The Wiley-Blackwell Handbook of Addiction Psychopharmacology
To Emily

–JM
Contents

About the Editors xi
About the Contributors xiii
Introduction: The Science of Addiction Psychopharmacology 1
James MacKillop & Harriet de Wit

Part I Distal Determinants of Drug Use 5

1 Developmental Factors in Addiction: Methodological Considerations 7
   Laurie Chassin, Clark Presson, Young Il-Cho, Matthew Lee, and Jonathan Macy

2 Executive Dysfunction in Addiction 27
   David P. Jarmolowicz, E. Terry Mueller, Mikhail N. Koffarnus, Anne E. Carter, Kirstin M. Gatchalian, and Warren K. Bickel

3 The Roles of Race and Sex in Addiction Research 63
   Ezemenari M. Obasi, Jaime L. Richards, Delishia M. Pittman, Jokae Ingram, Marian R. Beasley, and Kristen L. Ratliff

4 Understanding Psychiatric Comorbidities and Addictions 83
   James C. (Jim) Anthony

5 Personality and Addiction: A Critical Review of Assessment Approaches 111
   Joshua D. Miller and Donald R. Lynam

6 Behavioral Inhibition and Addiction 135
   Mark T. Fillmore and Jessica Weaver

7 Delay Discounting and Drug Abuse: Empirical, Conceptual, and Methodological Considerations 165
   Jeffrey S. Stein and Gregory J. Madden

8 Assessment of Risk Taking in Addiction Research 209
   Jennifer Dahne, Jessica M. Richards, Monique Ernst, Laura MacPherson, and Carl W. Lejuez
Contents

9 Distress Tolerance 233
Jessica F. Magidson, Bina Ali, Alyson Listhaus, and Stacey B. Daughters

Part II Proximal Determinants of Drug Use 257

10 Measuring Direct Effects of Drugs of Abuse in Humans 259
Harriet de Wit

11 The Role of Aftereffects and Withdrawal in Addiction 281
Jon D. Kassel, Jennifer C. Veilleux, Adrienne J. Heinz, Ashley Braun, and Stephanie Weber

12 Drug Self-Administration Paradigms: Methods for Quantifying Motivation in Experimental Research 315
James MacKillop and Cara Murphy

13 The Assessment of Craving in Addiction Research 345
Lara A. Ray, Kelly E. Courtney, Guadalupe Bacio, and James MacKillop

14 The Cue Reactivity Paradigm in Addiction Research 381
Elizabeth K. Reynolds and Peter M. Monti

15 Stress and Affective Inductions in Addiction Research 411
Suzanne Thomas and Amy Bacon

16 Substance Priming 435
Abigail K. Rose

17 Understanding the Role of Substance Expectancies in Addiction 459
Jane Metrik and Damaris J. Rohsenow

18 Implicit Cognition 489
Paul Christiansen and Matt Field

19 Experimental Methods for Understanding the Role of Social Context in Drug Addiction 515
Matthew G. Kirkpatrick and Margaret C. Wardle

20 Ecological Momentary Assessment 541
Thomas R. Kirchner and Saul Shiffman

Part III Insights from Cognitive Science 567

21 Startle Reflex and Psychophysiology 569
Jeffrey C. Meehan and Robert Miranda, Jr

22 Using Quantitative EEG and EEG Tomography to Understand Drug Abuse: A Quantum Leap in New Methods and Benefits 599
David G. Gilbert and Herman A. Diggins

23 Functional Magnetic Resonance Imaging in Addiction Research 643
Lawrence H. Sweet, Michael T. Amlung, and James MacKillop

24 The Role of Positron Emission Imaging (PET) in Understanding Addiction 677
Dean F. Wong, James Robert Brašić, Emily Gean, and Ayon Nandi
Contents

25 Application of Magnetic Resonance Spectroscopic Imaging to Addiction Research 707
   Sujung Yoon, In Kyoong Lyoo, and Perry F. Renshaw

Conclusions: Consilience as the Future of Addiction Psychopharmacology 751
   James MacKillop & Harriet de Wit

Index 755

Plate section between 688 and 689
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Introduction: The Science of Addiction Psychopharmacology

The scope of the problem of alcohol, tobacco, and other drug addiction is massive. In the United States, tobacco is the single largest cause of overall mortality – above all other causes of death, including poor diet and accidents – and alcohol and illicit drug use are the third and ninth largest causes (Mokdad, Marks, Stroup, and Gerberding, 2004). Together, use of licit and illicit drugs is estimated to cause over 500,000 deaths annually, resulting from diverse forms of morbidity. Nicotine dependence is the most prevalent substance use disorder, with a US prevalence of around 13% (Grant et al., 2004), and tobacco use is a major contributor to chronic illnesses, such as cardiovascular disease, pulmonary disease, and cancer (Centers for Disease Control and Prevention, 2008). Alcohol is the most commonly used psychoactive drug and excessive consumption is associated with acute risks, such as motor vehicle crashes, physical and sexual assault, and suicide, as well as chronic health problems such as cardiovascular disease and an array of cancers (Hingson et al., 2002; Hingson, Zha, and Weitzman, 2009; Room and Rehm, 2011). Similarly, illicit drug use is associated with both acute and chronic health risks (Degenhardt et al., 2011; Maraj, Figueredo, and Lynn Morris, 2010). Translated into economic terms, the estimated annual costs to society are onerous: for tobacco, $167 billion (Centers for Disease Control and Prevention, 2008); for alcohol, $223.5 billion (Bouchery et al., 2011); and, for illicit drug use, $193 billion (National Drug Intelligence Center, 2011). Although the preceding data pertain to the US, drug addiction is as pressing a public health problem worldwide (World Health Organization, 2011; Rehm et al., 2007; Rehm et al., 2009; Rehm, Taylor, and Room, 2006).

This devastating public health problem can be directly addressed via prevention and treatment, but these solutions require a full understanding of the determinants and mechanisms underlying addiction. To achieve this goal, carefully designed and experimentally rigorous research is essential. The current volume provides a comprehensive review of the methods developed to study addiction in humans. Historically,
Introduction: The Science of Addiction Psychopharmacology

drug addiction has been attributed purely to the pharmacological properties of a drug or to the moral failing of the user. More recently, the science of addiction psychopharmacology has provided multidisciplinary tools to study the complex interplay between the drug, the user, and the surrounding context. Drug use can be studied within a single experience, across episodes, and across the lifespan. It can be studied in relation to macro-level factors, such as personality and developmental experiences, as well as micro-level factors, such as the physical, psychological, and physiological contexts in which drug use takes place. Moreover, new technologies from cognitive neuroscience can now provide unique insights into addiction by revealing heretofore unobservable dimensions of the brain. Thus, contemporary researchers have a rich array of techniques at their disposal to study the complex phenomenon of addiction.

Nonetheless, many challenges remain to understand and treat drug addiction. One challenge is the multifactorial nature of the problem and the fact that research efforts tend to take a single perspective that reflects the disciplinary background of the researchers themselves. Addiction researchers include experts from many backgrounds, including basic scientists, such as behavioral pharmacologists or neuroscientists; clinical scientists, such as clinical psychologists or psychiatrists; and social scientists, such as sociologists or anthropologists. These disciplines reflect “silos” which stand in the way of truly interdisciplinary research that integrates methodologies across disciplinary boundaries. These silos have their own established literatures, set of validated experimental tools, and jargon, creating barriers to understanding and collaboration across fields.

We hope that the current volume will address this challenge and facilitate interdisciplinary exchanges in addiction psychopharmacology. Each chapter provides an overview of a domain, a review of its associated methods, and some directed insights into the causes and results of drug addiction. The authors describe methods that can be used in various contexts, and make “best practice” recommendations for different approaches. Finally, each chapter briefly characterizes priorities and future directions for the domain and methodology. Taken together, the goal of the volume is to provide current and future addiction researchers with a broad and deep grounding in diverse experimental methods to foster increased collaboration and transdisciplinary research on addiction.

The book is organized according to the methods used. The first section takes a macrocosmic approach and focuses on stable factors that may function across the lifespan. These include developmental influences, cognitive factors, and personality traits. Each of these influences is multifaceted. For example, impulsivity is a trait that has been consistently associated with drug addiction, but it is now thought to be comprised of multiple, distinct facets (Cyders and Coskunpinar, 2011; de Wit, 2009). Therefore, one chapter focuses on personality-based assessments of impulsivity while the following three chapters each individually focus on different dimensions of impulsivity and risk taking. The second section takes a microcosmic approach and focuses on studying the individual under experimental conditions. This includes essential methods for measuring the psychoactive and physiological effects of addictive drugs and how individuals self-administer drugs, as well as the influence of environmental cues, priming doses, or stress. The third section focuses on insights gleaned from cognitive neuroscience. Technical advances in electrophysiology, magnetic resonance
imaging, positron emission tomography, and magnetic resonance spectroscopy offer an unprecedented opportunity to study brain and behavior concurrently, and to study the neurobiological dimensions of addiction in humans.

Despite extensive research to date and substantial advances, the complexity of drug addiction is clear and the prospects for easy solutions or “silver bullets” are extremely low. Rather, via systematic scientific study from an array of fields, we believe a greater understanding of addiction is possible and this understanding, in turn, can be applied to improve treatment and prevention. In this spirit, we hope this volume ultimately contributes to alleviating the burden of addiction by assembling the “tools of the trade” and expanding the perspectives and research programs of the addiction scientists of today and tomorrow.

References


Part I
Distal Determinants of Drug Use
1 Developmental Factors in Addiction: Methodological Considerations

Laurie Chassin, Clark Presson, Young Il-Cho, Matthew Lee, and Jonathan Macy

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.

1 Preparation of this chapter was supported by Grants AA016213 from the National Institute of Alcohol Abuse and Alcoholism and DA013555 from the National Institute on Drug Abuse.
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...