

Longitudinal modeling of genetic and environmental influences on self-reported availability of psychoactive substances: alcohol, cigarettes, marijuana, cocaine and stimulants

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ABSTRACT

Background. Although an obvious environmental factor influencing drug use, the sources of individual differences in drug availability (DA) are unknown.

Method. This report is based on 1788 adult males from the Mid-Atlantic Twin Registry who participated in a structured telephone interview that included retrospective assessments of DA (cigarette, alcohol, marijuana, cocaine and stimulants) between ages 8 and 25. We fitted a biometric dual change score (DCS) model, adapted for ordinal data, to model latent growth and estimate the genetic and environmental components of variance over time.

Results. DA, despite being considered an environmental risk factor, is under both genetic and environmental control. For cigarette, alcohol, marijuana and cocaine availability, there was an overall increase in additive genetic variance and a decline in shared environmental variance over time. Non-shared environmental variance remained steady. Stimulant availability did not follow this pattern. Instead, there was an upswing in shared environmental effects with increasing age.

Conclusion. We have modeled the genetic and environmental architecture of changes in DA across adolescence. The rise in additive genetic variance over time coincides with acceleration in the expression of individual differences, probably brought on by an increase in personal freedom and a reduction in social constraints. Understanding the etiology of DA is likely to reveal key components, acting directly or indirectly, in the pathway(s) leading to drug initiation, abuse and dependence.

INTRODUCTION

Drug availability is the most obvious environmental factor that influences addiction.

(Volkow & Li, 2005)

This study explores the genetic and environmental etiology of drug availability (DA) from mid-childhood through early adulthood. The determinants of drug initiation, regular use and abuse are complex and include heritable

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characteristics as well as environmental factors. Although a number of twin studies reveal that both genetic and environmental effects explain significant proportions of variance in the liability to initiate nicotine, alcohol, cannabis and other illicit substances (Heath & Martin, 1988; Prescott *et al.* 1994; Kendler *et al.* 1999*a,b*; Sullivan & Kendler, 1999; Rhee *et al.* 2003), they do not provide any information on the antecedent pathways leading to drug initiation. The current goal should be to move beyond calculating heritabilities (basic genetic epidemiology paradigm), towards modeling developmental and environmental risk factors (advanced genetic epidemiology) contributing to drug initiation.

An obvious environmental risk factors for drug initiation is DA. Previous studies have repeatedly found higher rates of substance use among individuals with substance-using peers and among individuals in social and environmental contexts where drugs are easily available (Dembo *et al.* 1979; Hofler *et al.* 1999; Coffey *et al.* 2000; Alexander *et al.* 2001; Korf, 2002; Freisthler *et al.* 2005*a,b*). Although commonly assumed to be an environmental risk factor, it is plausible that variation in DA is partly a result of genetic factors. For example, the extent to which an individual seeks out drugs may be partly due to personality factors, such as extraversion and sensation seeking, for which there is evidence of substantial genetic variation (Eaves & Eysenck, 1975; Eaves, 1978; Eaves & Young, 1981; Eysenck, 1982; Loehlin, 1982). Likewise, deviant and substance-abusing peers are well-documented risk factors for drug use (Fergusson *et al.* 1995; von Sydow *et al.* 2002). The liability to report having deviant peers is partly determined by genetic effects (Iervolino *et al.* 2002; Walden *et al.* 2004; Cleveland *et al.* 2005; Saudino *et al.* 2005). Therefore, it is likely that some variation in DA may be under some genetic control.

The aim of this paper was to estimate, in a large population-based sample of adult male twins, genetic and environmental factors contributing to individual differences in self-reported DA. We have examined alcohol, cigarettes, marijuana, cocaine and stimulants across a developmental period spanning ages 8–25. To this end, we fit a biometrical dual change score (DCS) model, adapted for ordinal

data, that can estimate the genetic and environmental variation in DA over time.

METHOD

Sample and assessment procedures

This report is based on data collected in the third wave of interviews in a study of adult male twins from the Virginia Twin Registry. The sample is described in detail elsewhere (Prescott & Kendler, 1999; Kendler *et al.* 2003). In brief, twins were eligible for participation in the study if one or both twins were successfully matched to birth records, a member of a multiple birth with at least one male, Caucasian, and born between 1940 and 1974. Of 9417 eligible individuals for the first wave (1993–1996), 6814 (72.4%) completed the initial interviews. At least 1 year later, we contacted those who had completed the initial interview to schedule a second interview. The second interview (1994–1998) was completed by 5629 (82.6%) of those who had completed the first interview.

The third interview wave, or ‘MM3’ (1998–2004), was completed solely by members of male–male twin pairs. Individuals were only eligible for the MM3 if they were from a male–male pair and if both members had been interviewed in wave 2. Retrospective measures of DA were completed by 1788 twins, aged 24–62 years ($\mu=40.3$, $s.d.=9.0$), representing a response rate of 74.8%. This included 464 monozygotic (MZ) and 284 dizygotic (DZ) twin pairs and 292 incomplete twin pairs (MZ=154, DZ=138).

Most subjects were interviewed by telephone. A small number were interviewed in person because of subject preference, residence in an institutional setting (usually jail), or not having a telephone. This project was approved by the Virginia Commonwealth University institutional review board. Subjects were informed about the goals of the study and provided informed consent before interviews. Interviewers had a Master’s degree in a mental health-related field or a Bachelor’s degree in this area plus 2 years of clinical experience. The two members of a twin pair were each interviewed by different interviewers who were blind to interview information about the co-twin.

The interview included retrospective assessments (i.e. pseudo-longitudinal reports) of DA

Table 1. Item response frequencies, test-retest correlations (*r*) and estimates of means (standard deviations) for each drug class by age, plus the model implied polychoric correlations

Age (years)	<i>n</i>	Very difficult	Somewhat difficult	Somewhat easy	Very easy	Test-retest ^a		Polychoric correlations ^b				
						<i>r</i>	Mean (s.d.)	8-11	12-14	15-17	18-21	22-25
Cigarettes												
8-11	1786	20.7	15.1	20.4	43.6	0.78	1.91 (2.33)	1.00				
12-14	1788	6.8	12.0	24.3	56.9	0.78	2.62 (1.81)	0.86	1.00			
15-17	1786	1.9	4.1	15.4	78.4	0.88	3.68 (1.77)	0.67	0.81	1.00		
Alcohol												
8-11	1787	40.3	21.6	17.2	20.8	0.52	0.51 (2.06)	1.00				
12-14	1788	20.8	22.8	27.1	29.2	0.75	1.32 (1.69)	0.85	1.00			
15-17	1788	5.9	11.1	30.9	52.0	0.65	2.30 (1.45)	0.60	0.75	1.00		
18-21	1788	0.7	1.7	8.6	88.4	0.52	4.20 (1.65)	0.29	0.45	0.65	1.00	
Marijuana												
8-11	1787	87.8	6.2	3.5	2.4	0.40	-3.10 (2.66)	1.00				
12-14	1788	64.4	16.4	10.7	8.4	0.78	-0.81 (2.15)	0.79	1.00			
15-17	1789	35.8	19.2	21.0	24.0	0.85	0.73 (2.08)	0.61	0.79	1.00		
18-21	1781	16.4	14.3	24.4	44.4	0.75	1.94 (2.00)	0.45	0.61	0.77	1.00	
22-25	1788	13.4	14.3	26.0	46.2	0.62	2.03 (1.85)	0.39	0.46	0.61	0.78	1.00
Cocaine												
8-11	1787	96.3	2.4	0.7	0.4	0.32	-3.67 (2.05)	1.00				
12-14	1787	87.8	8.6	1.8	1.7	0.41	-2.06 (1.77)	0.82	1.00			
15-17	1788	68.2	17.7	7.7	6.3	0.69	-0.86 (1.80)	0.65	0.82	1.00		
18-21	1780	45.4	20.7	16.9	16.4	0.75	0.18 (1.79)	0.47	0.64	0.80	1.00	
22-25	1789	38.6	22.5	18.0	20.8	0.79	0.49 (1.75)	0.39	0.53	0.71	0.84	1.00
Stimulants												
8-11	1785	93.1	4.2	1.5	1.0	0.36	-3.36 (2.25)	1.00				
12-14	1787	83.3	9.6	4.1	2.9	0.45	-1.96 (2.02)	0.81	1.00			
15-17	1788	63.4	17.4	10.8	8.3	0.81	-0.66 (1.88)	0.67	0.84	1.00		
18-21	1780	39.9	22.1	18.1	19.5	0.73	0.42 (1.75)	0.51	0.65	0.79	1.00	
22-25	1789	35.0	24.8	17.8	22.4	0.71	0.61 (1.69)	0.45	0.57	0.70	0.84	1.00

^a Based on a sample of 141 randomly selected subjects for whom the retest interval was 14-56 days ($\mu = 29$ days).

^b Polychoric correlations assume that underlying an observed categorical or ordinal distribution, there exists a continuous, normally distributed latent liability, and that the joint distribution of this scale with liability scales underlying other items is bivariate normal (Tallis, 1962; Jöreskog & Sörbom, 1993).

for five categories of psychoactive substances (licit and illicit): alcohol; cigarettes; cannabis; cocaine; and stimulants (uppers). Subjects were asked to recollect DA at up to five age periods: 8-11, 12-14, 15-17, 18-21 and 21-25 years. Assessments of cigarette and alcohol availability were obtained only up to 17 and 21 years respectively, when use was no longer illegal in Virginia. Zygoty was diagnosed using a combination of self-report measures, photographs and DNA analysis (see Kendler *et al.* 2000).

We used a Life History Calendar (LHC) method to increase the validity of our retrospectively collected data (Furstenberg *et al.* 1987; Freedman *et al.* 1988b; Kessler & Wethington, 1991). This method has shown that although human memory is relatively poor at recall, it can be improved significantly when probed with careful questioning involving

specific time periods and events. For each drug class, subjects were asked, 'When you were [AGE] how easy would it have been to get [SUBSTANCE] if you wanted to use (it/them)?' Responses were recorded on a four-point ordinal scale ['very difficult or don't know', 'somewhat difficult', 'somewhat easy', and 'very easy']. Our decision to combine 'very difficult' and 'don't know' was based on the fact that during the pilot phase, interviewers consistently noted that 'don't know' responses typically meant not knowing how to obtain a drug rather than not knowing about the drug or what it was. Moreover, true 'don't know' responses were very rare. Item response frequencies are shown in Table 1.

Polychoric test-retest correlations are also shown in Table 1. All correlations are adjusted for the linear, quadratic and cubic effects of age at interview, which effectively removes most

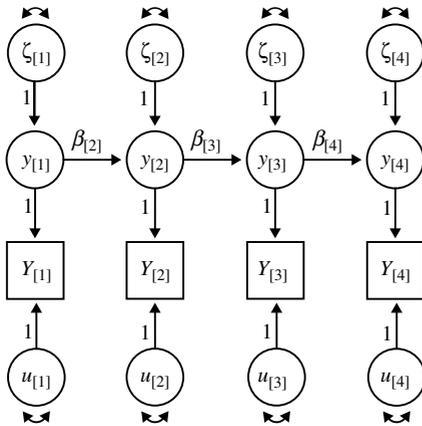


FIG. 1. Autoregressive/simplex model: $u_{[1-4]}$ = residuals or random error, $Y_{[1-4]}$ = observed scores, $y_{[1-4]}$ = latent true scores, $\zeta_{[1-4]}$ = latent innovations representing new variance at each time point, $\beta_{[2-4]}$ = transmission coefficients representing regression of true score on previous true score. Double-headed arrows are the variance components for the latent innovations.

potential cohort effects. Although the reliability is moderate to good, and improves with age, this trend is clearer in the illicit substances.

Statistical methods

Latent growth modeling

Based on previous work and modeling by McArdle and colleagues (2003, 2004), we predicted that changes in DA over time were better explained as part of a dynamic or dual change process. By modeling longitudinal change as deriving from two sources, this method, which is described in detail below, combines features from the autoregressive or simplex design (Eaves *et al.* 1986) with those from standard latent growth models (Nesselrode & Baltes, 1974; McArdle, 1994). It is also mathematically and statistically equivalent to random coefficient, multilevel or hierarchical linear models (Bryk & Raudenbush, 1987; McArdle *et al.* 1991; McArdle & Hamagami, 1992; Mehta & West, 2000; Miyazaki & Raudenbush, 2000).

We began with the assumption that for each person ($n = 1$ to N), their observed score at each time point ($Y_{[t]}$) is made up of a latent or unmeasured true score ($y_{[t]}$) plus measurement error ($u_{y[t]}$), such that $Y_{[t]n} = y_{[t]n} + u_{y[t]n}$. As illustrated in Fig. 1, any changes in true scores ($y_{[t]n}$) over time can then be modeled by fitting autoregressive or Markovian simplex designs to

longitudinal data (see Eaves *et al.* 1986; Boomsma & Molenaar, 1987), whereby each true score is now causally related to the immediately preceding latent true score in a linear fashion,

$$y_{[t]n} = \beta_{[t]n} \times y_{[t-1]n} + \zeta_{[t]n},$$

where $\beta_{[t]}$ is the linear regression of the latent factor ($y_{[t]}$) on the previous latent variable ($y_{[t-1]}$). The $\zeta_{[t]}$ represents any new input, change or variance innovation at time $[t]$ that is uncorrelated with $y_{[t-1]}$. Measurement error is assumed to occur at the level of the observed variable and is uncorrelated with the latent true score. The sizes of the innovations at each time point were typically investigated by dropping them from the full model and testing their significance using a likelihood statistic.

Because this approach takes advantage of the time series nature of the data (i.e. that causation is unidirectional through time; Boomsma *et al.* 1989), it is ideal for modeling potentially cumulative or enduring effects such as education or initial drug exposure, which may persist and explain variation in subsequent self-reports of DA. Unfortunately, it is limited in so far as it cannot account for mean changes over time, nor does it make explicit predictions about the etiology of the innovations (ζ) such as the rate of change or slope of the trajectory to describe change over time.

An alternative is to model any observable change as a latent growth process that predicts separate individual-difference components for curve characteristics such as levels, slopes, etc. As illustrated in Fig. 2, this approach predicts that change (Δ) in individual observed scores ($\Delta Y_{[t]n}$) is a function of time ($\Delta A_{[t]}$) such that $\Delta Y_{[t]n} / \Delta A_{[t]n} = y_{s,n}$. The $y_{s,n}$ is the individual slope or rate of change for each person. Each observed score can then be written as a linear function of an intercept or starting point (y_0), plus a linear (or non-linear) slope or rate of change (y_s) multiplied by a group-level age basis ($A_{[t]}$, usually equal to a centered age), and a unique or random error component ($u_{[t]}$). For each person ($n = 1$ to N),

$$Y_{[t]n} = y_{0,n} + (y_{s,n} \times A_{[t]n}) + u_{[t]n}.$$

Factors such as existing social networks, socioeconomic status, the number of drug dealers in a particular region or genetic predisposition

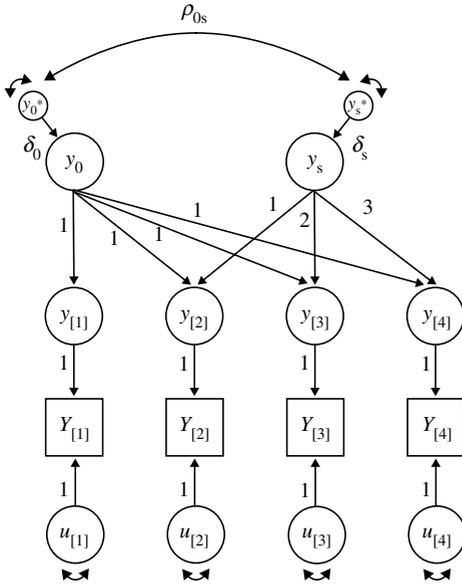


FIG. 2. Latent linear growth curve model: $u_{[1-4]}$ =residuals or random error, $Y_{[1-4]}$ =observed scores, $y_{[1-4]}$ =latent true scores, y_0 and y_s =latent intercept and slope factors, δ_0 and δ_s =latent intercept and slope standard deviations, y_0^* and y_s^* =latent intercept and slope variances, ρ_{0s} =correlation between the intercept (y_0) and the slope (y_s).

may determine an individual's starting point or intercept ($y_{0,n}$). Maturing social skills, developing personality or even an increasing tendency towards curiosity and sensation seeking might account for any constant rate of change in knowledge of DA ($y_{s,n}$). In addition, these factors driving change may correlate ($\rho_{0,s}$) with those that determine an individual's starting point. Non-linear rates of change can also be modeled to account for alternate trajectories or effects that are asymptotic (e.g. quadratic, logistic, exponential, etc.) (see Neale & McArdle, 2000).

Dual change score (DCS)

It is conceivable that differences in observed scores over time are better captured as part of a DCS process, that is a combination of the autoregressive and latent growth effects. As we are interested in modeling the etiology of change between true scores over time, we will include latent difference scores as the measure of differences between successive latent true scores. For each person ($n=1$ to N) we can write a latent

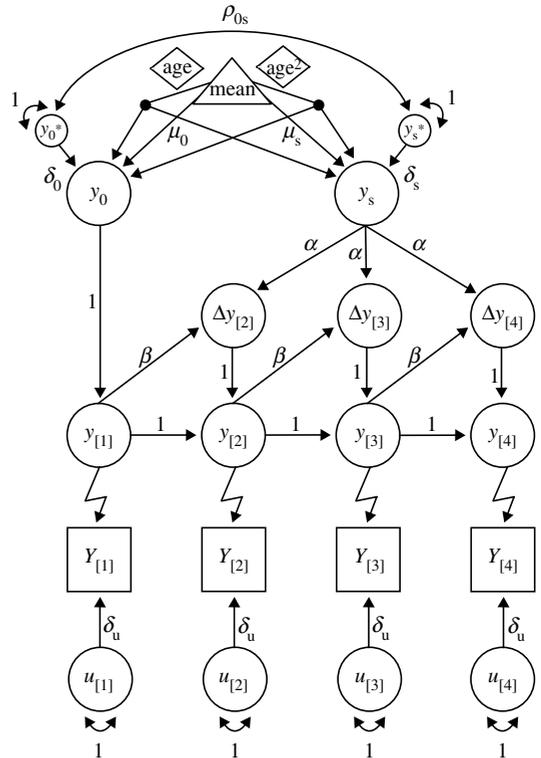


FIG. 3. Univariate dual change score (DCS) model: $u_{[1-4]}$ =residuals and random error, $Y_{[1-4]}$ =observed scores, $\Delta y_{[2-4]}$ =latent difference scores, y_0 and y_s =latent intercept and rate of change factors, μ_0 and μ_s =latent intercept and slope means, y_0^* and y_s^* =latent intercept and slope variances, ρ_{0s} =correlation between intercept and slope, α =systematic change, and β =systematic proportional change. The sharp S-shaped single-headed arrows represent the links between the observed ordinal measures (squares) and their corresponding underlying latent true scores (circles). Also included are definition variables (diamonds) to adjust each individual score by the mean (Δ) intercept and slope for the linear and quadratic effects of age at time of measurement. To estimate the means (μ_0 , μ_s) and standard deviations (δ_0 , δ_s) of the latent intercept (y_0) and slope (y_s), the systematic change (α) and the variances (y_0^* , y_s^*) components are set at 1.

difference score as,

$$\Delta y_{[t]n} = y_{[t]n} - y_{[t-1]n}$$

As shown in Fig. 3, these latent difference scores ($\Delta y_{[2]}$, $\Delta y_{[3]}$ and $\Delta y_{[4]}$) can be expressed with two sources of variance. There is the constant rate of change (α) for each individual (latent growth), plus carryover effects transmitted (β) from previous time points (autoregressive). The innovations are now modeled as part of the latent growth process (which is also analogous

to a common pathway model), which predicts that any additional variance is attributable to the slope or factors contributing to some constant rate of change. Therefore, each individual's latent true score ($y_{[t]n}$) can be written as a function of a starting point or intercept (y_0), plus the accumulation of changes or latent differences over time, plus error,

$$y_{[t]n} = y_{0,n} + \left(\sum_{i=1}^t \Delta y_{[i]n} \right) + u_{[t]n},$$

By incorporating these components into a full model, we can then test four alternate scenarios to account for observed phenotypic changes over time. Under model 1, where $\Delta y_{[t]n} = 0$, there is no latent change, and any observed phenotypic differences are therefore random. Model 2, where $\Delta y_{[t]n} = \alpha y_{s,n}$, corresponds to the latent growth model and is referred to as the constant change score (CCS) model because here we constrain the coefficient of change to be constant over time ($\alpha = 1$) to identify the slope mean (μ_s). Model 3, where $\Delta y_{[t]n} = \beta y_{[t-1]n}$, is referred to proportional change score (PCS) and corresponds to the autoregressive component because any latent differences are causally related to the preceding true score. Finally, Model 4, where $\Delta y_{[t]n} = \alpha y_{s,n} + \beta y_{[t-1]n}$, is the DCS, which includes both the constant and proportional change components. As the CCS and PCS models are nested within the DCS, their relative goodness of fit can be judged using a likelihood ratio χ^2 statistic.

Modeling ordinal data

To our knowledge, this DCS method has only been applied to continuous data. In the present study, the data are ordinal and therefore a different approach is needed to avoid statistical problems caused by scaling (Neale *et al.* 2006). One approach to modeling ordinal data is to assume that there is an underlying continuous liability scale that is normally distributed in the population. The ordinal data then demarcate slices of this distribution separated by thresholds. Typically, the underlying distribution is assumed to have a mean of zero ($\mu = 0$) and variance of unity ($\sigma = 1$), and so any changes in the thresholds will absorb any shifts in the underlying mean and variance. This

approach will therefore prevent the estimation of model parameters, such as those in the DCS, because information about changes in mean and variance is lost. However, as shown by Mehta *et al.* (2004), this problem can be overcome.

By assuming threshold invariance (see Mehta *et al.* 2004), whereby the ordinal data at different measurement occasions are represented on a common metric, it becomes possible to identify mean and variance changes. Constraining the thresholds to be equal across time (i.e. threshold invariance) effectively forces the time-standardized thresholds onto a common scale, so the latent means and standard deviations can be estimated as free parameters, or functions thereof.

The ordinal measures of DA have three thresholds. The 'common metric' approach reparameterizes these thresholds by fixing the first two arbitrarily to 0.0 and 1.0 respectively, at each time period. The third threshold is estimated freely, but is constrained to be equal over time. By 'anchoring' the thresholds to be the same across time, the distribution is forced to shift up or down depending on changes in item endorsement. The shifting up or down of the distribution can then provide the information for estimating means and standard deviations. Allowing the free (third) threshold parameters to vary across time provides a partial test of the assumption of measurement or threshold invariance (Mehta *et al.* 2004).

Genetic analysis

Our final step was to fit a biometrical DCS model to twin data by maximum likelihood (ML) using Mx (Neale, 1999) and decompose the variance of the latent intercept and slope factors into genetic and environmental components using standard biometrical genetic model-fitting methods (Jinks & Fulker, 1970; Neale & Cardon, 1992). Specifically, the total variance in latent intercept and slope factors was decomposed into additive (A) genetic as well as shared (C) and unique (E) environmental variance. As MZ co-twins are genetically identical, the additive genetic correlation is fixed to 1.0, whereas the DZ additive genetic twin correlation is 0.5 because DZ co-twins, on average, are assumed to share only half their genes. An important assumption of this biometrical model is that shared environmental effects correlate

to an equal extent in MZ and DZ twin pairs (Jinks & Fulker, 1970). Non-shared environmental effects are, by definition, uncorrelated and also reflect measurement error including short-term fluctuations.

RESULTS

Item response frequencies for each drug class are reported in Table 1. For all substances, DA increases, that is it becomes easier to obtain with increasing age. We also observe that, within ages, a consistent pattern is seen, where cigarettes are easiest to obtain and access becomes progressively more difficult in the following order: alcohol, cannabis, stimulants and cocaine.

For each drug class, the DCS provided a better fit to the data than either of the nested CCS and PCS models (results available on request). Because we are analyzing non-independent twin data, we cannot assume that within-occasion residual variances are uncorrelated across twins. We therefore tested a model that allowed for correlated residuals ($u_{[j]}$) or errors (separate correlations for MZ and DZ twin pairs) that we then compared to a more parsimonious restricted model without correlated residuals. The simpler model without correlated residuals provided a better fit to the data for alcohol ($\Delta - 2LL_{2df} = 0.22$), cigarettes ($\Delta - 2LL_{2df} = 2.58$) and stimulants ($\Delta - 2LL_{2df} = 1.34$), but not for marijuana ($\Delta - 2LL_{2df} = 37.57$) and cocaine ($\Delta - 2LL_{2df} = 7.94$).

The decline in variance over time is represented graphically on the left-hand side of Fig. 3, which shows the unstandardized proportions of genetic and environmental variance over time. For all drug classes there is a sharp decline in the total variance between time periods ages 8–1 and 12–4. Otherwise, there is no notable change in the unstandardized variance except for alcohol availability at 18–21 years as shown in Fig. 4.

The standardized genetic and environmental variance components are plotted on the right-hand side of Fig. 3. For all substances, non-shared environmental effects explained most of the standardized variance and, with the exception of stimulants, were longitudinally stable. These random environmental effects do not include measurement error, which is assumed to occur not at the latent variable level but

instead as part of the residual variance, that is $u_{[1-4]}$.

Starting with cigarette availability, there was a very modest increase in additive genetic variance and a decrease in shared environmental variance over time, while the non-shared environmental variance remained fairly stable. Across the five time periods, the non-shared environment explained approximately 50% of the variance in alcohol availability. Although shared environmental effects initially explained more variance compared to genetic influences, at 18 years there was a crossover and upswing in variance in the latter. A similar, but less marked, trend was seen for marijuana. Shared environmental effects peaked between 12 and 17 years but then began to decline slowly in favor of additive genetic variance. For cocaine, additive genetic effects accounted for very little variance between 8 and 17 years, after which there was a steady incline. Stimulants confounded all the previous trends. Additive genetic action accounted for more of the variance between 8 and 17 years, at which point there was a crossover and upswing in the variance explained by shared environmental variance.

DISCUSSION

For cigarette, alcohol, marijuana and cocaine availability, a common feature for the genetic and environmental trajectories was a decline in the unstandardized and standardized shared environmental variance plus an overall increase in standardized additive genetic variance over time. Non-shared environmental variance remained relatively steady across time.

Stimulant availability was the only drug class that did not follow this pattern. It is possible that stimulant availability is associated with different risk factors and outcomes compared to those that typify more recreational substances. For instance, Ritalin is widely prescribed to school-aged children in the USA (Barkley *et al.* 2003) for behavioral management. In terms of illicit use, stimulants may be abused less for their euphoric properties and more for the beneficial effects on academic or job performance. Use is also associated with different outcomes because, contrary to the sensitization hypothesis, once use has been established, children prescribed stimulants are not necessarily at

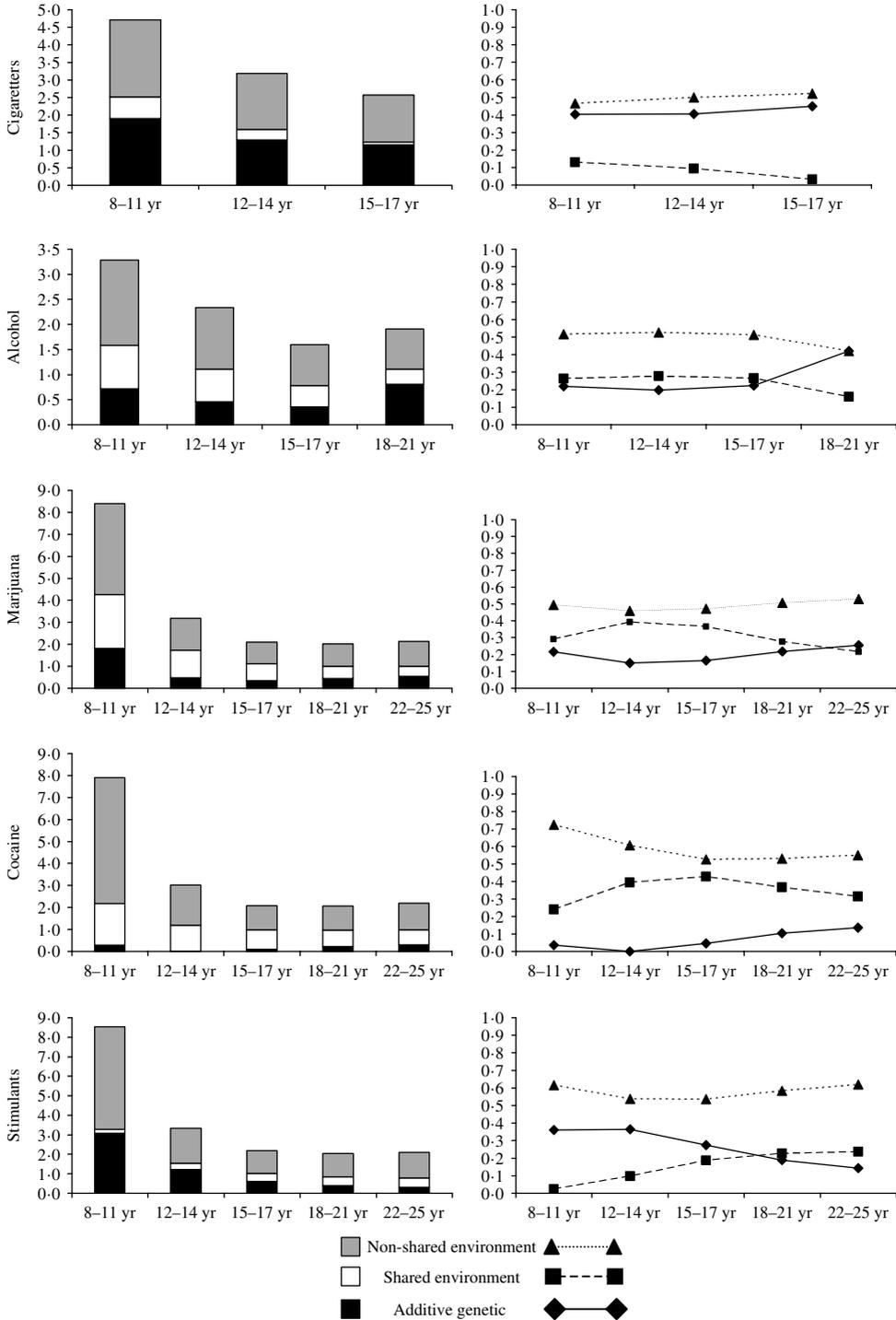


FIG. 4. Unstandardized (left) and standardized (right) proportions of variance in drug availability (DA). Variance components include latent genetic and environmental effects attributable to intercept and slope factors in the full biometrical dual change score (DCS) model.

increased risk of abusing stimulants or other drugs later (Klein & Mannuzza, 2002; Barkley *et al.* 2003; Mannuzza *et al.* 2003).

Although the precise mechanisms for the decrease in unstandardized shared environmental ('C') variance are uncertain, we can still speculate. Geographical, economical and political circumstances are all environmental features that can influence accessibility to drugs. Twins in this sample come from a range of different birth cohorts that vary between families but are the same within a family, and this may account for some of the shared environmental effects. However, all of our models were adjusted for age of measurement to remove potential cohort effects. Proximal environmental effects such as parental control and social influences might constitute more salient components of the shared environmental variance, particularly between 8 and 17 years. Less proximal social influences are likely to include schooling, church attendance and strength of religious affiliation and even the number of drug dealers and access points to drugs. There is some evidence that the importance of parental influence weakens across adolescence (Bush *et al.* 1994; Duncan *et al.* 1995), which would be consistent with the patterns found in this study. The fact that we see a large component of shared environmental variance suggests that some influences, at least from the early to mid-teen years, remain salient.

The most interesting trend is the notable decline in shared environmental variance as well as the marked upswing in both standardized and unstandardized genetic effects for alcohol between 18 and 21 years. This period coincides with waning social and parental constraint as teenagers typically begin to move or spend more time away from home, and expand their social networks. With this transition comes more personal choice and freedom to select oneself into high *versus* low DA environments. Under these circumstances of declining 'C' influence, genetic differences will begin to explain a larger relative proportion of individual differences in DA. This pattern dovetails with the concept of a genotype–environment interaction that describes ways in which genes affect environmental sensitivity or, conversely, how environments affect gene expression (Neale & Cardon, 1992). A genotype–environment

interaction would predict that genetic variation in DA will increase in environments with less social constraint. However, it leaves unanswered the question of how individuals select themselves into particular environments, that is the possibility of a non-random distribution of environments among different genotypes, or genotype–environment correlation.

Although numerous taxonomies for genotype–environment correlations exist (Eaves *et al.* 1977; Plomin *et al.* 1977; Scarr & McCartney, 1983; Neale & Cardon, 1992), an 'active' genotype–environment correlation would predict that as teenagers mature, they begin to select peers and create environments that are a function of their genotype. In other words, individuals have more opportunities to seek out environments of their choosing as they age, and this choice is increasingly under genetic control. This is likened to a smorgasbord model whereby society has a wide variety of environments from which individuals make selections based on their genetic preferences (Neale & Cardon, 1992). Indeed, twin studies have shown that variation in the formation of deviant peer-group friendships (which is also a predictor of drug initiation; see Duncan *et al.* 1994, 2006) is under both genetic and environmental influence (Iervolino *et al.* 2002; Walden *et al.* 2004; Cleveland *et al.* 2005; Saudino *et al.* 2005). It is possible that teenagers, who are in part genetically disposed to choosing deviant peers, select themselves into disruptive or unconstrained environments and, as a result, become more knowledgeable of DA, which in turn increases their risk of drug exposure and initiation.

Limitations

This paper integrates the DCS of McArdle & Hamagami (2003) with Mehta's (2004) threshold invariance model for longitudinal data. Our findings must be interpreted in the context of at least six potential limitations. First, our data were restricted to white males born in Virginia whose demography is more rural than urban. Previous analyses using the same data (Kendler *et al.* 2000) suggest that this sample does not differ from the general population in rates of psychopathologic conditions, including illicit substance use, and that it is likely to be broadly representative of US men. With regard to sex differences, although

rates of cannabis and forms of substance abuse are lower in females, the genetic and environmental pathways to abuse and dependence across a range of illicit substances appear to be the same for men and women (Agrawal *et al.* 2005). Similar results may therefore be expected for females.

Second, our data were collected retrospectively. Twins were asked to recollect DA during specific periods selected for specific reasons. It was thought that using age ranges tied to modal initiation through to completion of primary (elementary) school (grades 1–6), middle and high school (grades 7–12) would facilitate subject recall. These periods broadly represent ‘pre-adolescent’ and ‘early-to-middle adolescent’ developmental phases. To improve the quality of retrospective recall for these key periods of childhood, adolescence and early adulthood, our interview used an LHC format as developed by Thornton (Freedman *et al.* 1988*a*). By applying the principles of cognitive psychology, LHCs provide multiple cues to access relevant ‘memory files’, making the subject’s task more akin to the accurate and well-retained process of recognition than the less reliable task of free recall. In addition, LHCs have been shown empirically to improve the accuracy of retrospective reporting (Freedman *et al.* 1988*a*; Belli, 1998). Nevertheless, retrospective data still have the potential for recall bias and telescoping effects (Pickles *et al.* 1994). Retest correlations declined with greater intervening time periods, and were moderate for harder-to-obtain substances such as cocaine and stimulants. As non-shared environmental effects also include measurement error, the estimates of ‘E’ are likely to be upwardly biased. Despite this limitation, the retest correlations suggest that our form of life history data collection, which was developed from the interface of cognitive and survey methodology, does in fact ascertain reliable data.

Third, our measures are likely to reflect a mixture of perceived and actual DA. Whereas the former will always be more subjective, actual DA will be more sensitive to drug prices, the number of sellers within a particular area (Lettieri *et al.* 1980) and demand. Although some evidence suggests that perceived availability is in fact a better predictor of initiation, abuse and dependence (Smart, 1977; Iannotti

& Bush, 1992; Iannotti *et al.* 1996), in this instance we have no way of discriminating between the two.

Fourth, between 1934 and 1985, Virginia’s legal drinking age (LDA) oscillated between 18 and 21 years. Changes in genetic and environmental effects associated with the varying LDA are likely to be confounded with potential cohort effects on all drugs, which we have attempted to reduce by including age at measurement in our models. In any event, how LDA impacts upon access to alcohol and consumption is uncertain. For instance, Slutske (2005) studied a sample of 6354 young US adults aged 19–21 years and found that between 52% and 67% reported drinking alcohol in the past month, while 15–18% had suffered a clinically significant alcohol-related problem in the past year.

Fifth, for marijuana and cocaine, a biometric DCS model with correlated residuals provided a better fit to the data than a model without correlated residuals. Arguably, if the DCS process is adequate, then allowing the latent factors to be correlated across twins ought to account for all pairwise resemblance without the need for correlated residuals. Provided we conceive residuals as purely random error, then we should not expect them to correlate, and this line of reasoning is acceptable. However, if there is some systematic source of residual variation, then it may have a familial component, which appears to be the case for marijuana and cocaine. In any event, the idea that residual variance has to be entirely error has been rejected elsewhere (see Waller & Reise, 1992).

Sixth, our model fitting was not exhaustive. Alternate approaches may include modeling additional non-linear rate-of-change latent factors, or testing the fit of particular trajectories such as Gompertz, logistic and exponential curves (see Neale & McArdle, 2000). As our intention was to model the etiology of latent differences without *a priori* expectation as to the shape of the trajectory, our DCS approach was more appropriate in this instance. We also have data on parental bonding, monitoring and attitudes, peer-group deviancy, personality, household drug use and twin cohabitation from the same subjects in the current study. These are all likely to have strong etiological importance and possibly share covariance with DA, and might

elucidate the sources of shared environmental variance in DA.

CONCLUSION

We have investigated, by using latent growth curve modeling, the genetic and environmental trajectories of DA. Van Etten & Anthony (1999) have argued that understanding early stages of drug involvement is vital for epidemiological studies because this leads to better determination of whether variation in later substance use, abuse and dependence are related to differences in factors influencing initiation. We therefore plan to extend our focus on the sources of covariation between DA, initiation, abuse and dependence. Kendler *et al.* (1999b) have shown that there is significant genetic and environmental overlap between smoking initiation and nicotine dependence. Given the literature showing that drug initiation is strongly predicted by DA, for which we now have evidence of genetic variation, it is not unreasonable to predict that some of the genetic and environmental variance in availability will correlate with variation in liability to drug initiation, abuse and dependence. We now have subjects with complete data on DA, drug initiation and lifetime DSM-IV abuse and dependence diagnoses to test these predictions and elucidate key components in the complex pathways to drug use.

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DECLARATION OF INTEREST

None.

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