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The Developmental Behavior Genetics of Drug Involvement: Overview and Comments

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Abstract

The papers in this special issue have in common an interest in developmental variations in the heritability of substance use, abuse, and problems. A number of the studies are longitudinal, and even those that are cross-sectional are analytically focused on whether heritability, shared, and nonshared environmentality effects are constant or change over the period from onset of use to the time when problem use is more constant. This commentary provides an overview of the work from a developmental psychopathology perspective. Findings are linked to the existing longitudinal/developmental literature on the epigenesis of substance use disorders and similarities and contradictions are noted. Suggestions for next step work, involving the need for increased differentiation of the substance abuse phenotypes, the utilization of phenotypic measures that delineate heterogeneity of course, and more precise definition of the specific environmental variations that underlie shared and nonshared environmental liability, are provided.

Keywords

Developmental genetics; Substance use; Substance abuse; Phenotype definition

Over the past decade, a good deal of evidence from a number of heritability studies has accumulated that suggests the genetic risk for substance use disorders is carried through one major common factor and a number of specific factors, whose relative role and type varies with drug of abuse (Karkowski et al. 2000; Kendler et al. 2003; Tsuang et al. 1998). The common factor has been identified as an externalizing one, marked at the behavioral level by symptoms of undercontrol and behavioral dysregulation. Although less well known, the nongenetic evidence is even more compelling for a common causal factor cutting across drugs of abuse. This work, coming from six long term prospective studies (Caspi et al. 1996, 2002; Eron et al. 1987; Mayzer et al. 2002, 2003; Masse and Tremblay 1997; Cloninger et al. 1988) carried out over the past quarter century, provides a remarkable convergence with the genetic literature in demonstrating that externalizing symptomatology appearing in early childhood is predictive of SUD outcomes some 15–20 years after the first appearance of the drug-nonspecific behavioral risk (see Zucker 2006 for a review of this work). Moreover, these traits (a) are known to be relatively stable over the course of childhood and adolescence (Fuller et al. 2003; Olweus, 1979); and (b) are most likely to show a continuity pattern among individuals who thereafter develop the more chronic and severe forms of SUD (Biglan et al. 2004; Campbell et al. 2000).

These predictive relationships are not directly informative about the developmental topography of drug involvement, from exposure to onset of use, from onset of use to progression into

problem use, from problem use into substance use disorder, and from involvement with one drug to involvement in other, typically more illicit drugs (Kandel and Yamaguchi 2002). Although it would be reasonable to predict that the more such factors are present, the faster the move into drug involvement and the more rapid the progression into symptomatic use. However, the presence of the risky trait does not directly inform about these relationships. In addition, to the extent that the social environment plays a role in drug involvement, these transitions are potential nodal points of shift in environmental influence. Transitions such as onset of use, and transition from use of one substance to use of another can only take place when availability exists, and the transitions likewise are known to occur earlier, and affect more individuals when the drug availability is greater (Reich et al. 1988; Wagner and Anthony 2002a). For other transitions pertaining to speed of progression into more use and more problematic use, simple genetic effects potentially have a greater role to play because they do not require the presence of a facilitating social environment.

The editors of this special issue have selected a set of interesting papers that address both the common factor issue and the topography issue. Most are longitudinal, and they focus primarily on the three most common drugs of abuse, alcohol, nicotine/smoking, and marijuana. All but two of the phenotypes are studied in humans; one of the animal studies involves a cocaine use phenotype, albeit one that easily maps onto human drug taking behavior. All are cognizant of the emergent and epigenetic nature of this set of phenotypes, and a substantial amount of the work is devoted to characterizing developmental variations both in heritability and in environmental influence. I have organized the papers and my comments around four core issues: Common and Specific Risks; Timing, Initiation, and Progression; Specific Mechanisms of Risk Transmission, and Lessons from Animal Studies.

Section I: Common and specific risks, genetic and environmental (Young, McGue)

Ia

Young et al. (this issue), using a general population based composite sample of adolescent MZ and DZ twins, full biological siblings, and adoptive siblings, provides another study finding that tobacco, alcohol, and marijuana *problem* use are mediated by common genetic influences. Analyses modeling the trivariate relationships found that individual genetic influences at the problem use level were modest to substantial ($h^2 = 0.29$ for problem tobacco use at the low end, and $h^2 = 0.49$ for problem alcohol use at the high end ($h^2 = 0.41$ for problem marijuana use), but the correlations *among* these factors were all in the 0.6 range). Shared environmental influences for problem use were more substance specific and quite small. At the use level, substantial heritabilities were found for tobacco ($h^2 = 0.46$) and marijuana ($h^2 = 0.44$), but not for alcohol ($h^2 = 0.05$); these genetic factors were significantly correlated but at a much lower level than for problem use ($r = 0.14$ to 0.31). Shared environment influences were the obverse, with the largest effect for alcohol ($c^2 = 0.46$), and the lowest for tobacco ($c^2 = 0.12$) (marijuana was 0.27), and the relationships among these factors was also modest. Special twin shared environment effects were also found, with the strongest effect for tobacco and alcohol use and for tobacco and marijuana problem use levels. The Young et al. study also found high drug comorbidity among all three substances, at both the use and problem use levels ($r = 0.66$ to 0.78), suggesting that, at least in adolescence, polydrug involvement is the rule rather than the exception.

These findings are supportive of the investigators' original hypothesis that problem use, across drugs, would be more heritable than use. They also are consistent with the argument that relationships affected to a lesser degree by progression factors rather than availability ones (i.e., problem use) are more likely to be regulated by genes. However, their expectation that

both across-drug genetic and across-drug environmental risks would have a significant common component was not supported. Environmental risk was more strongly linked for use, not for problem use.

These findings also highlight a theme that emerges in other studies, namely that the genetic and environmental architecture for different drugs of abuse varies by drug, and also by level (type) of use. The contrast of findings for alcohol and tobacco *use* provides a good illustration of this issue. Both are licit drugs and therefore highly available, but one (tobacco) has a much greater heritable component than the other. With those parameters, shared environment plays a minimal role for tobacco and a substantial role for alcohol. From a prevention standpoint, one would predict that decreases in exposure and early involvement (i.e., creating roadblocks to availability and cueing) would be far more important as precursors of nicotine abuse/dependence than they would be for alcohol. If this hypothesis can be confirmed, prevention strategies would need to be very different for the one drug than the other.

The Pagan et al. paper (this issue, see below), provides an important footnote to the Young et al. study, by adding a developmental dimension to the topography. The Pagan study, as well as a number of others before it, shows that heritability for alcohol (use) and problems increases and shared environment effects decrease in adulthood. Again, the strategy implications for intervention vis a vis adult alcohol involvement would therefore be changed from what they were in adolescence, and would approach those needed for tobacco.

1b

While the Young et al. paper indicates substantial common heritability for problem use across drugs of abuse, it does not inform about the nature of the common variance. In contrast, the **McGue et al. paper** (this issue) has this as its central focus. McGue, Iacono, Krueger and colleagues have already produced an impressive series of studies demonstrating the key role of a drug-nonspecific disinhibitory trait, rather than drug specific characteristics (such as age of onset of first use) as a mediator of the SUD pathway (e.g., Iacono et al. 1999; Krueger et al. 2002; McGue et al. 2001). The study they present here examines another part of that matrix, concerning the degree to which the association between problem behavior occurring before age 15 and disinhibitory psychopathology in early adulthood (age 20) is mediated by a common heritable liability. The study involved twin participants from the Minnesota Twin Family Study, and the index of adolescent problem behavior used was actually a precocious development indicator involving a count of the number of different adolescent deviant behaviors (use of alcohol, tobacco, illicit drugs, having sexual intercourse, and having police contact for other than traffic problems) which took place prior to age 15. The adult disinhibitory psychopathology indicator was even more heavily a substance abuse measure, involving a count of DSM-III-R SUD symptoms for nicotine dependence, alcohol abuse or dependence, drug abuse or dependence for a wide variety of illicit and illegally used licit drugs, and adult antisocial behavior symptomatology, all as reported at their age 20 follow-up.

The findings they report are intriguing, namely that while early adolescent problem behavior was only weakly heritable (~20%), the common factor underlying disinhibitory psychopathology was strongly so (~75%). In addition, a strong phenotypic correlation existed between the adolescent deviancy indicator and the adult psychopathology measure ($r \sim 0.6$), and its strength was largely genetically mediated by a factor common to the two domains. The authors interpret this initially puzzling finding by suggesting that a gene-environment correlation effect is in operation between early adolescence and young adulthood, with the heritable characteristics leading to the selection of relationships which amplify the underlying diathesis, and which ultimately lead to the unfolding of the genetically mediated symptomatic outcomes of early adulthood.

Although this explanation is a plausible one, it does not fit well with a substantial literature indicating that the heritability of undercontrolled traits (aggressiveness, delinquency, conduct problems) in childhood and adolescence is quite robust (e.g., Leve et al. 1998; Schmitz, et al. 1994; van der Valk et al. 2003), is particularly strong when the disinhibitory psychopathology is more aggressive (Eley et al. 1999; van Beijsterveldt et al. 2003); but appears to be less so for delinquent behavior as compared to more straightforwardly undercontrolled behavior (Deater-Deckard and Plomin 1999). In accounting for this disparity, an issue central to the argument for a common liability needs to be examined. The phenotypic relationship of the adolescent problem behavior indicator to the adult psychopathology indicator, as well as the expected finding of strong heritability of both phenotypes is based on the presumption that both are assessing the same problem/disinhibition content domain. However the content differences between the two measures raise some question about the parallelism of the indicators, as well as the even more central question of what the core defining characteristics are for this phenotype. Despite the 0.6 correlation between the adolescent and adult behavior measures, the adolescent indicator is a measure of what Richard Jessor and colleagues (Jessor and Jessor 1977; Donovan and Jessor 1985) some 25–30 years ago referred to as the “problem behavior syndrome,” a cluster of behaviors that have in common the violation of social norms, and that range from precocious involvement in age-graded activities reserved for adult status (drinking, sex) on the one hand, to aggressiveness, rebelliousness, and law breaking (including involvement in illicit drugs) on the other. In contrast, the adult indicator is much more heavily an index of level of SUD symptomatology. Although there is substantial overlap between these constructs at the behavioral level, the overlap is far from perfect, and the divergence of parallelism is undoubtedly even larger at the neurophysiological level, given the differences in brain sites of action for response inhibition and aggression on the one hand, and addictive reward on the other. On these grounds the expectation for parallel patterns of heritability is not so obvious.

To take this point a bit further, it is not yet clear what are the central defining elements of the disinhibitory psychopathology/deviancy construct. The range of content just described highlights the multidomain nature of the disinhibition construct being used. It extends substantially beyond undercontrol, and it includes drug use per se. The inclusion of the antisocial content in the adult indicator (and police trouble in the adolescent indicator) also implies a level of social oppositionalism that is beyond impulsivity and borders on a capacity to carry out harm to others. It is likely that these multiple content domains will need to be dissected at a more fine grained level before meaningful genetic as well as phenotypic connections can be established.

Section II: Timing, initiation, progression (Neale, Lessem, Pagan, Vargas-Irwin)

Ila

The Neale et al. paper (this issue) provides a creative extension of Mx as an alternative to Heath et al.’s (1993) combined liability dimension model of drug onset and progression (either independent liability for onset and progression, or single liability with multiple thresholds). By incorporating some of the newer missing data routines into the analyses of twin data, they are able to integrate data previously lost to the analysis when one twin had not yet initiated. Their new variation allows modeling of causal contingencies (initiation liability *causes* progression liability), allows more effective integration of covariates, simultaneous examination of onset and progression in two or more substances, and permits the modeling of multi-step transition models of drug progression. These issues are critical to the understanding of all psychiatric disorders, but are especially so for the substance use disorders along with other addictions and compulsions. All of these disorders require an object in the environment

as well as a set of trait vulnerabilities for the disorder to manifest itself. Thus, relationships to the object having to do with discovery and first use may be quite different than those which take place once dosing is taking place. Or to frame this differently, factors for initiation may be only partially shared with those that cause progression from use to abuse, to dependence, or alternatively, from diagnosis to remission. The issue is of special importance when studying youthful populations given that those who initiate later are known to have different trajectories of drug involvement than those who initiate earlier (Gruber et al. 1996; Grant and Dawson 1997). Alternatively, where the drug being studied is illicit and therefore of low incidence, onset data are also more likely to be missing from one member of the twin pair. If there is no way to incorporate these pairs into the modeling, the solutions will be biased.

Although their paper provides a number of interesting re-analyses of existing datasets, to illustrate the value added of this new variation I highlight only one involving a reanalysis of data from a longitudinal population based study of female twins originally described by Kendler et al. (1999). The modeling focused on univariate and parallel process analyses of the pathways of liability to initiation of nicotine use and dependence, to cannabis use and abuse, and their possible inter-relationship. Individual causal models of liability for both nicotine and cannabis were similar to those found in the previously reported univariate analyses, with liability to initiate use accounting for a substantial proportion of liability for dependence or abuse. Bivariate models that did not take reciprocal causation into account show a strong relationship between initiation of tobacco use and initiation of cannabis use, and a smaller but substantial cross-correlation between liability for initiation of the one substance and progression to abuse/dependence in the other (correlations of 0.5–0.6). Results are consistent with a common factor explanation for liability to both initiation and abuse/dependence across substances. However, when reciprocal processes are included in the model, liability to initiate smoking also increases liability to initiate cannabis, but the obverse is not true. In fact it is reverse, with liability to initiate cannabis decreasing liability to initiate smoking. Conversely, the liability for the cross paths, from use of one substance to dependence/abuse of the other is zero. These findings would not have been articulated without the new multivariate modeling capability, although they bear some parallelism to longitudinal relationships that have been observed phenotypically (Bentler et al. 2002).

IIb

The **Lessem et al. paper** (this issue) focuses on another progression nodal point further up the line, that involving transitioning from marijuana use to other illicit drug use. Making use of the National Longitudinal Study of Adolescent Health (Add Health) sample (<http://www.cpc.unc.edu/projects/addhealth>), and a genetically informed design utilizing a subsample of MZ and DZ twins, full sibling and half sibling pairs, they examined three components of gateway theory pertaining to (a) the prediction of illicit drug use from precedent marijuana use, (b) whether the association was sustained when controlling for family environmental factors, and (c) whether common genetic or environmental factors contributed to the relationship. The gateway hypothesis was replicated (adolescent marijuana users were approximately twice as likely to use other illicit drugs in young adulthood), and although the relationship was replicated even in discordant sib pairs (suggesting that even when controlling approximately for family environment, earlier marijuana use predicted later illicit drug use), analyses of the genetically informative subsample suggested that shared environmental effects play a stronger role in the relationship.

Although this study uses a population based study for its analyses, there are some design issues that make it unclear how robust the findings may be. Sample sizes, and presumably sample representativeness, varies greatly across the three reported sets of analyses, and vary from 64% of the final Add Health sample (which itself had significant subject loss at study enrollment)

for the regression analysis to 5% for the Cholesky analysis. The population to which these results generalize shrinks dramatically, and in unknown ways across the three analyses. Equally importantly, it cannot be assumed that environmental and genetic effects play identical roles at different developmental points (*cf.* McGue et al. this issue), and given what is known about differences between earlier versus later onset users, the particular age at which the “gateway” is being examined is highly relevant both to theory and to what outcomes to expect. The Lessem et al. study, beginning with adolescents at mean age 16.4 (age based on the reported combining of Wave 1 and Wave 2 data) is examining the beginning phenomenon when Ss are sophomores or juniors in high school, and is well past the mean age of first marijuana use for lifetime users of cocaine/crack (15.7) or heroin (13.9) as reported in national sample data (Kandel and Yamaguchi 2002). The more general point is that the picture of progression vis a vis the relationships being reported here was occurring at a start point that was substantially after “early” use was in place; hence relationships—to the extent that they are generalizable—are about ongoing marijuana use and its gateway relationship to illicit drug involvement, not early marijuana use. The environmental contribution to this relationship may very well be different than the one that occurs earlier in the natural history.

llc

Pagan et al., provide a highly sophisticated analysis of two long term Finnish twin studies involving 5 cohorts and multiwave assessment, one beginning at age 12 with follow ups at 14 and 17.5, the other at age 16 with follow-ups at 17, 18.5 and 25. They examine genetic and environmental influences on alcohol involvement within a developmental framework that conceptualizes the process as one involving multiple stages—initiation, level of use (frequency of drinking) in adolescence and young adulthood, and the emergence of drinking problems (measured here in young adulthood)—with the potential for different contributions of genetic, shared and nonshared environmental effects at each stage, as well as the possibility of different variable networks contributing to these stage-specific components.

The study replicated findings reported earlier by this group and others of large shared environmental influences, and additive genetic influence relating to age of onset of use of about half the magnitude, and an even smaller contribution of nonshared environment. Of special interest are the relative gender differences that appear even at drinking onset, as well as the changes in importance of genetic and environmental influences during the young adult period. Among males, additive genetic influences for frequency of use are approximately double (~0.5) what they were for initiation liability, and the magnitude of the effect is the same for drinking frequency as it is for drinking problems. In addition, the genetic factors responsible for the consumption effect at age 25 overlap considerably with those influencing alcohol problems (this is also true at age 16, but the magnitude of the relationship is lower), but the genetic factors influencing earlier drinking *do not overlap* with those influencing drinking behaviors at age 25. It is not clear whether this lack of parallelism is another manifestation of the differences in heritability observed in the Minnesota study (McGue et al. this issue) for their problem behavior index in adolescence and early adulthood, but the possibility is an interesting one. In contrast, effects of shared environment on drinking frequency and later drinking drop to a very low level for both drinking and problem indicators, while unique environmental influences more than double in importance.

For females, additive genetic influences were stronger on initiation liability, and common environmental influences, although robust, were weaker than for males. Unique environmental influences were also weaker. However, common environment effects, although decreased, remain a substantially more important source of influence in young adulthood on drinking frequency (3.5 times as great), and drinking problems (twice as great) as was true for males. The contribution of unique environmental influences meets or exceeds that found for males at

age 25. Although the overlap of genetic factors responsible for initiation and consumption in young adulthood are of the same magnitude as for males, overlap of environmental influences, both common and unique, between initiation liability and later consumption level is substantially lower.

What is to be made of this complex set of relationships? The general patterning of these effects suggests greater genetic responsivity to alcohol initiation among females than males, and a lesser responsivity to shared environment *initially*. The low level of overlap between genetic factors influencing onset and those influencing consumption and problems some 7–8 years later is consistent with the work indicating that initiation effects are driven by traits non-specific to alcohol, but effects thereafter are related considerably more to drug responsivity. Thereafter, both shared and nonshared environmental influences play a stronger role for women, at least relating to how often drinking takes place. These results are consistent with longitudinal studies of changes in women's drinking following marriage (Leonard and Rothbard 1999; Curran et al. 1998). At the same time, sex differences in alcohol use patterns disappear when the proxy measure is the more clinical one pertaining to problems and abuse.

Mention was made at the beginning of this commentary about the longitudinal data indicating that early appearing risky phenotypes, in some instances identified as early as age three (e.g., Caspi et al. 1996), predicted alcohol use disorder and other SUD outcomes in early adulthood. The trajectory patterns from those studies and from related work (Fuller et al. 2003; Zucker et al. 2003) indicate also that the phenotypic trajectories of risk, most heavily pertaining to externalizing traits, show strong continuity patterns over the course of childhood and adolescence. Findings from the Pagan et al study, however, point in a different direction, suggesting that what appears phenotypically to be a straightforward continuity trajectory into alcohol problems and alcohol use disorder is actually a matrix of genetic vulnerabilities and environmental risks that comes into play at different points in development, and that is not always the same across the interval leading to initiation of use on the one hand, and to problem involvement later on.

IId

Although the title of the **Vargas-Irwin et al. paper**: "A method for analyzing strain differences in acquisition of IV cocaine self-administration in mice"(this issue) would not suggest it has any immediate relevance to human studies of drug involvement, in fact, it has a considerable amount to offer. These authors, at the mouse level, provide a sophisticated account of the architecture of drug acquisition, albeit at the level of the naive animal in the cage, involved in the initial stages of drug initiation and progression into habitual use and addiction. In a fine-grained and high resolution analysis of this sequence, they point out that there are three parameters to the acquisition process: The first is latency to first response (or to put this in human terms, time to onset of use following availability and cueing); the third is asymptotic rate of dosing, and the intermediate step is rapidity of transition from onset to asymptote (or in operant terminology, the *abruptness* or steepness of the response curve between initiation and time of asymptotic steady state). Following Gallistel et al. (2004), they observe that these three phases of response acquisition, at least at the micro-response level in animal studies, show little relationship to each other, suggesting they are independent phenotypes, under different genetic control. A similar analysis at the human response level by Mayhew et al. (2000) for smoking behavior demonstrates the immediate utility of this phenotypic differentiation. Another not well known but important variant on this phenotypic typography is catch rate (Wagner and Anthony 2002b). At the population level the catch rate is the probability, once use is initiated, of moving on to dependence. At the individual level, it is akin to the abruptness rate. The concept has not yet received the attention it deserves.

Although the human scale measures I have described here are by no means identical to the microtime measures being collected in the animal work, it is still gratifying to be able to make such direct, cross-species translations. For this reason, it is surprising that the authors felt their analytic models were untestable in human paradigms.

Section III: Specific mechanisms of risk transmission (Dick, Agrawal, Pergadia)

IIIa

The Dick et al. study (this issue), using the COGA child sample, provides a developmentally informed and highly imaginative study of the role of GABRA2 as a mediator of risk development for AUD and other drug involvement. The GABRA2 genetic variant has already been identified as one significantly associated with alcohol dependence among adults. Working from the considerable literature indicating (a) that conduct disorder is an early drug nonspecific risk factor for AUD; (b) that early alcohol related symptomatology is not as heavily under genetic control even though it is so developmentally later on, they argued that this genetic variant—as a mediator of alcohol use disorder—should be related to the conduct disorder pathway into AUD, but *it should not be related to the nongenetically regulated, early appearing alcohol dependence symptoms*. This dual hypothesis was confirmed.

They also hypothesized that the active variant of this genotype would show an increasing age relationship to incidence of AUD. And given the possible drug nonspecific relationship of this mediator, they hypothesized there might also be an increasing age relationship to incidence of drug use disorder (DUD). This hypothesis was also confirmed, most clearly in the analyses of the adult COGA sample, while showing some age instability for the AUD child analyses. The authors compellingly suggest that the weakness of the gene-symptomatology incidence effect was most likely a function of “noise” created by the heavy population increase in symptomatology around age 21, the legal age for drinking initiation. No such dilution of effect was evident for the DUD–GABRA2 relationship, and none would be anticipated given that illicit drug involvement never changes its (il)legal status. And last, they demonstrated that the active form of the gene was the homozygous form.

Although these findings need to be replicated longitudinally, the fact that they fell out exactly according to theory is suggestive of their robustness. What is especially intriguing about the work is that it tests a well thought through, developmentally stepped mediational model of when heritable connections should and should not be present. It also demonstrates, at the population level, the developmental emergence of the GABRA2-AUD/DUD relationship.

IIIb

Assortative mating on the basis of drug use phenotypes is an important factor in potentiating genetic risk for offspring. It can change the distribution of genetic risk in the population, it may increase the contribution of shared environment to risk transmission, it may increase the likelihood of genetic transmission by way of parallel assortment on genetically correlated but drug-nonspecific phenotypes (e.g., behavioral undercontrol). **The Agrawal et al. paper** (this issue) examines assortative mating on two smoking phenotypes (regular use and dependence) and two parallel alcohol phenotypes in a sample of Australian twins and controls assessed at the time subjects were around 40 years of age. Given that the premarital assortment took place perhaps 20 years prior, a good deal of recollection is present in the results, and their findings need to be tempered by that awareness. Even so, the study was able to replicate assortative mating on both smoking and both drinking phenotypes. Cross-stage assortment was also found vis a vis drinking but not smoking; female regular drinkers were more likely to assort not only with partners who were regular drinkers, but also were more likely to select a mate who had a

history of alcohol dependence. Little evidence of reciprocal spousal influences was found for either drug. Given the behavioral evidence for couple changes over time in patterns of drinking, even when controlling for baseline differences (Miller-Tutzauer et al. 1991; Leonard and Mudar 2004), it is difficult to know how to evaluate the lack of observed effect.

More generally, the Agrawal et al discussion of (the lack of) reciprocal effects brings up another issue, one that its authors are well aware of, but that is worth repeating. The hypothesis of assortative influence being evaluated here is a narrow one, based on the presumption that assortment on the drug specific phenotype will (a) occur (it does), and (b) that it will operate in a unidirectional manner to change spousal drug involvement. The first premise has been well tested, the second one, only weakly, and the third one they describe (see below) was not evaluated here. The putative mechanism of effect for change on the basis of assortment for the drug use phenotype would be exposure and heightened cueing, which in turn would lead to higher levels of use. However, a plausible counter-mechanism may also be in operation, whereby one spouse's cueing serves as an aversive stimulus to the other's continuing drug taking behavior. If both are operative to differing degrees, the two opposing mechanisms would work to cancel out two real effects. Only microlevel prospective designs will be able to evaluate such a process.

The third plausible competing hypothesis is that factors more central to the marital relationship, such as marital conflict, or stress, will have a stronger, albeit indirect effect on the phenotype. To my knowledge this hypothesis has not yet been tested. It clearly needs to be.

IIIc

The **Pergadia et al. study** (this issue) provides an interesting exploration of the proposal by Merikangas and Risch (2003) that targeting social influences on smoking might be a more effective public prevention strategy than identification of specific genetic risk. The authors reasoned that such an approach would only be useful if one could establish that social influences early in the process of smoking acquisition would have long term effects on smoking outcome as well as short term effects on initiation. They also hypothesized that such influences, to the extent they existed, should be differentially operative in MZ vs. DZ twins. Given the greater similarity of social experience for MZ twins, influence effects should elevate MZ–DZ concordance rate differences and lead to spuriously higher heritability estimates.

To test these questions, the study used a novel design that evaluated (a) whether simultaneous smoking initiation (SSI) occurred to a greater extent in MZ twin pairs, (b) if so, whether such effects then led to higher concordance for later stages of smoking, and (c) whether social experience differences in childhood and adolescence (e.g., sharing peers, dressing alike) were mediators of these relationships. The study was able to show that although rates of SSI were greater in MZs, among twins with greater parallelism of social experiences, and among males, such differences did not lead to variation in estimates of genetic, shared, and nonshared environmental parameters for smoking outcomes between SSI and nonSSI pairs, *except for* regular smoking among females. And even here, the differential effect was small.

The Pergadia study provides a good example of how a genetically informed design can be used to evaluate a proposed social policy. The study is also unusual in its effort to go beyond a simple exploration of whether ACE variations do or do not exist downstream. Because its design was set up to decompose the SSI phenomenon into specific environmental exposure elements, should an effect have been present, these investigators would have been in a position to evaluate what aspects of the social experience were moderating or mediating the effect.

Section IV: Lessons from animal studies (Crabbe et al. (this issue); Vargas-Irwin et al. (this issue))

IVa

What is a developmental psychopathologist/behavioral scientist, albeit once engineer, to glean from a series of animal studies concerning the stability of mouse strain task differences for two much used alcohol phenotypes, on the one hand, and from a micro-analysis of response-acquisition change points during initial episodes of cocaine use? Despite the great disparity of content, several issues of considerable importance are brought sharply into focus by these animal studies. I comment on three.

One is the great attention to standardization of assessment techniques across laboratories and across time that is carried out here, driven by the understanding that potentially even small differences in technique or laboratory method may lead to substantial differences in outcome. Although the Crabbe et al. studies are in fact reassuring that strain differences are robust across the procedural variations that exist over as long as a 20 year interval, their attention to this issue has almost no parallel in the human literature. Questionnaire measures of the same construct often differ substantially across studies, and the parameters of content variation, as well as “handler differences” in administration remain relatively neglected.

A second issue is the attention to population characterization—i.e., strain and substrain differences—which can affect the pattern of genetic correlations. Again, this issue is one about which little is known in the human literature, even though there is steadily increasing racial/ethnic variation in U.S. society. Despite this variation, nearly all the research reported here (even that coming from Australian samples) is based on whites of Northern/Western European descent. The Addhealth data (Lessem et al. this issue) and to some extent the COGA samples (the Dick et al. study), are the only exceptions. It will be interesting to see if the results obtained here are replicated in ongoing and future studies of more diverse populations.

Third, there is a special design characteristic found in animal studies, one that I have already alluded to in Section II. I refer to the parsing of the phenotype at a considerably more microscopic or dissected level of analysis. The tightly controlled and narrowly defined subcomponential phenotypes of the animal laboratory are essential for the characterization of the subject species. But while meeting those requirements, the animal models also encourage a process that is only beginning to take place at the human clinical level. The process can be found in the evolving discussion of potential DSM-IV revisions (Helzer and Hudziak 2002); it can also be found in current efforts to differentiate alcohol dependence from abuse (Hasin and Grant 2004; Ridenour et al. 2003; Schuckit and Smith 2001). These are but small examples from the field that are not being carried far enough.

The challenge for human behavior genetic studies of risk is to develop the equivalent of animal models of risky traits, and of addictive behavior, that can be applied to human study. Two observations guide this advocacy: One is that, if gene-trait connections that relate to quasi-addictive phenotypes can be identified in animal studies, this implies that similar, “simplistic” connections can be made for micro level human phenotypes. The second observation is that an increasing number of behavioral studies are reporting relationships between a broad array of drug specific and drug nonspecific risk factors and diagnostic outcomes, or their proxies. These relationships are sufficiently robust that they remain *even when a large number of previously known risk factors are controlled* (cf., Wong et al. 2004; Nigg et al. in press). This large number of connections is a persistent reminder that the substance use disorders are complex genetic disorders, with multicomponential behavioral manifestations under the likely control of multiple genes.

IVb

The work reported in this special issue is indicative of what nonbehavior geneticists have come to expect from the field. It reflects a high degree of statistical sophistication, is cautious in its conclusions, careful and considered about the potential biases and confounds implicit in its work. The field has by now also effectively made the case that behavioral variation which is not genetically informed will always provide an incomplete explanation for the phenomena being studied. At the same time, within the past decade, and more heavily in the past 5 years, another set of questions is beginning to be examined, concerning the pathways by which genetic influences act. An increasing amount of this work is concerned with understanding what the specific mediators and moderators of the genetic and environmental effects are, how to integrate specified genetic variants into the models, provision of more fine grained definitions of the phenotype, and more careful delineation of the specific environmental variations that underlie the shared or nonshared environmental liability.

Along with this sea change has come an awareness that these relationships take place upon and within a maturing organism, embedded in a dynamic system of family, peers, community, and culture, which themselves undergo change as development proceeds. From an analytic standpoint, with the exception of transition points, the phenotypes of interest become trajectories whose level of presence can vary over time. The design of choice to capture this variation is longitudinal; it allows the characterization of phenotypic and environmental variation to be more fine grained, and it decreases the problems of retrospective measurement error. At the same time, when drug related phenotypes have been characterized longitudinally, it is not uncommon to discover developmental heterogeneity of course, a problem which is not well summarized by measures of central tendency and cannot be assessed retrospectively (*cf.* Schulenberg et al. 1996a; Jacob et al. 2005). In addition, changes in trajectory shape and course are often a function of an environmentally or biologically triggered stage transition (Collins et al. 2000; Lanza and Collins 2002; Walls and Schafer 2005) which may in turn imply a change point for heritability/environmentality relationships.

The behavioral community has had a bit of a head start in modeling this level of developmental complexity as well as characterization of time varying covariation of trajectories of phenotype and of environmental exposure (*cf.* Jester et al. 2005). Several of the studies in this issue have been able to carry out such characterization, primarily at the phenotypic level, but also with beginning forays into the dissection of environmental variation. If the field is to stay current, more need to do so.

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