends, job, or police had moderate-to-high heritability for cannabis, sedative, and stimulant users, but heritability was estimated at zero for cocaine, hallucinogen, and opiate users. Finally, there were non-zero estimates of heritability for using the drug in a situation that increased likelihood of getting hurt among cannabis, stimulant, opiate, and hallucinogen users.

There is slightly more consistency in results for the seven traditional symptoms of dependence. Both spending a lot of time using the drug and giving up important activities to use the drug showed non-zero heritabilities among cannabis and stimulant users, although genetic influences on giving up important activities to use the drug were also non-negligible (.30) among sedative users. Reports of using more drugs than intended and developing a tolerance for the drug were heritable for sedative, stimulant, and opiate users. Stimulants and opiates also showed non-zero estimates of heritability for developing a tolerance to the drug, as was the estimate for cocaine. Interestingly, heritabilities for the two indices of physical addiction showed the most amount of consistency across substances. Specifically, feeling

dependent and being unable to stop using the drug had non-zero estimates of heritability for cannabis, stimulants, cocaine, and opiates, but not for sedatives or hallucinogens.

Finally, although the relatively broad 95% confidence intervals for most substances suggest caution in interpretation of these results, there may be some utility in focusing on patterns of heritability within a substance class. Both cannabis and stimulants had non-zero estimates of heritability for most of the symptoms (i.e., 9 out of 11), whereas non-zero heritabilities were obtained for only four symptoms among hallucinogen users, and only four symptoms among sedative users. Although this may be related to differences in the overall prevalence of using these substances, it is noted that heritabilities of six of the symptoms for opiate users were also estimated as non-zero, despite the fact that rates of endorsement of individual symptoms were lower for opiate use than for any other substance (individual *N*s ranged from 15 to 71).

4. Discussion

Although some studies have found that drug abuse and dependence criteria load on a single factor, our results indicate a significantly better fit for a two-factor solution for cannabis, sedatives, stimulants, cocaine, and opiates. Even though we found evidence for two factors for most drugs, it is important to note that the factors for the different drug classes did not separate neatly into an abuse factor and a dependence factor. Rather, the factor structure for each substance was somewhat—if not entirely—distinct from the structures seen for other drugs, and the factors represented within each drug class represented many dimensions beyond simple abuse and dependence. For example, most drug classes had a factor that corresponded to adverse consequences or social problems, either of which are arguably simpler constructs than either abuse or dependence, and thus might be presumed to have simpler causes (genetic or otherwise) that are easier to detect. This reinforces the value in pursuing alternate phenotypes in the study of SUDs.

The fact that the heritabilities were very different for particular criteria across different drug classes could indicate that they reflect different genetic influences for different substances. But they could also reflect pleiotropic effects; that is, it may be that common genetic influences manifest themselves in different ways depending on the substance being used. Further analysis of heritabilities might indicate that some symptom clusters (rather than individual symptoms) will provide more robust measures. The table of heritabilities is merely descriptive in nature, and the wide confidence intervals for the heritability estimates preclude definitive conclusions. Nevertheless, we believe that this approach may be useful for making inferences for future hypothesis-generation regarding alternate drug abuse or dependence phenotypes. Future directions may include developing more robust traits for molecular genetic studies via multivariate genetic analyses as well as efforts to map the heritabilities onto the drug abuse/dependence factors.

The results of this study represent an initial “filtering” step in moving away from traditional definitions of SUDs, such as DSM abuse or dependence, and toward alternate phenotypes of these conditions, which may be more amenable to molecular genetic analysis. There is a strong rationale and many potential advantages to be realized in pursuing alternate

phenotypes of SUDs. For example, the detection of inter-substance differences in core symptoms and heritabilities that we have revealed helps to identify both similarities and differences between substances that should be recognized and exploited in subsequent diagnostic schemas and molecular genetic studies. Thus, those symptoms with the highest factor loadings and highest heritabilities may be, in isolation, prime candidate phenotypes for analysis. In addition, if certain substances have similar profiles of factor loading and heritability for a particular symptom—and if subsequent analyses bear out that the genetic contribution to the symptom across substances is due to shared genetic factors—then subjects expressing that symptom in response to either drug might be pooled for genetic analyses. Another obvious ramification of this rationale is that substances that have very different factor structures and patterns of symptom heritability should be studied in isolation of each other.

Some limitations of the present study should also be noted. Our twin sample included men only, so we do not know how the results may generalize to women. In addition, we focused on lifetime endorsements, so we were not able to model the severity of symptoms (e.g., duration, quantity, etc.) across individuals. Similarly, the liability for endorsing a given symptom is known only for those respondents that have tried the substance five or more times; individuals who had never tried the substance or tried it less than five times were given missing data. Thus, the results of the factor analysis and biometrical modeling may only generalize to the population of substance users. In addition, this bselection effectQ has the potential to bias heritability estimates (Martin & Wilson, 1982; Neale, Eaves, Kendler, & Hewitt, 1989). Generally, selection effects result in an attenuation of correlations for both MZ and DZ twins, suggesting that the use of a selected sample may increase the amount of variance attributed to non-shared environmental effects, and decrease estimates of both genetic and shared environmental factors. For the biometrical analyses, bivariate analyses including both the initiation bstemQ question and the response to the individual symptoms can lessen these effects, and can similarly estimate the degree to which genetic factors influencing substance use and substance misuse are overlapping (e.g., Heath, Martin, Lynskey, Todorov, & Madden, 2002; Kendler, Neale et al., 1999). These complex analyses are beyond the scope of the present study, but may be the focus of future investigations.

Rates of endorsement of some questions were low for all substances, but especially for opiates, hallucinogens, and cocaine; this is reflected in the very wide confidence intervals on these heritability estimates, most of which include zero. However, additional analyses (Not shown) suggest that models which assume non-shared environment as the sole source of variance do not fit as well as models which also include familial influence (i.e., genetic and shared environmental factors), indicating that our limited power pertains primarily to our ability to differentiate genetic and shared environmental influences. The 11 items selected for analysis for each drug generally map onto DSM-III criteria. It may be that there are characteristics (either broader or narrower) that are not part of the DSM that would be useful for defining strong traits or phenotypes for genetic analysis. Likewise, more basic, biologically based phenotypes might be better for analysis as alternate phenotypes because they presumably map more tightly to the risk genes. We note as an additional limitation that there are other ways of examining alternative phenotypes for SUDs, including the use of

multivariate analysis to look for patterning of genetic factors both within and across substance classes, and the use of co-morbidities with other psychiatric disorders to define subgroups of individuals whose SUD may be more or less heritable. Nevertheless, we believe that the present study represents a reasonable first step in this direction, and that future studies can and should address these issues.

Finally, in addition to identifying between-substance heterogeneity as we have presently illustrated, a focus on more elemental symptom-based phenotypes may allow us to identify heterogeneity within some of the SUDs as presently defined. For example, some subgroup of opiate-dependent individuals may express extreme physical withdrawal and no other ill effects, another group may have limited withdrawal symptoms but extremely risky patterns of use, and still other individuals may experience neither set of symptoms. These distinctions might be useful in forming more homogeneous subgroups of subjects who may also have more uniform genetic etiologies for their SUD. The ultimate goal of this line of inquiry is to identify those symptoms (or, from our next phase of work, symptom clusters) that identify core features of an SUD, which are also maximally heritable. Overall, this “alternate phenotype-hunting” strategy should allow us to identify phenotypes that provide greater genetic “signals” relative to the noise that is inherent in studying complex human phenomena such as SUDs (i.e., yield greater power). This, in turn, should facilitate the discovery of the genes that predispose individuals to these conditions.

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Fig. 1.
Univariate ACE model.

Fig. 2.

Percent of those subjects reporting use of at least one of the drugs more than five times, endorsing each of 11 DSM-III-R abuse and dependence symptoms for each drug class.

Table 1

Frequency and percent of self-reported use of cannabis, cocaine, opiates, sedatives, stimulants, and hallucinogens in the VETR registry

Drug	Number (%)	
	Ever use?	Ever use>5 times?
Cannabis		
No	3546 (52.7)	4679 (69.6)
Yes	3181 (47.3)	2047 (30.4)
Cocaine		
No	5731 (85.2)	6203 (92.2)
Yes	995 (14.8)	523 (7.8)
Hallucinogens		
No	5864 (87.2)	6339 (94.2)
Yes	862 (12.8)	387 (5.8)
Opiates		
No	6228 (92.6)	6510 (96.8)
Yes	498 (7.4)	216 (3.2)
Sedatives		
No	5902 (87.8)	6263 (93.1)
Yes	824 (12.2)	463 (6.9)
Stimulants		
No	5414 (80.5)	5911 (87.9)
Yes	1312 (19.5)	814 (12.1)

Table 2

Relative support for one- and two-factor models from factor analysis

Drug	- 2 Log(likelihood)	df	Difference χ^2	df	p
Alcohol					
One-factor model	43,473.405	66,725			
Two-factor model	43,365.231	66,714	108.174	10	<0.001
Cannabis					
One-factor model	14,475.470	22,467			
Two-factor model	14,397.908	22,457	77.562	10	<0.001
Cocaine					
One-factor model	3830.054	5714			
Two-factor model	3872.158	5724	42.104	10	<0.001
Hallucinogens					
One-factor model	2256.547	4229			
Two-factor model	2247.486	4219	9.060	10	0.530
Opiates					
One-factor model	1681.071	2349			
Two-factor model	1640.128	2339	40.943	10	<0.001
Sedatives					
One-factor model	2890.789	5062			
Two-factor model	2859.463	5052	31.326	10	<0.001
Stimulants					
One-factor model	5254.734	8930			
Two-factor model	5210.555	8920	44.179	10	<0.001

Table 3Factor loadings^a after varimax rotation of two-factor models of symptoms in six drug classes^b

A) Cannabis	Factor 1	Factor 2
	Patterns of use	Physical addiction
Spent time using or getting drug	0.655	0.501
Gave up activities to use drug	0.770	0.338
Used substance while at work (taking care of children)	0.618	0.413
Used more than intended	0.598	0.433
Tolerance	0.476	0.555
Felt dependent	0.479	0.730
Tried to stop but couldn't	0.290	0.909
Health problems	0.442	0.278
Social/legal problems	0.599	0.428
Emotional problems	0.643	0.339
Hazardous use	0.641	0.197
B) Cocaine	Adverse consequences	Over-consumption
Spent time using or getting drug	0.425	0.894
Gave up activities to use drug	0.664	0.611
Used substance while at work (taking care of children)	0.651	0.464
Used more than intended	0.432	0.762
Tolerance	0.534	0.652
Felt dependent	0.641	0.593
Tried to stop but couldn't	0.685	0.526
Health problems	0.714	0.290
Social/legal problems	0.737	0.501
Emotional problems	0.756	0.480
Hazardous use	0.598	0.395
C) Opiates	Physical addiction	Adverse consequences
Spent time using or getting drug	0.641	0.539
Gave up activities to use drug	0.341	0.811
Used substance while at work (taking care of children)	0.173	0.535
Used more than intended	0.666	0.409
Tolerance	0.732	0.396
Felt dependent	0.882	0.361
Tried to stop but couldn't	0.889	0.244
Health problems	0.323	0.648
Social/legal problems	0.394	0.919
Emotional problems	0.541	0.568

Hazardous use	0.357	0.557
D) Sedatives	Dependence	Social problems
Spent time using or getting drug	0.588	0.597
Gave up activities to use drug	0.383	0.782
Used substance while at work (taking care of children)	0.539	0.529
Used more than intended	0.640	0.439
Tolerance	0.609	0.469
Felt dependent	0.811	0.383
Tried to stop but couldn't	0.959	0.069
Health problems	0.487	0.274
Social/legal problems	0.540	0.633
Emotional problems	0.659	0.457
Hazardous use	0.116	0.822
E) Stimulants	Adverse consequences	Dependence
Spent time using or getting drug	0.696	0.469
Gave up activities to use drug	0.806	0.359
Used substance while at work (taking care of children)	0.500	0.512
Used more than intended	0.688	0.490
Tolerance	0.627	0.517
Felt dependent	0.445	0.816
Tried to stop but couldn't	0.327	0.907
Health problems	0.446	0.529
Social/legal problems	0.750	0.423
Emotional problems	0.700	0.431
Hazardous use	0.586	0.211
F) Alcohol	Dependence	Over-consumption
Spent time using or getting drug	0.383	0.884
Gave up activities to use drug	0.529	0.734
Used substance while at work	0.501	0.466
Used more than intended	0.510	0.579
Tolerance	0.568	0.497
Felt dependent	0.678	0.455
Tried to stop but couldn't	0.361	0.153
Health problems	0.647	0.375
Social/legal problems	0.674	0.449
Emotional problems	0.664	0.518
Hazardous use	0.515	0.412

^a Factor loadings 0.50 are presented in **bold** font.

^b Hallucinogens were excluded since those data equally supported one- and two-factor models.

Table 4

Estimated heritabilities for 11 drug use symptoms for 6 six illicit drug categories from the Harvard twin study

Symptom	Cannabis	Sedatives	Stimulants	Cocaine	Opiates	Hallucinogens
Spent time using or getting drug	.39	0	.43	.08	0	0
95% CI	.23; .48	0; .34	0; .67	0; .81	0; .95	0; .67
Gave up activities to use drug	.19	.30	.20	0	0	0
95% CI	0; .44	0; .82	0; .61	0; .82	0; .81	0; .74
Used substance while at work (taking care of children)	.04	0	0	.25	0	.20
95% CI	0; .54	0; .66	0; .58	0; .80	0; .57	0; .85
Used more than intended	0	.41	.26	0	.28	0
95% CI	0; .38	0; .74	0; .55	0; .66	0; .84	0; .50
Tolerance	0	0	.25	.41	.38	0
95% CI	0; .36	0; .71	0; .53	0; .73	0; .87	0; .77
Felt dependent	.33	0	.32	.43	.34	0
95% CI	0; .49	0; .36	0; .63	0; .75	0; .86	0; .97
Tried to stop but couldn't	.44	0	.12	.59	.10	.01
95% CI	0; .61	0; .74	0; .61	0; .88	0; .82	0; .95
Health problems	.13	0	0	0	0	.66
95% CI	0; .57	0; .83	0; .71	0; .86	0; .75	0; .97
Social/legal problems	.14	.61	.40	0	0	0
95% CI	0; .45	.10; .91	0; .70	0; .86	0; .96	0; .93
Emotional problems	.12	.23	.12	.48	.93	0
95% CI	0; .42	0; .71	0; .49	0; .88	0; .99	0; .91
Hazardous use	.27	0	.09	0	.34	.76
95% CI	0; .40	0; .30	0; .43	0; .47	0; .89	0; .94