

Part I

Distal Determinants of Drug Use

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I

Developmental Factors in Addiction: Methodological Considerations¹

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1 Introduction

Epidemiological data show that substance use and substance use disorders follow characteristic age-related trajectories, such that the onset of substance use typically occurs in adolescence, peaks in rates of substance use (and in rates of clinical substance use disorders) occur during emerging adulthood (ages 18–25), and rates of both substance use and substance use disorders decline later in adulthood (Bachman *et al.*, 2002; Masten, Faden, Zucker, and Spear, 2008). Moreover, adult substance use outcomes and substance use disorders are predictable from early childhood factors (Caspi, Moffitt, Newman, and Silva, 1996; Masten, Faden, Zucker, and Spear, 2008). These age-related patterns of substance use and their association with early childhood predictors suggest the value of applying a developmental perspective to the study of addiction. Accordingly, this chapter focuses on methodological issues in research on developmental factors in addiction. We focus on methodological issues in studies of substance use among children and adolescents, and particularly on longitudinal studies, which are well suited for examining developmental trajectories and prospective predictors of addiction outcomes. However, it is also important to recognize that each of the topics that are covered in the other chapters of this volume also present methodological challenges when the particular domain of interest is studied in childhood and adolescence. Thus, studies of drug administration, psychophysiology, imaging, genetics, intellectual functioning, psychiatric comorbidities, impulsive and risky behavior, distress tolerance, expectancies, social context, implicit cognition, ecological momentary assessment, etc. each present both opportunities and methodological challenges when applied to child and adolescent samples and studied in a developmental context.

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Clearly, no single chapter could cover the numerous methodological issues involved in studying developmental factors in each of those many different domains. Therefore, instead we focus on more general methodological and conceptual issues involved in studying substance use (and risk factors for substance use) during childhood and adolescence, and we illustrate some of the unique methodological challenges in this research.

2 Empirical Relevance of Developmental Factors for Substance Use Research

Research on developmental factors is critical to an understanding of substance use disorders for multiple reasons. First, these studies are needed to inform etiology by identifying prospective predictors of substance use outcomes and testing the multivariate and multilevel etiological mechanisms that are hypothesized to underlie addiction. Second, these studies inform the design and targeting of preventive intervention. They identify the risk and age groups who are the target audiences for preventive intervention and, to the extent that malleable risk and protective factors can be identified, these studies pinpoint the factors to be targeted for modification in prevention programs. Third, studies of developmental factors are needed to understand the impact and consequences of substance use. Cross-sectional comparisons of individuals with and without substance use disorders cannot disentangle the causes of substance use disorders from their consequences. Thus, studies of children and adolescents before the onset of substance use are needed to separate the antecedents from the consequences of substance use.

Another sense in which developmental factors are critical to addiction research is that substance use involvement itself can be conceptualized as a series of stages or developmental milestones ranging from initial exposure to experimental use, regular and/or heavy use, substance use-related problems, and diagnosable clinical substance use disorders (e.g., Jackson, 2010; Mayhew, Flay, and Mott, 2000). The time that it takes to pass through these stages varies for different individuals and substances and is predictable by factors such as gender and family history of substance use disorder (Hussong, Bauer, and Chassin, 2008; Ridenour, Lanza, Donny, and Clark, 2006; Sartor *et al.*, 2008). Such predictable variability in the speed of transition from first exposure to addiction suggests that the speed of progression may itself be an important phenotype to study in order to understand the etiology of addiction.

Importantly, particular etiological factors may not only determine the speed of progression but may show unique prediction of specific transitions such that different factors may influence substance use initiation than influence substance use progression (e.g., Sartor *et al.*, 2007). For example, Fowler *et al.* (2007) found that common environment influences were more important for initiation whereas genetic influences were more important for progression. Methodologically, this suggests the need for researchers to disaggregate predictors of different developmental milestones in the development of addiction.

Moreover, developmental progressions may be important not only within “stages” of the use of a single substance but across different substances. It has been suggested

that individuals progress from involvement with “gateway” drugs such as alcohol, tobacco, and marijuana to the use of other illicit drugs (Kandel, Yamaguchi, and Chen, 1992). This progression might reflect a common propensity to use drugs, an affiliation with a drug-using social network that promotes the use of multiple substances, or a causal effect in which the use of one drug sensitizes an individual to the use of other substances (Kandel, Yamaguchi, and Klein, 2006; MacCoun, 2006). Methodologically, the notion of developmental progressions across the use of different substances implies that researchers who study the use of any one particular substance should measure and consider the co-occurring use of other substances.

Another developmental milestone that is important for the study of addiction is the age at which an individual first begins to use substances. Early onset of use is associated with a greater likelihood of developing dependence, and this has been reported for cigarette smoking (Breslau and Peterson, 1996), alcohol use (Dawson *et al.*, 1998) and illicit drug use (Grant and Dawson, 2008). There have been multiple interpretations of these findings, including the idea that they are spurious and caused by correlated “3rd” variables that are associated both with early onset and with risk for addiction (Prescott and Kendler, 1999). Other studies that have considered various hypothesized confounding variables have still supported a relation between early onset and greater likelihood of dependence or heavy use in adulthood. This pattern was found by Buchmann *et al.* (2009) for alcohol use and by King and Chassin (2007) for drug dependence. It has also been suggested that age of onset is a feature that might distinguish different subtypes of substance disorder. For example, Zucker (1986) distinguished among different forms of alcoholism with early-onset forms being either antisocial or developmentally limited (compared to older-onset negative affect forms of alcoholism). Other disorders have similarly considered age of onset in formulating subtypes. For example, Moffitt (1993) distinguished between adolescent-limited and child-onset life course persistent forms of conduct disorder. Methodologically, the possibility that age of onset is a marker for a particularly high-risk group for addiction suggests that age of onset is a useful phenotype for study. For example, Schmid *et al.* (2009) found effects of DAT1 on tobacco and alcohol use for individuals who started daily smoking or drinking to intoxication at a young age. Finally, it is possible that the relation between early onset of use and elevated risk of developing dependence occurs not because of particular subtypes of substance disorder or particular high-risk phenotypes, but rather because the central nervous system, early in development, is particularly vulnerable to substance use effects. For example, Levin *et al.* (2003) found that female rats who were randomly assigned to begin self-administration of nicotine in adolescence showed higher levels of later adult self-administration than did those whose self-administration began in adulthood.

These findings thus suggest that both age of onset of substance use and the speed of progression from initiation to heavy use or to clinical substance use disorder might be important developmental factors to study in order to better understand addiction. Some researchers have built on these findings by attempting to identify heterogeneity in longitudinal trajectories of substance use that consider multiple features, including age of onset, steepness of acceleration in use, peaks of use, and stability of use over time. These studies have often used mixture modeling techniques to identify clusters of trajectories, and have suggested that such dynamic trajectories might be better

phenotypes for the study of addiction than static features of the addictive behavior (see Chassin *et al.*, 2009 for a review). For example, Chassin *et al.* (2008) reported that parents' smoking trajectories had a unique effect on their adolescents' cigarette smoking over and above parents' current smoking. Parents whose smoking showed early onset, steep acceleration, high levels, and greater persistence were more likely to have adolescent children who smoked. That is, over and above parents' current smoking, their different smoking trajectories showed different levels of intergenerational transmission.

The potential value of developmental trajectories as phenotypes for addiction research raises important methodological issues. Measuring these trajectories is challenging because it requires either a reliance on retrospective data, which are limited by recall biases, or longitudinal studies, which are expensive and difficult to implement. Moreover, statistical methods for identifying and clustering trajectories (such as mixture modeling) have limitations (Bauer and Curran, 2003; Chassin *et al.*, 2009; Jackson and Sher, 2006; Sher *et al.*, 2011; Sterba and Bauer, 2010), requiring that researchers interpret their findings cautiously and follow recommended practices for establishing the validity of the findings (see Ialongo, 2010), including making decisions about competing models based on theoretical considerations in addition to empirical means of comparison (Sher *et al.*, 2011).

Finally, given the evidence reviewed to this point concerning the etiological significance of age of onset, speed of progression, and developmental milestones or "stages" of substance use both within and across substances, it is not surprising that different findings are produced by studying addiction among participants of different ages and stages of use. For example, behavioral genetic studies often report that the heritability of substance use phenotypes is lower in adolescence than in adulthood (Dick *et al.*, 2007; Kendler, Schmitt, Aggen, and Prescott, 2008). One interpretation of this finding is that developmentally limited, peer-driven forms of substance use in adolescence may mask the effects of genetic risk, which are then more clearly detected in adulthood when developmentally limited forms of use have remitted. In addition, adults probably have greater control to select their own social environments than do adolescents. Thus, there is probably greater gene-environment covariation in adult peer social environments than adolescent peer social environments because of greater adult "niche picking." Methodologically, this suggests that researchers should carefully consider the effects of age and "stage" of substance use in sample selection and data analysis.

3 Methodological Issues in Sampling Child and Adolescent Populations

Many studies of child and adolescent populations use school-based samples because of their relative ease of access, cost-effectiveness, and ability to accrue large sample sizes. However, although school-based samples contain quite diverse samples of children and adolescents, there are also limits to their representativeness. School-based samples may under-represent pathology, because truant, homeless, runaway, and institutionalized children are unlikely to be accessed. Moreover, because of school drop-out, the

representativeness of school-based samples in terms of including high-risk individuals is likely to diminish with the age of the participants, particularly after the age of legal school drop-out. The need for active parent consent also limits sample representativeness in school-based settings (e.g., Anderman *et al.*, 1995; Esbensen, Miller, Taylor, and Freng, 1999) as well as other settings (Rojas, Sherrit, Harris, and Knight, 2008), and active parental consent has been found to under-represent higher-risk and lower-socioeconomic-status participants.

Recruiting community-based samples of children and families using techniques like random digit dialing or birth records has the potential to achieve greater representativeness, but is expensive and labor intensive. Moreover, recruitment using telephone screening has become more difficult with changes in telecommunications and declining participation rates. Recruiting community samples may require mixed methods including using address-based sampling frames to mail surveys or to send advance invitation letters followed up by phone contacts (Mokdad, 2009).

Methods for improving recruitment rates (and parent consent rates) include mailing parent consent forms directly to parents (with telephone follow-up for non-responders) rather than attempting to obtain parental consent by going through the adolescent, and also stressing that participants include both users and non-users of substances so that the adolescent's privacy is protected (Kealey *et al.*, 2007). The use of incentives also improves recruitment, within the ethical constraint that the incentive cannot be large enough to create coercion (Moolchan and Mermelstein, 2002). Of course, sampling methods and selection criteria will necessarily vary with the specific research questions of interest. For example, if clinical substance use disorders are outcome variables of interest, then researchers must weigh the time it takes for these outcomes to develop, given various initial ages as well as the sample size required to produce sufficient "cases." It might be necessary to over-sample high-risk groups, older participants, or initial users in order to produce sufficient prevalence of clinical substance use disorder outcomes. Accelerated longitudinal designs (i.e., cohort sequential designs) can also be used to reduce the time that is required for observation of substance use outcomes (Collins, 2005).

4 Age, Cohort, and Time of Measurement Effects in Studying Development

Although we noted earlier that substance use outcomes show clear age-related patterns, age, per se, is rarely an important theoretical construct in understanding these phenomena. Rather, "age" is a proxy for complex developmental processes. These processes might include maturational changes (e.g., the onset of puberty, maturation of top-down central nervous system pathways for cognitive control) or age-graded social change (e.g., the transitions to middle school or to high school). When these proxies are known, studies can test them directly. For example, the onset of puberty has been studied with respect to increases in reward seeking (particularly peer reward), which, in combination with incompletely developed central nervous system top-down control systems, are believed to contribute to making adolescence a particularly high-risk period for substance use (Casey, Jones, and Somerville, 2011; Forbes and Dahl,

2010; Steinberg, 2010). Social transitions such as the transitions to middle school and then high school environments are particularly important periods to consider, as they are periods in which adolescents' social networks expand or change, and adolescents are potentially exposed to new contextual opportunities and influences. These transitions are periods of sensitivity to and openness to change in the new contexts to which adolescents must adapt. Finally, the greater time spent out of parent supervision, which accompanies normal development, contributes to risk during the adolescent years.

In examining age effects as proxies for complex developmental processes, an interpretational problem is that intertwined within any developmental data set are potential effects of age, time of measurement (period), and cohort (typically, year of birth). The problem is that these parameters have a linear dependency, such that they are non-independent in any specific data set. This problem has been long recognized (Baltes, 1968; Schaie, 1965; Nesselroade and Baltes, 1979), and various strategies have been proposed to address it.

The most typical designs used to examine developmental factors are cross-sectional studies (comparisons of different age groups at a single point in time) and longitudinal studies (observations of a single birth cohort over multiple times of measurement). The problem with these simple designs is that in focusing on one factor, they confound others. Cross-sectional studies are the most efficient in identifying age differences, but they do so for different groups, so that observed age differences are confounded with cohort differences. Similarly, in longitudinal studies, the observed differences are again typically interpreted as general age effects, but the design confounds age and the period effects, so that it is unclear if they would generalize to other cohorts.

Period effects (i.e., effects of the particular time/historical period of measurement) include things ranging from disease epidemics, war, or secular changes in the social context. For example, changes in laws, access, or price of a substance might influence the development of addiction. One relevant example is the introduction of the Surgeon General's report on smoking in 1964, which was an historical event that began a long and profound social change in the way that people thought about cigarettes and smoking in the United States. It is important to realize that period effects can influence different birth cohorts in different ways. For example, significant social change regarding the perceived negative effects of cigarette smoking might have greater effects on later birth cohorts (i.e., younger people) who have grown up in a social climate with a lowered prevalence of smoking, more stringent tobacco control policy, and more awareness of the negative health consequences of smoking. Indeed, cohort effects have been reported for adolescent cigarette smoking, with each successive cohort (i.e., 12th-grade class) smoking less between the years of 1976 and 1982 (O'Malley, Bachman, and Johnson, 1984).

Thus, a general goal of developmental research in addiction would be to know whether particular age-related effects generalize across different birth cohorts or historical periods. For example, Little *et al.* (2008) found that the relation between "deviance proneness" and marijuana use for adolescent boys was weakest at the cohort in which there was the lowest population prevalence of marijuana use. However, just because there are secular changes in the prevalence of a substance use behavior does not automatically mean that the etiological influences on that substance use behavior

will also change (Donovan, Jessor, and Costa, 1999). Thus, it is important to know whether the etiological factors or predictors of substance use outcomes vary over birth cohorts or historical periods.

The proposed strategies to achieve these goals have a common thread of combining features of longitudinal and cross-sectional designs. Schaie (1965) proposed various cohort sequential designs that combined features of longitudinal and cross-sectional studies to study several cohorts of individuals across time. Although these designs cannot realistically fully disentangle age, period, and cohort effects empirically (Masche and van Dulmen, 2004), they do provide replications of the critical comparisons of age differences (at differing time points) and, most importantly, of longitudinal sequences across separate birth cohorts. Moreover, compared to studying a single cohort, a further advantage of the cohort sequential design is that it collapses the time required to gather longitudinal data over a broader range of ages.

5 Methodological Issues in Measuring Adolescent Substance Use and Substance Use Disorders

Fundamentally, addiction research depends on the measurement of substance use behaviors, which are most often assessed by self-reports. Questions have been raised about the validity of self-reported substance use, given concerns about social desirability in reporting a behavior that is often illegal and socially stigmatized. These concerns may be particularly important when there are motivations to under-report, such as treatment outcome studies when treated participants may wish to portray themselves as improved or “cured.” Although these concerns apply to both adolescents and adults, they may be magnified for adolescent reports because more behaviors are illegal for adolescents than for adults (i.e., alcohol and tobacco use are illegal for adolescents but legal for adults), and because parents and other authority figures have more control over adolescents than over adults. Thus, adolescents may be more motivated than adults to hide their substance use from others. It has also been suggested that adolescents may be particularly confused by the terminology that is applied to drug classes in research studies and that allowing adolescents to write in the substances that they use might improve measurement (Morrall, McCaffrey, and Chien, 2003). Finally, adolescents’ reports of substance use may be also influenced by situational constraints that limit their opportunity for use, and thus provide mistakenly low estimates of substance use behavior. For example, the presence of parental supervision, school attendance, and time spent in supervised settings such as juvenile correctional settings will limit opportunities for use and thus possibly produce misleading reports (Piquero *et al.*, 2001).

One method for validating self-reported substance use is to compare self-reports with biological measures. Of course, biological measures themselves have limitations, including often being limited to the assessment of relatively recent substance use, varying rates of false positives and negatives, and substantial expense. Adolescent self-reports of substance use (including both calendar methods such as the Time Line Follow-Back and quantity-frequency items) show significant correlations with biological measures, both for non-Hispanic Caucasians and for ethnic minority adolescents

(Dillon, Turner, Robbins, and Szapocznik, 2005; Dolcini, Adler, Lee, and Bauman, 2003), although under-reporting has also been demonstrated (e.g., Delaney-Black *et al.*, 2010). Research with adults (Lennox, Dennis, Scott, and Funk, 2006) suggests that combining data from biological assays and self-reports can be useful in overcoming the limitations of each individual method.

Although adolescent self-reported substance use correlates with biological methods, there are systematic influences that affect the rates of substance use that are obtained. Higher self-reported use rates are obtained in contexts that maximize privacy and minimize risk of disclosure, particularly to parents. For example, self-reported substance use is lower when it is measured in household settings than in school settings (e.g., Griesler *et al.*, 2008) and lower in interviews than in self-administered questionnaires or computer-administered surveys (Turner *et al.*, 1998). Of course, these differences may reflect either under-reporting in household and interview contexts or over-reporting in school contexts and self-administered surveys. Inconsistent reporters tend to be younger, lighter substance users, more conventional (i.e., less delinquent) and members of ethnic minority groups (see Griesler *et al.*, 2008 for a review). Similar characteristics predict recanting of earlier-disclosed substance use in longitudinal studies of adolescents (Fendrich and Rosenbaum, 2003; Percy *et al.*, 2005). Light-using and socially conventional adolescents may recant because they re-consider their self-definitions as “users” and/or because they are more sensitive to social norms and adult disapproval. Even more worrisome, inconsistent reporting by adolescents who were receiving substance use treatment was associated with self-reports of improvement over time, suggesting that reporting biases might inflate findings of treatment success (Harris, Griffin, McCaffrey, and Morral, 2008). These problems dictate that researchers collect data on self-reported adolescent substance use in conditions that reinforce confidentiality and privacy and that minimize motivations for false reporting. Federal Certificates of Confidentiality may be useful for achieving this goal, although they do not necessarily eliminate under-reporting (Delaney-Black *et al.*, 2010).

In addition to using biological measures, one useful method of compensating for limitations of any single report (including self-report) is to use multiple informants. For research on children and adolescents, these are typically parents and teachers (Achenbach, McConaughy, and Howell, 1987). Indeed, such multiple reporter data are important in studies of the development of addictive behaviors not only as a way to compensate for individual biases and measurement error, but as a way to capture variability in behavior across contexts, which are differentially observable by different informants (Achenbach, 2011). However, for reports of substance use as outcome variables, parents may lack awareness of the extent of their child’s use and thus under-report, and parent–adolescent agreement in reports of use and disorders is typically small to moderate (e.g., Fisher *et al.*, 2006; Green *et al.*, 2011).

Thus, in terms of assessing adolescent substance use, it is recommended that researchers assess self-reports under conditions that reinforce privacy and confidentiality and minimize demand characteristics and social desirability concerns, including the use of a Certificate of Confidentiality when possible. Situational constraints that misleadingly suppress reports of use (e.g., time spent incarcerated) should be assessed. If resources allow, self-reports can be supplemented with biological measures (Lennox, Dennis, Scott, and Funk, 2006) and other informant reports.

There are also methodological complexities in assessing adolescents' substance-use related social consequences and dependence symptoms, resulting in dilemmas for diagnosing adolescent substance use disorders. Adolescents report more substance use-related symptoms than do adults even at comparable levels of use (Chen and Anthony, 2003; Kandel and Chen, 2000). There are multiple interpretations of this finding. One interpretation draws on developmental differences in substance use effects that are shown in animal studies (Spear, 2000; Torres, Tejeda, Natividad, and O'Dell, 2008) and argues that adolescents are more vulnerable to developing dependence than are adults even at low levels of use. In fact, some researchers have suggested that adolescents develop indications of dependence quite quickly after the onset of use (DiFranza, 2007). However, although animal data show greater rewarding effects of substances for adolescents than for adults, this does not necessarily translate into greater intake for adolescents. Moreover, animal studies suggest that adolescents are less sensitive to withdrawal effects than are adults (Schramm-Sapota *et al.*, 2009). Thus, the animal data do not clearly and consistently point to greater vulnerability to substance dependence among adolescents than among adults. Moreover, there are other possible interpretations of age differences in symptom reporting. Chen and Anthony (2003) point out that age and duration of use are confounded in cross-sectional studies and that there may be cohort effects. For example, more potent forms of cannabis have been introduced in recent years, and thus younger individuals' initial exposure to cannabis probably constituted a different dose than did older individuals' initial exposure.

It is also possible that age differences in the reporting of symptoms are due to problems in the diagnostic criteria, which are identical for adolescents and adults, at least in the *Diagnostic and Statistical Manual of the American Psychiatric Association* (American Psychiatric Association, 2000). For example, Chung *et al.* (2004) note that tolerance, rather than being a symptom of dependence, might represent a relatively normal part of adolescent substance use as adolescents move from experimentation to regular use. Thus, tolerance may not have the same clinical significance for adolescents that it does for adults. Chung and Martin (2005) conducted focus groups and interviews with substance-disordered adolescents and found that the diagnostic criterion of "impaired control" may also be problematic because adolescents rarely reported any intention to limit their use. Without such an intended limit on use, it is not possible to assess failed attempts to control. These findings suggest that simply applying adult diagnostic criteria to adolescent substance use disorders may not be optimal. Finally, there is some evidence that adolescents over-report symptoms. Chen and Anthony (2003) found that adolescents reported more symptoms than adults even with just 1–2 days of cannabis use. MIMIC models which compared adolescents and adults at equal overall levels of cannabis dependence found that adolescents over-reported the symptoms of tolerance and inability to cut down on use, which have also been identified as possibly problematic in Chung and Martin's studies (described above). Moreover, these same two symptoms of tolerance and an inability to limit use were also found to be early appearing symptoms of tobacco dependence in adolescents (Kandel, Hu, and Yamaguchi, 2009). Thus, tolerance and failed attempts at control may be problematic as symptoms for assessing adolescents' alcohol, tobacco, and cannabis disorders. If these symptoms are over-reported, then

using the same symptom thresholds for diagnosis for both adolescents and adults will also be problematic (Winters, Martin, and Chung, 2011).

As evident from the above discussion, the possibility that measures and constructs have different meanings at different ages means that researchers need to examine the extent to which their measures demonstrate invariance over age. If measures do not demonstrate age invariance, then this needs to be considered within longitudinal statistical models. For example, Item Response Theory (IRT) methods provide one approach to accommodating non-invariance within longitudinal models (Flora, Curran, Hussong, and Edwards, 2008).

Finally, a methodological challenge in analyzing substance use data that is particularly acute for child and adolescent populations is the large percentage of non-users who are typically sampled. This results in a non-normal, zero-inflated distribution of substance use outcomes, violating the normality assumption of most of the statistical models used in analyzing longitudinal data. Moreover, as discussed earlier, a large number of non-users in these analyses also risks blurring distinctions between “stages” of substance use, since the predictors of abstinence versus use may differ from the predictors of gradations of use among users. To address this problem, analyses can use a zero-inflated model (Liu and Powers, 2007) or a two-part random-effects model (Blozis, Feldman, and Conger, 2007). These models separate the frequency of substance use into two parts (i.e., log-odds of substance use and frequencies of substance use). Thus, these models provide prediction of two separate outcomes within a single model – the propensity to initiate substance use and the extent of substance use.

6 Creating Multilevel, Probabilistic Models of the Development of Addiction: Methodological Issues in a Developmental Psychopathology Approach

As reflected in the many domains covered in this volume, the development of addiction is considered to be the result of multiple, interacting processes that occur at different levels of analysis. It is beyond the scope of any individual chapter to exhaustively review all of these determinants. Here we provide a brief discussion of some of the major risk pathways that have been proposed and illustrate their conceptual and methodological implications when studying addiction from a developmental perspective.

Sher (1991) identified three interrelated biopsychosocial pathways to substance use disorders, which are not mutually exclusive. They are termed the deviance proneness pathway, the stress and negative affect pathway, and the enhanced reinforcement pathway. Although these pathways were developed to specifically understand the increased risk of substance use among children of substance users, the same processes are hypothesized to increase risk for substance use disorders more broadly, regardless of family history. Briefly summarized, the deviance proneness pathway suggests that adolescents who are temperamentally poorly regulated, and have poor executive functioning, and who are also exposed to poor parenting will be at elevated risk for later school failure and affiliation with deviant peers, who model, encourage, and provide opportunities for substance use behavior. The stress–negative affect pathway hypothesizes that adolescents who have poor emotion regulation and coping skills and who are exposed to

high levels of environmental stress will be more likely to use substances to self-medicate the resulting negative affect. The enhanced reinforcement pathway focuses on individual differences in substance use effects, suggesting that individuals who derive either stronger positive reinforcement or less negative effects from ingesting a substance will be at greater risk for substance use disorder. All of these pathways view substance use as more likely when individuals have positive expectancies about substance use. For example, individuals will be more likely to use substances to self-medicate negative affect if they believe that the substance use will successfully change their mood.

Sher's models are an excellent illustration of some of the key features of a developmental psychopathology approach to understanding substance use disorders (Cicchetti, 2006; Sroufe, 1997). Some of these features are that a developmental psychopathology perspective: (a) recognizes the interplay of genetic and environmental risk and protective factors and, more generally, of factors that operate on multiple levels of analysis; (b) recognizes that the same outcome (i.e., substance use disorder) can be the result of different pathways for different people (a principle termed "equifinality"); (c) posits probabilistic models recognizing that individuals at the same level of initial risk may not all develop a clinical disorder (a principle termed "multifinality"); (d) recognizes that early (distal) risk can be "re-modeled" by exposure to later (more proximal) influences but that, conversely, early risk exposure may constrain an individual's ability to adapt to later challenges; (e) recognizes that risk processes can cascade over domains, creating deeper and broader levels of problems (Haller, Handley, Chassin, and Bountress, 2010; Rogosch, Oshri, and Cicchetti, 2010); and (f) recognizes that individuals actively participate in creating and selecting their own environments.

These features of a developmental psychopathology approach to addiction have several methodological implications. Longitudinal designs or validly measured retrospective data are needed to test the ways in which early risk factors may constrain later adaptation. Moreover, in terms of longitudinal study design, researchers must match the timing of the measurement lags to the theoretical lags of effect that are hypothesized for the variables in question (Collins, 2005). This becomes increasingly challenging when studying complex mediational processes (e.g., developmental cascades; MacKinnon, 2008). For example, consider the effects of life stress. Life stress can have acute (i.e., time-specific) effects on substance use through self-medication mechanisms in which individuals use substances to reduce the levels of negative affect that are created by the stressor. To test these acute self-medication effects in a longitudinal study would require closely spaced measurements, such as those used in ecological momentary sampling (see Chapter 7, this volume). However, the effects of stress exposure early in development on risk for substance use disorders may operate in quite different ways and with a quite different lag of effect. Early exposure to adversity may create long-term lingering risk for substance use disorders through multiple mechanisms and complex, cascading influences. Early adversity can sensitize the hypothalamic-pituitary-adrenal axis, such that individuals who are exposed to high levels of adversity early in development may be more sensitized to respond to stress (Sinha, 2008). Early adversity also affects the development of the prefrontal cortex, influencing self-regulation, executive functioning, and behavioral control (Sinha, 2008; Andersen and Teicher, 2009), and early adversity can affect the accumbens

dopamine system, producing anhedonia, with the possibility of enhanced reinforcement from substance use (Andersen and Teicher, 2009). Moreover, the full effects of these changes may not be manifest until adolescence, when stress influences maturation of the prefrontal cortex, influencing vulnerability to drug-associated cues (Andersen and Teicher, 2009). These mechanisms have been tested mostly with animal models. To do so in humans requires carefully constructed long-term longitudinal designs in order to establish temporal precedence between exposure to early adversity and later magnitude of stress response or carefully validated retrospective measures of exposure to early adversity.

Moreover, the example of early adversity effects on addiction also nicely illustrates the methodological challenges associated with establishing causal inference in passive, observational, longitudinal studies. Although animals can be randomly assigned to conditions that vary in early adversity, in human studies, individuals who are exposed to high levels of early adversity are also likely to be exposed to other risk factors as well. Thus, there are many potentially confounding “third variables”, which may be responsible for what appears to be effects of early adversity. For instance, parental substance use disorder may drive a spurious (i.e., non-causal) relationship by increasing both exposure to early adversity and heritable risk for later substance problems. Further, other early risk factors such as behavioral under-control may operate as third variables by evoking the experience of early stressful events and also producing later risk for substance problems.

In terms of solutions to address the methodological challenge of establishing causal inference in passive, observational, longitudinal studies, there are multiple strategies that can be used. In general, they can be conceptualized as attempts to equate individuals on potential third variables (Morgan and Winship, 2007; Rubin, 1974). Using the example of early adversity as the predictor of interest, the most common approach uses conditional models where the effect of early adversity on later substance use is estimated while including potential third variables as covariates. A less commonly used alternative is propensity score matching (Rosenbaum, 2002; Rosenbaum and Rubin, 1983) where, for example, a preliminary model could predict early adversity from a set of potential third variables, thereby producing predicted scores representing each participant’s propensity to experience early adversity. Then, participants with and without early adversity can be matched on propensity scores, and the resulting matched (i.e., equated) groups can be compared on later substance use. A propensity scores approach holds several advantages over conditional models, including (a) greater statistical power and stability of estimates, particularly when considering many potential third variables, and (b) more straightforward confirmation that groups were successfully equated and that key assumptions of accounting for third variables were met (e.g., adequate third variable overlap between groups; Little and Rubin, 2000; Morgan and Winship, 2007; West and Thoemmes, 2008). However, both approaches are limited in that it cannot be determined whether there are other important third variables that were unmeasured and whose effects are therefore not considered. Thus, to effectively employ these approaches, design and theoretical considerations are critically important to increase the likelihood that all important third variables are appropriately measured (Rubin, 2008).

In addition to the importance of considering the appropriate time lag of effect and potential third variables, another methodological challenge to testing these multivariate risk pathways is that they are characterized by reciprocal directions of influence. For example, to this point, we have been discussing risk factors for adolescent substance use, such as poor parenting, substance-using peers, or life stress. However, substance use itself is likely to affect these variables. Adolescents who use drugs are likely to seek out similar substance-using peers. They may also evoke poor parenting and create life stress – for example, being more likely to lose a job because of their poor performance. These effects of adolescent characteristics in creating their environments must be considered in testing etiological models. The effects of substance use itself on these risk factors is particularly important because substance use exposure may change reward pathways and self-regulatory abilities in addition to cognitive functioning (Volkow, Baler, and Goldstein, 2011). As can be seen from this discussion, testing these probabilistic risk models requires appropriate statistical tests of reciprocal influences, of mediation, and of moderated mediation within longitudinal data.

As noted earlier, a developmental psychopathology approach as exemplified in Sher's models also incorporates interactions among etiological factors that operate at multiple levels, including genetic risk, individual dispositions, and parent and peer relationship contexts. Moreover, although not a major focus of Sher's models, higher-level macro social determinants of adolescent substance use, such as schools and neighborhoods, and social policy also play important roles and interact with individual and more proximal social context factors (Siegel *et al.*, 2005; Thomson *et al.*, 2004; Brook, Nomura, and Cohen, 1989; Perry, Kelder, and Komro, 1993; Petraitis, Flay, and Miller, 1995). Bronfenbrenner's Ecology of Human Development Theory (Bronfenbrenner, 1979) provides a theoretical framework to guide research to explore these multiple layers of influence within a developmental perspective. Bronfenbrenner described three higher levels of environmental influences that interact with individual variables to influence behavior. The microsystem refers to interpersonal interactions in specific settings, such as within the family and peer networks. The mesosystem stems from the interrelations among the microsystems (e.g., the family competing with an adolescent's peer influence). Finally, the exosystem is the larger social system that can affect individuals and includes neighborhoods, cultural beliefs and values, and policy.

From a methodological standpoint, testing the effect of multiple levels of influence on adolescent substance use requires multilevel modeling approaches (Raudenbush and Bryk, 2002) due to the nesting of data (e.g., adolescents nested within families, schools, and neighborhoods). For example, Ennett *et al.* (2008) used multilevel modeling to apply Bronfenbrenner's theory to characterize multiple levels of influence on adolescent alcohol use. Their microsystem model included variables describing family, peer, and school contexts. Their mesosystem models included interactions among the family, peer, and school influences. Their exosystem model added the variables representing the influence of the neighborhood. Ennett *et al.*'s (2008) findings showed that attributes of family, peer, school, and neighborhood contexts all uniquely predicted adolescent alcohol use. As these multilevel models show, studies of developmental factors in addiction have become multidisciplinary because they span levels ranging from the cellular to the macro social policy environment and historical context.

In addition to the multilevel nature of the data, studying these models, which attempt to capture the interplay and reciprocal influence among multiple factors, and which also change over time, requires complex statistical approaches. These include the need to test longitudinal multiple mediator processes and moderated mediation (MacKinnon and Fairchild, 2009) and to accommodate the non-normal, often zero-inflated distribution of the outcome variable (Liu and Powers, 2007). Such mediational models require large sample sizes (Fritz and MacKinnon, 2007).

7 Summary, Limitations, and Future Directions

Given evidence of age-related patterns of substance use disorders as well as evidence of their predictability from early childhood risk, the study of developmental factors is clearly important to research aimed at understanding addiction. Moreover, the study of developmental factors is critical for the design of preventive intervention programs. However, as described in this chapter, there are also significant methodological challenges to this research. These challenges include the difficulties of recruiting and retaining large, representative child and adolescent samples, choosing appropriate ages and measurement lags to evaluate the effects of interest, obtaining valid reports of adolescent substance use and substance-use related symptoms, creating valid diagnoses of clinical substance use disorders for adolescent populations, creating phenotypes that reflect developmental milestones both within the course of use of an individual substance and across different substances, obtaining multiple informant reports of risk and protective factors, establishing invariance of measures across age ranges, and testing complex longitudinal, multilevel, mediation and moderated mediation models, including reciprocal effects. In addition, of course, each specific domain of addiction research (discussed in the other chapters in this volume) presents its own specific methodological dilemmas when applied to child and adolescent populations.

Given these challenges, there are several relevant newly emerging research directions. As might be expected, research on developmental factors in addiction is becoming increasingly multidisciplinary, in order to be able to capture the influence of etiological factors that operate on multiple biopsychosocial levels of influence. Moreover, the need for very large samples has created an interest in data sharing and in methods that allow researchers to combine data across different studies. For example, Curran and Hussong (2009; Curran *et al.*, 2008) used IRT methods to combine data from different longitudinal studies. These methods allowed them to reconstruct trajectories and test hypotheses about the effects of parent alcoholism across a broader age range than would be possible using any of the individual studies taken alone (see e.g., Hussong *et al.*, 2007). Moreover, these methods allow the identification of study-specific effects compared to findings that generalize across multiple studies. The use of IRT methods helps to harmonize data from multiple studies that use different measures of key constructs. However, another approach is to encourage studies to use consensus measures, making it easier to combine studies and/or compare results across different studies. A current example of this approach is the PhenX project, which is reviewing and recommending consensus measures for the integration of genetics and epidemiological research, including applications to substance use outcomes.

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Because most of the impact of addictions occurs in adulthood, it is possible to overlook the fact that the roots of substance use are typically established in adolescence. It is important to study the precursors and the process of onset of drug use and the emergence of dependence in order to fully understand those processes and to successfully prevent or intervene to reduce the problems of addiction. Whether one studies the developmental progression of use of a single drug, or the co-relations among the use of several drugs, researchers need to take into account developmental issues in the onset of addiction. As we have seen, these factors affect the conceptualization of the phenomena, the measurement of the behaviors themselves (as well their predictors), and the issues of unraveling the entwined causal factors involving time and change across development. Some of these issues are complex, but they are of both practical and theoretical importance to our understanding of addiction and are central for its prevention.

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