4

Biological Risk Amplification: Disease Vulnerability

Learning Points

- **People with greater addiction vulnerability acquire the disease more easily and more rapidly than people in the general population**. They are also prone to having more severe and damaging disease courses.
- **Heightened addition vulnerability is generally *not* drug-specific although there are specific factors that can increase (or decrease) vulnerability that is specific to certain drugs.**
- **Addiction vulnerability is associated with earlier age of onset and the acquisition of multiple types of addictions (involving two or more drug classes) happening sequentially and/or concurrently.**
- **Genetic factors, including those tied with various forms of mental illness, and adverse environmental conditions (e.g., traumatic experiences) that also produce or worsen a wide spectrum of mental illness all conspire to increase addiction disease risk.**
- **The neurocircuitries of mental illness and addiction are integrated**. This convergence of pathologies represents

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a fundamental design motif of the mammalian brain where the primary motivational neural network (in the NAC), which is most directly altered by addiction, is a convergence zone of projections from cortical–limbic networks (PFC, AMY, HCF) that are involved in the pathogenesis of mental illness. The integration of brain circuits involved in mental illness and addiction produce bidirectional causality and disease worsening of dual-diagnosis illness components.

- **Both *abnormal* brain states of mental illness, and *normal* brain transitions of adolescent neurodevelopment represent *common, involuntary, neurobiological* contexts that can separately or interactively amplify addiction vulnerability**. A neuroscientific understanding of how these vulnerability states increase addiction risk and produce disease acceleration translates to a better understanding of addiction disease on both the individual patient (clinical) and population (epidemiological) levels. This neuroscience of addiction psychiatry (synonymous with the neuroscience of dual diagnosis) has important implications for optimizing the prevention and treatment of addictions via the integration of mental health and addiction clinical training and treatment services.

Introduction

What Is Addiction Vulnerability?

Understanding addiction vulnerability is a key scientific bridge and translation of the basic neurobiology of addiction covered in Chapter 3 that moves us closer to the clinical level of diagnosis and treatment covered in Chapter 5. Addiction vulnerability understood at the neurocircuit level helps us explain why the disease strikes certain populations so avidly, producing a wide range of secondary medical and psychiatric consequences for them. In turn, this neuroscience, which explains why dual-diagnosis disorders are so common, has major implications for how we should diagnose and treat addictions and the mental illnesses as integrated diseases.

Chapters 2 and 3 have reviewed the behavioral and neurobiological processes that happen as an individual acquires addiction. Given that the

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disease process is based within a complex neural network composed of many "parts" that are governed by vast numbers of subsidiary mechanisms and neural systems, we can expect that many factors and forces that act on or within these systems can impact the threshold or speed by which a person becomes addicted.

Many readers will agree with this observation from their own college-age experiences: Although bouts of drug experimentation and binge drinking are quite common across college campuses (e.g., about a third get into binge drinking; Krieger et al., 2018), most of these students are still able to successfully pursue their studies and transition into adult life without developing chronic severe substance use problems. Still, there is a subset that will go on to have heavy, life-threatening addictions. How can we account for the fact that many people can have similar initial exposure patterns to a substance, yet only a subset become addicted? To answer this question let's begin with defining terms:

> ***The degree of addiction vulnerability*** **can be conceptualized as individual differences in the number of "hits" (i.e., uses) of a substance that it takes for a person to develop the pathological changes in motivated behavior (and brain systems) that underpin addiction.**

Of course, reality is a bit more complicated than this. It's not just the number of "hits" of the drug it takes to kindle an addiction. It also has to do with the frequency (temporal pattern), dose, and route of use of the drug. Also, there is a "chicken or the egg" dilemma in play where, as discussed in the last chapter, addiction pathogenesis involves an acceleration of a vicious behavioral–brain cycle. More drug hits drive the addiction process, and worsening addiction increases the frequency of drug hits. But in the laboratory setting at least, many of these variables and complex interactions can be held fairly constant, so that it is possible to observe that there is a normal variance across a population of animals, in terms of how soon they start to show acquisition of addictive behaviors, and how stubbornly installed these behaviors become. That is to say, there is considerable variation of addiction vulnerability in any population of animals. For most mammals, including humans, the question is not so much about if the individual can get addicted; rather, it is about how much drug does it take, how quickly can the disease manifest, and how severe can the disease get? In terms of thinking

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about severity, the observables boil down to (a) how much total damage (medical, psychiatric, financial, legal, social) the addiction is generating and (b) how hard it is to treat.

Addiction vulnerability thus varies widely across individual animals and humans and there are resilience factors that allow some individuals at the more favorable end of the vulnerability spectrum to be remarkably disease-resistant. Again, this reminds us of that friend from college who could smoke cigarettes on weekends but never go on to become a regular smoker. The wide range of addiction vulnerability in the general population reveals addiction to be a biomedical disease process similar to virtually all other major complex biomedical diseases processes of vital body organs (e.g., cancer, heart disease, type II diabetes, dementia, and so on) that are highly multifactorial and affected or accelerated by many biological and environmental risk factors. In this chapter, we will review the major genetic, environmental, neurobiological, and neurodevelopmental contexts that produce addiction vulnerability and enhance disease acceleration.

Addiction as a Heritable Disease

A vast catalogue of research has accumulated on the genetics of addiction disease risk, especially for alcohol. It is estimated that more than 1,500 genes, most of which are expressed via mRNA transcription in the brain, play a role in the variation in addiction risk. These genes are involved in many functions ranging from drug metabolism (happening in the body) to a multitude of mechanisms and systems that subserve brain function.

As is the case for understanding the genetics of other psychiatric and medical disorders, identical twin studies have been important for defining the heritability of addictions. **Heritability** is a data-supported estimation for what percentage of variation in the disease incidence can be attributed "purely" to genetics. In addiction risk and pathogenesis, there is a very rich mixture of both genetics and environmental factors that conspire together to increase disease risk. Having read Chapter 3, this should not come as a surprise for the reader because the brain (and the brain regions where addiction occurs) are profoundly and intricately sculpted, *biologically*, by both genetic determinants and environmental experiences. This interaction of many genes and environmental conditions has made it difficult or even impossible for studies focused on addiction (that look at different subpopulations) to converge on

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a *narrow* range of genetic factors responsible for addiction risk. So, for example, in contrast to identical twin studies that have fairly consistently found about a 50% heritability rate for schizophrenia (roughly equivalent to the average rate of concordance of the disease among identical twins), the heritability for addiction has been characterized across studies in a much broader range, 30–80%. Some of this increased variance is also due to how addiction is defined (in terms of clinical severity) and the wide range of substances that could be involved, which each impart their own average degree of addiction risk (e.g., tobacco/nicotine is generally more addictive than cannabis/tetrahydrocannabinol (THC)). In sum, although addiction risk is highly heritable, *addiction genetics have a probabilistic effect but not a concretely predictive or deterministic effect*, because the risk is so exquisitely dependent on so many genetic and environmental factors.

Animal Modeling Alcoholism with Inbred Rats

Animal modeling, most of it involving rats and mice, has played a major role in helping us understand the complex genetic basis and neurobiology of addictions, especially in the case of alcohol. For example, the alcohol "Preferring '**P rat**'," developed and characterized at Indiana University School of Medicine since the 1970s, became one of the most widely studied and informative genetic animal models of addiction in the world. This animal model was created not by modern gene knock-out or gene turn-on technologies, but the old-fashioned way, by repeatedly inbreeding rats – generation after generation – based on whether they liked to drink high amounts of pure ethanol in water solutions (even with no flavor or sugars added). Because P rats were so well bred to prefer alcohol and did not require food reinforcers to show this phenotype, they represented excellent animal models for alcohol addiction. So, with P rats, all the following could be studied in one animal model: (a) the complex biology of genetic risk to alcohol addiction; (b) the behaviors intrinsic to and surrounding alcohol addiction; and (c) the biology resulting from toxic/chronic exposure to alcohol.

Although it was initially hoped the P rats (and other inbred rodent models) could help us define a small set of genes responsible (and specific) for alcohol addiction, they revealed a quite different and much more complex story. First, even though these rats were created exclusively

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by means of selection for the trait of high alcohol consumption, the outcome phenotype of excessive drug use was not specific to alcohol! P rats also show elevated addiction risk profiles to other drugs that have very different pharmacological-intoxicating effects from alcohol, including nicotine and cocaine. Moreover, P rats, even before they are exposed to alcohol, show abnormal behaviors that can be categorized as nonspecific signs of underlying mental illness (e.g., like excessive novelty-seeking). Thus, as we will consider next, the genetic risk set of addiction is not only very complex and multifaceted, but it is also largely not drug-specific, and at the same time overlapping with the genetic risk of mental illness.

Toward A Complex Recipe for Addiction Risk

Within the genetic risk set for addiction, it is helpful to categorize these factors as falling into one of two groups: one where the genetic risk factor(s) is largely drug-specific and the other where the factor(s) (e.g., as in the P rats) increase addiction risk to multiple drugs. It turns out that both of these classes of risk factors certainly exist. But by and large, the major component of heritable addiction risk appears to be nondrug-specific. Hence, many of the genetic determinants that affect motivational neurocircuit function that are downstream from the postsynaptic DA release that different addictive drugs produce (as described in Chapter 3) could have a general addiction disease risk impact rather than a drug-specific impact.

In fact, most patients with severe addictions typically have more than one addiction (i.e., involving more than one drug) as manifested either serially or concurrently. At least two major causal dynamics (which can also happen in the same individual as compounding effects) can create this **polysubstance vulnerability**, described as follows:

(1) Cross-sensitization: In cross-sensitization, chronic exposure to an addictive drug is understood as initiating the addiction disease process in a way that not only sensitizes the brain to motivational cues specific to that drug (see sections on sensitization in Chapters 2 and 3), but also in a way that allows a second (different) addictive drug more efficiently become part of the addictive drug use pattern. This dynamic is closely related to the idea of the "gateway" drug, where the initial use of one drug, say in adolescence, is thought to increase the risk of acquiring addiction to multiple other drugs. Animal studies have broadly supported the existence of cross-sensitization

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and have suggested the presence of multiple pharmacological and biological mechanisms by which it may take place. For example, taking two addictive drugs (e.g., nicotine and alcohol) at the same time might produce a stronger DA surge or postsynaptic (NAC network) impact than what the same dose of either drug alone might create. Or, if two different drugs are similar in their neuropharmacological actions (e.g., cocaine and amphetamine), then after addiction has set in with respect to one drug, the other drug might readily substitute for the other.

(2) **Brain attractor states for addiction**: In the brain attractor state for addiction, it is understood that there is an initial brain context or condition affecting the individual that confers increased addiction risk that is not drug-specific. Thus, when the individual with this condition is eventually exposed to more than one addictive drug, they are more likely to acquire addiction involving *multiple* addictive drugs. This attractor state dynamic is analogous to our understanding of how, in astrophysics, large gravitational fields of very massive objects can pull in multiple other objects into its orbit (e.g., the Earth has one moon, but the much larger Jupiter has more than 50 moons). So, when certain brain contexts or conditions that exist premorbid to addiction operate as strong addiction attractor states, they often produce polyaddictions. As we will discuss in much of the rest of this chapter, two major brain states/conditions are prime examples of this kind of vulnerability: mental illness and adolescent neurodevelopment. Again, as in the research supporting the existence of cross-sensitization, animal research has also been important for demonstrating the existence of these addiction attractor states.

Multifinality and Equifinality in the Nature and Nurture of Addiction Risk

In considering and comparing cross-sensitization and brain attractor states as mechanisms that convey nondrug-specific risk of addiction, it is important to realize that both dynamics may take place in the same individual as either separate or integrated processes. For example, an individual, "Jack," may carry a gene "C" that can get turned on in response to heavy alcohol consumption that could also (after having been turned on by alcohol) convey increased likelihood of getting addicted to cocaine. At the same time, Jack may carry a different gene "D," which enhances his

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risk of having schizophrenia. But because having schizophrenia is also a kind of brain attractor state for acquiring addiction (to cocaine and alcohol), then gene "D" also counts as a risk gene for addiction. So, Jack carries at least two gene loci that work through different intermediate pathways to impart enhanced addiction risk.

Yet another individual, "Dana," may carry a gene "E" that is involved in multiple causal dynamics all at once. Gene "E" could enhance single-drug sensitization. It could also enhance cross-sensitization, and it could be a fundamental ingredient of susceptibility to schizophrenia. For both Jack and Dana, we can end up with the same phenotype: schizophrenia and polyaddictions, even though the genetic determinants for their diseases are different and work through different (albeit similar) intermediate pathways.

This "Jack and Dana" scenario, however simple, provides a glimpse at why the genetics of addiction is so complex and multideterminant, likely involving many hundreds or thousands of different genes and gene combinations. Indeed, although many genes or gene loci have been described as elemental to both addiction and/or mental illness risk, each such risk gene is not very powerful all by itself in conveying this risk. The genetic evidence on addiction thus overwhelmingly refutes the idea of simple Mendelian genetics being at work where major addiction risk is imparted through just a small number of genes (within or across individuals). In fact, the potency of any given addiction risk gene is not only small, but it is likely to be highly dependent on the presence of many other addiction risk genes *and* the particular environmental experiences that the individual has had, which may be permissive or suppressive to the activities of different risk genes. Moreover, because many addiction risk genes may not even be phenotypically pure to addiction (e.g., they could also convey risk of bipolar disorder), attempts to understand the genetics of addiction as something other than being a highly polygenetic state that is highly overlapping with the genetics of mental illness have not panned out.

Getting our heads wrapped around the complex genetics of addiction and dual-diagnosis disorders is greatly facilitated by understanding the concepts of multifinality and equifinality. In **multifinality**, an individual might carry a gene E, for example, that encodes for both addiction risk (one phenotype) and schizophrenia (a second phenotype). So, as for "Dana" in the "Jack and Dana" scenario, her one gene E imparts

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increased risk of *multiple* phenotypes. But there is also the situation where you have two different genes, "C" carried by Jack and "E" carried by Dana, that both impart risk of the same phenotype of addiction. In this way, genes "C" and "E" show **equifinality**; they are different genes with different proximal functional roles that nevertheless ultimately encode elevated risk for the same (or "equal") phenotype.

A Synergy of Genotypes and Ecophenotypes in Addiction and Dual-Diagnoses Risk

In considering the large number of genes that are implicated in addiction pathogenesis (>1,000), we can reasonably hypothesize that many of them have their phenotypic effects through either multifinality or equifinality type pathways. As if this complexity was not enough, we also know that environmental experiences while growing up (or during adulthood) can also contribute *biologically* to addiction risk. The importance of environment and experience to the pathogenesis of addiction and mental illness has unfortunately been largely neglected in psychiatric research and practice over the last quarter century due in part to the tremendous resources and effort the field has devoted to defining the genetic basis of these disorders. Nevertheless, we are now entering an era of renewed interest in the neurobiological impact and behavioral consequences that various forms of psychologically traumatic experiences have on both children (encompassing childhood emotional, sexual, physical abuse and neglect) and adults (in terms of the impacts of domestic violence, crime and war trauma, racism, sexism, and extreme poverty, and so on).

In the brain, extreme environmental experiences (often termed **traumas**) can work as *biologically potent insults*. Depending on the dose (severity), degree of convergence (how many different types of traumas fall onto one person over the same time period), duration (chronicity), and developmental timing of these kinds of traumatic experiences, they can be quite neurotoxic. So, on par with what genetic determinants can do (or even what toxic drug exposures can do to the brain), traumatic experiences can produce profound changes in brain architecture and function that are long-lasting, and sometimes very difficult to reverse. With attention to the rapidly growing body of neuroscience in this area, Martin Teicher (a developmental neuroscientist and psychiatrist at Harvard) has introduced the term **ecophenotype** to represent the

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phenotypic change in brain and behavior that results from a traumatic (and neurobiologically impactful) experience. This terminology is very helpful in creating a scientific and clinical framework that restores emphasis on both genes *and life experiences* as key determinants of mental illness and addiction, while also highlighting that not only are these different classes of disease-causing factors interactive, but they are *both* biologically active forces that have *both* psychological and behavioral consequences.

It is beyond the scope of this book to adequately review how traumatic experiences can change the brain on par with what genetics, drug exposures, or even mechanical mild traumatic brain injuries (mTBIs) can do. But it is important to give the reader a glimpse of some of the many brain and behavioral pathways that are involved.

A theory that enjoys broad-based empirical support from both the clinical and basic science literatures holds that traumatic experiences and experiential poverty or neglect can have a direct neurobiological impact because the brain is fundamentally a machine that is designed to adaptively respond to the environment through experiential learning (corresponding to experience-induced changes in neural wiring that result in behavioral change). Thus, major life experiences (or lack thereof) can be expected to have profound long-term effects on neural network development, particularly those networks integral to the emotional, cognitive, and motivational systems of the brain outlined in Chapter 3. Indeed, we know that traumatic experiences can generate extreme changes in both glutamate and dopamine neurotransmission (remember from Chapter 3 that both of these transmitters are key mediators of information processing and learning and memory within motivational neural networks). And, when paired with extreme fluxes of stress hormone levels (e.g., corticosteroids) or the abnormal regulation of these hormones that traumatic experiences can also generate, stress-indued glutamate neurotransmission can actually become neurotoxic, damaging axons and dendrites that interconnect neurons, or even contributing to neuronal death. Such effects are well documented in *in vitro* and animal modeling work on a microanatomical–cellular scale. These effects have also been observed (although more indirectly) in humans with trauma-related psychiatric conditions (post-traumatic stress disorder (PTSD), borderline personality disorder, depression, and so on). These patient populations show evidence of **cortical–hippocampal**

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atrophy and network dysfunction as measured by neuroimaging, and abnormalities of social–emotional and cognitive functions that are tied to these systems. These changes are accompanied by alterations in neurohormonal systems (e.g., the **hypothalamic–pituitary–adrenal (HPA) axis**) involved in regulating brain plasticity needed for optimal responses to drastic changes in the environment. Two emerging and remarkably interesting frontiers in understating the neurobiology of trauma (as a foundation of addiction pathogenesis) are the fields of *neuropsychoimmunology* and *attachment neuroscience*.

In **neuropsychoimmunology**, there is growing awareness that many of the genes (or gene products) expressed in the body that are involved in immune defense overlap with genes (or gene products) in the brain that are involved in neuroplasticity. This is super interesting considering that although the immune system is geared up to protect us against microorganism attacks, most trauma-spectrum experiences involve some form of human-on-human threat or attack, or natural disaster threat or attack. Of course, it is the brain rather than the immune system that is key to responding to these kinds of large-scale, nonmicroorganism threats. However, our genetic evolution has found a way to use some of the same cellular signaling and morphological control systems (one involving the immune system, the other in the brain) to deal with both classes of threats. The key implication of all this is that too much neurohormonal responsivity happening as a result of too much human-initiated trauma and threat (or other breakdowns in human-to-human care-taking), especially as experienced during childhood, can semi-permanently "overadapt" the individual's brain to that level of insecurity and danger. This leads to increased risk of the individual acquiring certain personality disorders, PTSD, recurrent depressions, or even psychotic disorders.

Attachment neuroscience, launched by the British psychiatrist John Bowlby in the middle of the twentieth century and elaborated on by the primate work of Harry Harlow (University of Wisconsin) and others, describes the critical role that secure, engaged, and psychologically nurturing relationships (e.g., especially between children and their parents) have in contributing to long-term mental health. It turns out that chronically deficient or chaotic parental care-giving, abnormal physical contact, and/or overaggressive social interaction can have serious effects on brain development, particularly involving those neural networks that govern emotions, social behavior, and *motivation*.

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In adult life, individuals who have suffered from severe parental neglect, sexual or physical abuse, and/or attachment failure as children not only show extreme risk of a wide range of mental disorders, *including addictions*, but they are also at risk of propagating the damage transgenerationally, because their own damage can prevent them from forming healthy secure attachments to their own children. Although a thorough review of the biology of how this happens is beyond the scope of this book (and much remains to be discovered), **oxytocin** has emerged as a key neurohormonal factor that is involved in healthy attachment formation between both children and their parents and between adults in close relationships. The endogenous opioid system is also involved in the development and regulation of brain systems that mediate healthy attachment.

A bottom line for both the neuropsychoimmunological and attachment neuroscience underpinnings of traumatic experiences is that *all of these pathophysiological pathways lead to both mental illness and heightened addiction risk*. In other words, extreme environmental experiences produce **ecophenotypes** that work biologically with **genotypes** to produce disease outcomes of comorbid mental illness and addiction risk via both **multifinality** and **equifinality**. Understanding this complexity is made easier when we give up on trying to assume that simple Mendelian genetics is key for understanding mental illness or addiction, and we let go of mythologies that promote strict dichotomizations and splitting between nature versus nurture, mind versus brain, psychology versus neurobiology, and mental illness versus addiction. In fact, both the genetic and environmental ingredients that produce different forms of mental illness and addictions are so overlapping and interactive, in terms of generating abnormalities of brain development and integrated neurocircuit function (that govern motivation, cognition, and emotional control), that it should be no surprise that mental illness and addictions often occur together – and biologically drive one another – to a very high degree, so that dual diagnosis emerges as a mainstream public health problem.

Thus, analogous to the structure of a tree, the wide range of genetic and environmental risk factors that generate addictions and dual-diagnosis disorders can be thought of as a list of ingredients (roots of the tree) that contribute to the pathological neuroanatomy of dual diagnosis (trunk of the tree), by which mental illness *causes* increased addiction risk and

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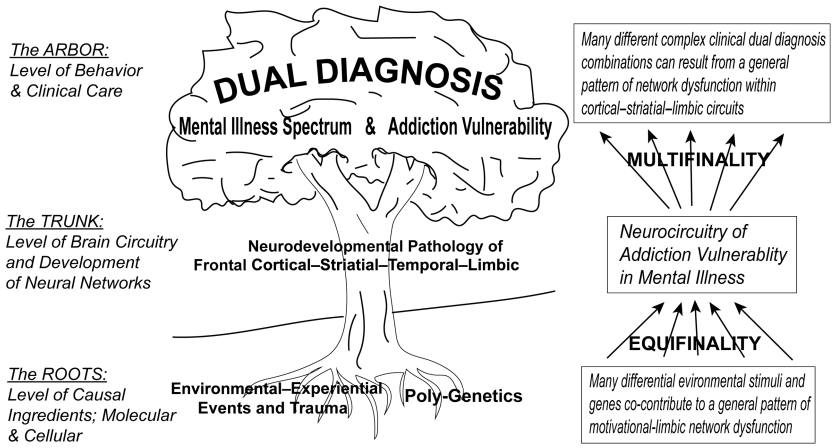


Figure 4.1 Developmental pathogenesis of mental illness and addiction: the integrated tree of dual diagnosis. The causal ingredients, developmental neurocircuitry, and clinical phenomenology of addiction and mental illness are integrated processes that resemble the structure of a tree. This integration of pathological processes reflects the fundamental network architecture of the mammalian brain where decision-making/motivational circuits (PFC/NAC) are directly and densely connected with circuits that mediate emotion (AMY) and short- and long-term memory (vHCF).

severity, generating a wide spectra of dual-diagnosis clinical presentations (arbor of the tree; Figure 4.1).

In this formulation, it is more accurate to view the genetic and environmental "ingredients" as causal elements that do not by themselves represent the neural mechanisms of dual-diagnosis disease comorbidity. Rather, these ingredients are like actors in the plot, and it is actually the plot (of many actors) that represents the disease mechanism. This is because the disease mechanism of dual-diagnosis comorbidity is so highly polygenetic and contributed to by so many complex environmental conditions – and is happening on so many scales of brain function (spanning molecular, neurochemical, cellular, neural network, regional, and global anatomical scales). For our best, most comprehensive view on the neuroscience of addiction psychiatry, the focus needs to be more on the plot of the story (rather than only one or a few of the many actors that play in it). Thus, we need a systems perspective that illuminates what is happening on the scale of

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motivational neural networks that incorporates what we reviewed in Chapter 3 to understand how mental illness accelerates addiction risk. Moving forward with this approach, we will consider the pathophysiology of addiction with an overlay of what is happening in the brain when the addiction–attractor states of mental illness and adolescent neurodevelopment are in play.

Neuroscience of Dual Diagnosis: Mental Illness Amplification of Addiction Vulnerability

Bidirectional Causality in Mental Illness–Addiction Pathogenesis

Although the association between mental illness and addiction is very clear to psychiatric clinicians and is overwhelmingly supported by the epidemiological evidence, the rigorous discovery, characterization, and testing of the *causal mechanisms* that drive this association has be difficult to accomplish and limited when pursued exclusively on clinical and epidemiological levels of investigation. Certainly, a wealth of clinical evidence has accumulated over many decades, making it clear that heavy, uncontrolled use of virtually all addictive drugs spanning cocaine, amphetamines, opioids, alcohol, cannabinoids, nicotine, and so on can at least transiently produce or worsen psychiatric symptoms (e.g., during acute intoxication and/or withdrawal). Many of these drugs, especially alcohol, are also well known to be able to produce longer-lasting changes in brain anatomy and physiology leading to more permanent neuropsychiatric conditions (e.g., consider alcohol neurotoxicity in **fetal alcohol syndrome**, or **Wernicke–Korsakoff's syndrome** with its alcohol-induced dementia of adulthood). This form of causality – where drug use causes mental illness (as either transient cognitive–emotional symptoms or as a long-term syndrome) is so routinely observed and well-established clinically that we really don't need direct experimentation to prove that it happens. In fact, we are so firmly sure that it can and does happen that it wouldn't even be ethical to try to prove that this causality exists in controlled, prospective human experiments. For example, there is no legitimate **institutional review**

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board (IRBs are committees charged with providing ethical oversight for studies involving human subjects) that would approve of a human-subjects study that aims to demonstrate that given enough alcohol, a researcher can make an otherwise healthy adult become demented, or, given enough methamphetamine, the investigator can cause a substantial number of people to develop a long-lasting psychosis, or bipolar-like illness, or addiction, and so on.

So, it is well accepted that substance use, especially heavy, chronic forms, at least temporarily induce mental illness-like syndromes. But what about the flip side of the causal relationship between mental illness and addiction? *How do we show that the causal relationship is bidirectional – also happening in the opposite direction where mental illness is a root cause, illness exacerbator, or biological vulnerability state of addiction?* As we discuss in the "myth-busters" section of Chapter 2, a longstanding and quite dominant hypothesis that entertains this direction of causality is the "self-medication hypothesis" – the idea that people with mental illness use drugs so much because drugs somehow alleviate their symptoms. An interesting implication of this hypothesis has been that because it merely assumes that drug exposure must have a benefit for mental illness, then it is more ethically testable in humans (regardless of whether it is actually true). Thus, it would be much easier to get a study approved by an IRB to show, for example, that introducing a nicotine patch for a patient with dementia might slow progression of the dementia than it would be to do the same study if the expected or to be proven outcome pertains to the acquisition of nicotine addiction, or nicotine-induced mood disorders, or strokes in demented people.

Regardless of the relative amenability of the self-medication hypothesis to human research (which is one of the reasons this flawed theory has held on for so long in psychiatric research), one of the major weaknesses of the hypothesis comes precisely from the evidence we have considered above: A major part of the causality that contributes to the association between mental illness and substance use is flowing in the opposite direction from what the self-medication hypothesis asserts (i.e., where chronic, heavy drug use worsens or generates mental illness). Thus, as pointed out in Chapter 2's Myth-Busters, it is illogical to accept the idea that we can explain the tight association between mental illness and substance disorders as happening because heavy drug use reduces

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mental illness, when by and large the data are clear that heavy drug use generates psychiatric symptoms and worsens mental illness.

It turns out there is a straightforward way we can avoid this logical–empirical failure of the self-medication hypothesis and still consider a plausible causal direction starting from mental illness leading to heavy substance use, even though heavy substance use *worsens* mental illness. *All that's needed is to consider mental illness as being a disease accelerator of addictive risk and severity.* This perspective understands enhanced addiction risk as a fundamental biological feature inherent to many forms of mental illness. In this "**primary addiction hypothesis**" (first described by Chambers et al. in the case of schizophrenia in 2001), the causal relationship between mental illness and addiction can be considered bidirectional, but without being conflicted or illogical (as happens with the self-medication hypothesis). The logical coherence of the primary addiction hypothesis is anchored on the fact that addiction pathogenesis, by definition (see Chapter 1) encompasses *compulsive drug use despite negative consequences.* So, with mental illness and substance use, we have a perfect storm of bidirectional causality on our hands, described even in the very definition of addiction itself: mental illness (or symptoms of it) is a negative consequence of compulsive drug use, even as mental illness can pathologically accelerate the process whereby drug use becomes compulsive (Figure 4.2). In this kind of bidirectional disease synergy, we not only have a clear explanation for why mental illness and addictions so usually occur together, but we also have an explanation for why increasing degrees of mental illness severity correspond to increasing degrees of addiction risk and severity. As we will describe in Chapter 5, this science also has significant translational implications for treatment delivery.

A scientific challenge with this primary addiction hypothesis of mental illness, despite how well it sidesteps virtually all the logical and empirical failures of the self-medication hypothesis, is that you cannot ethically conduct a prospective, controlled study in humans necessary to demonstrate that it is true (i.e., no well-controlled, human study could be done ethically to prove it). For example, no IRB should ever approve a study that would randomize groups of healthy versus mentally ill 18-year-old boys to snorting a line of cocaine once a day for 10 days to see which group acquires greater rates or severities of cocaine addiction.

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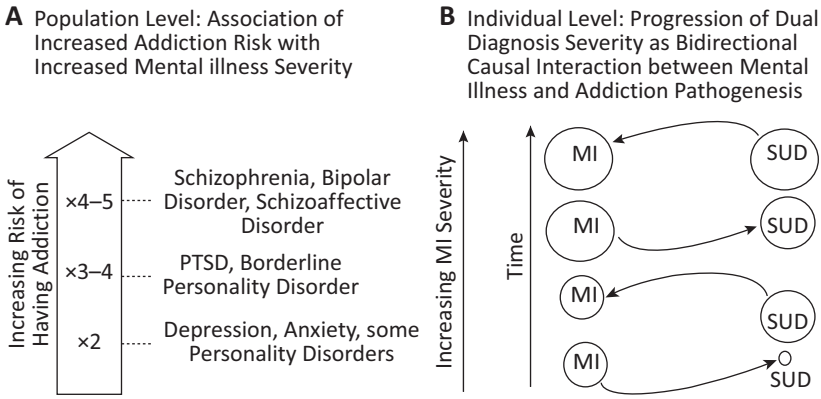


Figure 4.2 Interactive causality of risk and pathogenesis of mental illness and addiction on the population and individual levels. **A**. On the population level, increasing severity of underlying mental illness (MI) is generally associated with greater likelihood of acquiring addiction and greater addiction severity. **B**. On the individual case level, mental illness elevates substance use disorder (SUD)/addiction risk (directional arrow from MI to SUD). Then as the SUD is acquired and becomes heavy, it can rebound to increase MI severity. The underlying MI continues to accelerate SUD severity and risk of acquiring multiple forms of addition; active heavy multidrug use in polyaddiction further exacerbates underlying MI symptomatology and risk of medical morbidity and mortality.

So, how do we get around this ethics problem to do the science we need to find empirical support for the primary addiction hypothesis? This is where animal modeling has come in very handy. We have the rats to thank for showing us much about how mental illness accelerates addiction acquisition and severity.

Animal Modeling as a Key Approach to Addiction Psychiatry Neuroscience

It turns out that addiction, among all psychiatric diseases, is arguably the most amenable to animal modeling research, because the symptoms of the disorder are objectively measurable through behavior (drug use) and do not rely heavily on subjective–verbal symptom reports, which rats cannot provide. Also, the inciting elements of addiction – the drugs themselves – produce concrete pharmacological and biological actions in the brain providing key mechanistic clues about addiction

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pathogenesis. Such concrete inciting elements are just not as available to us for unlocking the mysteries of pure mental illness.

So, we have excellent rat models of addiction. But do we have rat models of mental illness? Absolutely we do, and in fact we have over a hundred different ones that vary widely in terms of which mental illness they model (e.g., schizophrenia or PTSD), what etiological methods are used to create them (e.g., a brain lesion, a gene knockout, heavy exposure to a neurotoxic drug, exposure to repeated stress, or combinations thereof), and the quality and scope of symptoms. Different models can be used to produce narrow (**endophenotypic models**) versus broader sets of symptoms (**comprehensive** or **syndrome models**) consistent with a given human disorder. For asking how mental illness may accelerate addictive disease in the preclinical laboratory, the investigator needs to judiciously choose an appropriate animal model of mental illness and then see how avidly those animals acquire addiction compared to healthy animals.

Part of the process in selecting good animal models of mental illness for testing addiction acceleration, comes from considering what we already know about how the neuroanatomy of the key brain regions of mental illness and addiction intersect. Building on Figures 3.1 and 3.2 where we diagramed the key neurocircuitry of motivation, we now need to consider the key brain regions that are involved in the pathophysiology of the major mental illnesses. It turns out that the PFC, AMY, and HCF have all been variously implicated across a vast wealth of studies that have characterized what is pathologically altered in the brains of people with schizophrenia, bipolar disorder, depression, PTSD, personality disorders, and many other psychiatric illnesses. An important neuroanatomical fact to also know is that all of these key brain regions, the PFC, AMY, and HCF – aside from being pan-implicated in mental illness – are also directly wired into each other *and the NAC /ventral striatum neural network*.

Thus, not only are:

> **All the brain regions chiefly implicated in major mental illness directly connected with primary motivational circuits altered by addiction**

but also (see Chapter 3):

> **These distributed systems (PFC, AMY, HCF) send physical connections (axons) and neural information streams that *converge***

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into the *NAC/ventral striatum* as a means to *inform* and (based on experience) *restructure* and *revise* motivated behavior.

The significance of these themes for understanding the connection between mental illness and addiction becomes clear when considering that addiction is essentially a *pathological* restructuring of motivated behavior (as detailed in Chapter 3). So, the pathology of addiction, as it occurs in core motivational circuits (i.e., the NAC), can be expected to be augmented, if the NAC is already pathologically interconnected (in the context of mental illness) to other limbic regions that should under normal circumstances inform healthy motivation. In other words, the neuroanatomies where addiction and mental illness occur are totally wired into each other; these diseases are anatomically and biologically predestined to be interlinked!

Although this anatomy indicates how the mammalian brain is built in a way such that the pathogenesis of mental illness and addiction are often inextricably interlinked, animal models are still needed to demonstrate this linkage behaviorally, and to find out more about *how* they are linked causally and mechanistically. For this kind of investigation, we first need to apply animal models of mental illness in which one or more of these key brain regions (PFC, AMY, HCF) are disordered in ways that substantially simulate what is known to be characteristic of these brain systems in human mental illness. Second, it is important that the animal model of mental illness has several other behavioral and biological attributes that map credibly onto known illness attributes of the human condition (e.g., a comprehensive model). Third, we want good "construct validity" for the mental illness model as a "dual-diagnosis" condition, which is possible if the class or type of human mental illness we are trying model in the animals is also known in humans to encompass high levels of addiction comorbidity.

In a 25-year span of animal studies starting at Duke in 1995 then moving to Yale and Indiana University Medical Schools (and onto other labs around the world), the neonatal ventral hippocampal lesion (NVHL) rat model of schizophrenia has been a highly productive research platform with respect to all three of these criteria for animal modeling addiction vulnerability in mental illness. Originally developed and characterized by Barbara Lipska, Danial Weinberger and colleagues at the NIMH in Washington, DC (see Lipska et al., 1993), the NVHL model is

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produced by causing neurotoxic damage to the ventral hippocampal formation (vHCF) in very young (e.g., 7-day-old) rats. In rats, this neurodevelopmental age is roughly equivalent to the second to early third trimester of human prenatal neurodevelopment – a time window when various lines of evidence suggest the human brain is susceptible to developmental insults that can seed schizophrenia later in life. Initially, in the rats, this damage is very focal. In fact, the acceptable target zone for the damage in the baby rat's brain (vHCF) is on the order of 1 mm in diameter (which makes accurate reproduction of the lesion a technical challenge!). However, the secondary effects of the damage become much more widespread and distributed throughout the brain as the rat grows up. This is because of where the lesion is located, and how the target zone is normally wired into other limbic areas over the course of postnatal development. The vHCF is not only bidirectionally cross-wired with the amygdala (Figures 3.1 and 3.2) but it also projects directly into PFC and NAC microcircuits. This means that healthy versus abnormal ventral hippocampal development has significant implications for the normal development and function of these other limbic regions. If the vHCF microcircuit is disrupted, then there is a progressive domino-like effect, taking place over the course of postnatal to adult development on the architecture and function of the AMY, PFC, and NAC networks as well. In this way, Lipska and Weinberger's developmental model of schizophrenia ingeniously incorporates both the focal neurodevelopmental problems (involving abnormal hippocampal development and anatomy) and distributed network features (encompassing atrophy of the PFC and AMY) of human schizophrenia. Lipska and colleagues went on to show that not only was the gross neuroanatomy of the NVHL model accurate to human schizophrenia, most of the major neurodevelopmental, behavioral, pharmacological, and neurophysiological features of the model were as well. Finally, meeting the third criterion for a good animal model of a human "dual-diagnosis" condition, the NVHL model is an excellent platform for understanding schizophrenia, which among all mental illnesses is one of the most highly comorbid with substance use disorders (i.e., it has some of the highest rates of co-occurring addictive diseases among mental illnesses to the extent that nearly 90% of schizophrenia patients are "dual-diagnosis" patients).

In 2002, the first work characterizing accentuated addiction vulnerability (to cocaine) in the NVHL model was published in *Neuropsychopharmacology*.

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While helping to advance a new genre of animal modeling focused on dual-diagnosis disorders, this study demonstrated for the first time that the same neurodevelopmental abnormality could lead to *both* major mental illness and accelerated addiction disease. This form of **multifinality** (i.e., where the same underlying neurobiological abnormality leads to two behavioral disorder phenotypes) hinted at the core connectedness that exists between many types of mental illness and addiction. Subsequent studies using the NVHL model also demonstrated that the addiction vulnerability was not specific to cocaine, but was general to other addictive drugs (e.g., including nicotine, alcohol, and methamphetamine). Also, this addiction vulnerability was shown to be *involuntary* in that it did not require the animals' decision or action to self-administer the drug: When researchers administered the drugs involuntarily and chronically to NVHL versus healthy rats, the NVHL animals showed increases in addiction-related phenotypes that are neither drug- nor intoxication-specific. Further, this elevated addiction risk was not shown to be accompanied by any clear "benefit" or medicinal value that the drugs could specifically impart to the mentally ill animals (e.g., as the self-medication hypothesis would predict). Indeed, and particularly in the case of cocaine, the addiction vulnerability of the mental illness model was also associated with increased capacity of the drug intake *to exacerbate* the underlying mental illness. Hence a bidirectional exacerbation of mental illness and addiction was demonstrated.

In parallel to the NVHL model, other forms of mental illness models in rats that also alter frontal cortical–striatal/temporal limbic (PFC/NAC/AMY/HCF) circuit function in different ways (e.g., via olfactory bulbectomy, severe environmental stress, impoverished rearing, polygenetic addiction models) have also been shown to produce complex, co-occurring mental illness/addiction phenotypes, reflecting the equifinality-like nature of dual-diagnosis conditions, in which different biological/environmental/neurodevelopmental factors can lead to dual-diagnosis phenotypes. Together, these preclinical findings map very well to what we see in the human epidemiology spanning the dual-diagnosis spectrum in which high rates of mental illness and addiction comorbidities occur "across the board" in pervasive patterns that are neither mental illness nor drug type specific.

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The Neurocircuit Basis of Addiction Psychiatry: How Mental Illness Accelerates Addiction

As the NVHL model has proven to be useful for understanding both mental illness pathogenesis and heightened addiction risk as being tightly interconnected disorders – or even one and the same – it has also served as a platform for observing on a more brain-mechanistic level how mental illness *accelerates* addiction pathogenesis. This acceleration then leads to a more severe addiction disease phenotype. To better understand the mechanisms that underpin this **acceleration of addiction**, we want to focus on how circuits effected by mental illness impact those involved in addiction.

An additional key phenotypic feature (behavioral abnormality) of the NVHL model is that in adulthood these rats are generally impulsive, showing an array of impulse control-related cognitive impairments that involve the PFC. Neurobiologically, and in parallel to these behavioral issues, these rats show quite a long list of molecular, neurochemical, cellular, and neural network abnormalities of the PFC. Remembering that the NVHL model is generated (or "unleashed!") by neonatal excitotoxic damage delivered to a zone within the hippocampus (the ventral part) in 7-day-old rat pups, it becomes clear that these PFC abnormalities are secondary consequences, downstream in anatomical space and developmental time from the original vHCF hit. In fact, this is exactly what electrophysiological studies of the PFC of NVHL rats show: as NVHL rats develop from their rat "childhoods" through adolescence and into young adulthood, the principal pyramidal neurons (see Figure 3.6) and local inhibitory neurons in their PFCs show increasingly abnormal regulation and activity of their firing patterns. Anatomically, PFC neural networks in NVHL rats also show loss of interconnectivity, increased cell packing, and overall atrophy of cortical layers. These biological abnormalities quite accurately resemble what we see in the brains of humans with schizophrenia, and they account in part for why we see similar PFC-based *behavioral and cognitive* abnormalities in both the NVHL model and schizophrenia.

Importantly, impulsivity and PFC-based neural network abnormalities are not specific to either the NVHL model or human schizophrenia. Rather, these themes are pervasive across many forms of mental illness

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(and basically all those that involve increased addiction risk) and in patients with addiction disorders spanning all the major addictive drug groups. In other words, PFC dysfunction (and its behavioral manifestation of impulsivity), represents an **endophenotypic** "keystone" of dual-diagnosis pathogenesis, where mental illness and addictions are biologically and phenomenologically interlinked. This is not to say that every different type of mental illness that accelerates addiction risk (e.g., schizophrenia, bipolar, depression, PTSD, borderline personality, and so on) has the exact same biological abnormality pattern in the PFC, or the same form of behavioral impulsivity. And certainly, these differential psychiatric diagnoses are underpinned by differential forms and patterns of neural network problems in other subcircuits as well (e.g., spanning AMY, HCF and many other regions) that also impart illness-specific features to these conditions. Nevertheless, it appears to be the case that these differential disorders involve PFC-based functional problems that create impulsivity-spectrum conditions (variously labeled as "executive-decision making problems," "lack of insight," "lack of judgment," "disinhibition," and so on) that are similar enough to produce comparable downstream effects on NAC (ventral striatal) motivational networks and addiction pathogenesis. Ultimately, most of the "dual-diagnosis spectrum mental illnesses" – and especially the most severe ones – do involve some form of distributed frontal–cortical–temporal limbic network dysfunction in which two or even all three of the key regions implicated in mental illness (PFC, HCF, and AMY) are all pan-involved in the individual's illness in some way or to some degree. Then, as all three of these key brain areas (implicated in mental illness) also project directly into the NAC (implicated in addiction pathogenesis), it should follow that having mental illness in the brain can be expected to have an impact in altering the natural disease course of addiction within the brain. Accordingly, we can begin to understand the connection between mental illness and addiction as representing an unfortunately all too common vulnerability of an otherwise highly efficient and powerful design motif of the mammalian brain. In this architecture, the primary motivational neural network is directly and intricately regulated by distributed limbic regions that control cognition, expectations, memories, and feelings. The NVHL model has thus proven itself to be a particularly useful neuroscientific and behavioral model of dual-diagnosis pathogenesis, even beyond schizophrenia, because it encompasses multiple mental illness symptoms including impulsivity (which is not specific to any one mental illness) and

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heightened addiction vulnerability (which is not drug-specific). It also entails developmental neural network abnormalities that span all three of the key cortical–limbic centers (PFC, HCF, and AMY regions) that are (a) cross-implicated in mental illness and (b) project into the NAC where motivation is most directly damaged in the addiction disease process.

Three Animal Modeling Studies Illuminating Mechanisms of Mental Illness Addiction Vulnerability

A series of three studies looking at the effects of a chronic, *behaviorally sensitizing* regimen of cocaine injections in NVHL rats has advanced our understanding of how abnormal frontal cortical–striatal circuitry of mental illness can accelerate addiction pathogenesis. To introduce this research, we need to return briefly to the topic of *sensitization*. As discussed in Chapters 2 and 3, sensitization is a core pathological growth process in addiction that has both biological and behavioral dimensions. In **motivational sensitization**, as the drug is repeatedly used by the individual, they subjectively experience a growth in urges and craving associated with a growth in motivation to use the drug even more. This growth process drives increases in the frequency and amounts of drug use over time, the loss of normal decision-making and control over drug use, and the displacement, subservience, and/or sacrifice of healthy motivations and behaviors in favor of drug acquisition and use. A gold standard way of generating and modeling this disease process (motivational sensitization to an addictive drug) in animal models, of course, is to allow them to acquire **self-administration** of the drug, where they learn how to acquire and use the drug on their own (typically via oral or intravenous routes). Then the researcher can observe how the drug use pattern grows over time, how animals may work harder to get the drug, and how the drug use becomes more compulsive and automatic (despite consequences). As mentioned above, precisely this kind of addiction modeling work has been done in NVHL–schizophrenia model rats, which show accelerated patterns of cocaine, nicotine, and alcohol use in self-administration studies, resulting in greater, more efficient installment of compulsive drug use behaviors compared to rats with healthy brains.

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A parallel experimental approach to modeling addiction pathogenesis is the **behavioral sensitization paradigm.** Compared to self-administration experiments, which more directly reveal motivational sensitization, behavioral sensitization is technically a much easier and quicker paradigm to perform in the lab, while being safer for animals and easier to measure outcomes for. In behavioral sensitization, the researcher delivers doses of the addictive drug to the animals over time, instead of the animals self-administering the drug to themselves. Also, the outcome being looked at in behavioral sensitization (i.e., the behavior that is growing) is more concretely simple to measure and observe. Rather than it being a quantification of the accumulating pattern of drug use behavior (e.g., lever pressing for drug deliveries) or amount of drug being consumed as in self-administration, behavioral sensitization studies measure how the animal's motor programming evolves over time (days to weeks) as the animal *involuntarily* receives repeated drug doses. Typically, this measurement focuses on how much the animal moves around, couched as locomotor distance traveled, for a given period of time (typically 30–90 minutes) in an arena where the animal has just received the drug. What is quite remarkable about behavioral sensitization is that, in parallel to motivational sensitization, animals are observed to show abnormal increases in locomotor activity responses to the drug in the arena, day after day, with as few as one hit of the addictive drug per day. Notably, this growth pattern does not reflect increases in intoxication, *because it occurs even as the animals are being given the same exact dose of the drug day after day, during which time they are becoming more tolerant to the intoxicating effects of the drug* (i.e., intoxication levels are weakening over time after each dose). The resulting behavioral sensitization growth curves also closely resemble learning curves (even as the animals are not voluntarily trying to learn anything). Also, in parallel to what we understand happens in addiction in terms of motivational sensitization, behaviorally sensitizing drug regimens have a long-term impact on brain and behavior. An animal that has been behaviorally sensitized to cocaine will continue to show an abnormally elevated locomotor response to a new dose of cocaine for weeks and even months after their last cocaine dose (that was part of a prior sensitizing series). As we see in addiction, essentially all addictive drugs (including cocaine, amphetamines, nicotine, alcohol, opioids, and so on) can produce behavioral sensitization, regardless of their differential intoxication profiles, and

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even though some of them are CNS stimulants whereas others are CNS depressants. So, the behavioral sensitization effect is a simple and direct way to examine how repeated doses of addictive drugs *involuntarily* change the brain and behavior in a lasting way, in large part via invoking neuroplastic changes in ventral (NAC) and dorsal (CA-PU) striatal circuits that control motivated behavior and motivational-behavioral learning. Essentially, in behavioral sensitization, repeated delivery of the addictive drug causes abnormal increases in (and compulsive-like selection of nonspecific exploratory locomotion), which (with saline injections) should normally habituate or go away with repeated exposures to the same arena where the behavior is being measured. Notably, the abnormal elevations in drug self-administration that occur in NVHL rats (measuring motivational sensitization involving cocaine, alcohol, and nicotine) has also been confirmed with respect to behavioral sensitization. Compared to rats with healthy brains, NVHL rats also show leftward and upward shifted behavioral sensitization curves to cocaine, alcohol, and nicotine, and more robust, chronic retention of these imprinted drug-response effects over time.

In three different studies looking at how mental illness and addiction pathogenesis may synergize neurobiologically, the behavioral sensitization paradigm has been used as it allows precise control and balancing of how much addictive drug each experimental group may get. Also, the involuntary nature of the disease process is directly and unambiguously observed, as it is the researcher (not the animals themselves) who is delivering the drugs. So, with behavioral sensitization, it is possible to observe how the mental illness biology can accentuate the drug sensitization process *both behaviorally and biologically, and as a completely involuntary process*, even when the cumulative dosages delivered to the mentally ill versus healthy brain treatment groups are exactly the same.

The experimental set up of these three studies followed a similar design: NVHL and healthy rat groups were randomized into saline versus chronic cocaine exposure (behaviorally sensitized) groups. Thus, these studies all followed a 2 × 2 cell design motif in which the presence of mental illness (or not) was crossed with an addiction drug history (or not), creating four different study subgroups modeling a clinical spectrum of dual-diagnosis comorbidity as follows: (1) healthy brain/nonaddicted; (2)

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mentally ill/nonaddicted; (3) healthy brain/addicted; (4) mentally ill/addicted. Notably, multiple behavioral studies have established that in this order of progression ($1 < 2 \simeq 3 < 4$), these groups show increasing levels of locomotor activation in response to a challenge injection of cocaine occurring weeks after the initial injection series (of saline versus cocaine, alcohol or nicotine). That is, in the NVHL rat model preparation, there is a mental illness–based amplification of long-term sensitization to cocaine (and other addictive drugs) that is clearly observable and reliably reproduceable.

In Study #1, **a brain microdialysis study** (Chambers et al., *Psychopharmacology*, 2010), it was shown, as a replication of prior findings, that cocaine challenge injections elicit greater locomotor responses if animals had previously experienced prior cocaine sensitization, or if they were NVHL rats. As usual, NVHL rats with prior cocaine experience showed the greatest response among all groups (i.e., NVHL and cocaine history in the same rats produced the most extreme sensitized phenotypes). However, when looking directly at what was happening with the levels of cocaine-induced DA efflux into the NAC in these animals (brain microdialysis allows for real-time measurement of neurotransmitter levels in specific brain areas in awake, behaving animals) when they were receiving cocaine challenge injections, an interesting pattern of results emerged. There was actually *no* corresponding growth in the levels of DA efflux into the NAC caused by the animals having a prior cocaine history, or by having NVHL lesions, or both. In other words, although the cocaine delivery did cause a massive burst in DA into the NAC (as would be expected by the addictive drug delivery), the acquisition of greater extremes of the behavioral sensitization phenotype (which prior cocaine history and the NHVL model both produced, with the combination producing the greatest behavioral extreme) did not actually correspond to any increase in the size of the DA efflux produced by the cocaine injections. This finding highly suggested that the addiction process and its acceleration/amplification by mental illness *were not* determined by pathological changes in the amount of DA efflux that a cocaine injection produces. This finding indicated that these disease states were more directly reflective of brain changes that had occurred *postsynaptic to the DA release*, involving striatal networks that DA neurotransmission regulates and mediates plasticity for.

In Study #2, **a neural activation mapping study** (Chambers et al., *Biological Psychiatry*, 2010), a molecular marker of nonspecific neuronal

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activation (**c-Fos**) was used to examine how striatal (ventral versus dorsal) regions and prefrontal cortical networks (medial prefrontal cortices versus posterior frontal cortices) were differentially activated by cocaine challenge injections based on rats having had a prior cocaine sensitizing history, being NVHL animals, or both (addiction and mental illness models combined). Notably, these anatomical selections dichotomized regions fairly accurately into circuits primarily involved in motivational processing (medial PFC/ventral striatum (NAC)) versus motor processing (posterior frontal cortex/dorsal striatum(CA-PU)) (see Figure 3.3). The results confirmed that the addiction-related phenotype (drug sensitization) was indeed encoded by brain changes occurring in cortical–striatal neural networks that were *postsynaptic* to the DA release (consistent with Study #1), and that NVHL-induced abnormalities in these same regions were exacerbating the addiction-related effects. More specifically, *a prior sensitizing cocaine history* increased the level of dorsal striatal (CA-PU) neural network activation (and its ratio of activation compared to the ventral striatum (NAC) that occurred with a challenge cocaine injection). Also, as would be expected (given that the dorsal striatum encodes and executes well-learned motor programs), across all the animals and treatment groups, dorsal striatal (CA-PU) activation was tightly correlated with degree of cocaine-induced locomotion. In summary, these findings demonstrated that the dorsal striatal (CA-PU) network was operating as a motor output system, and that prior cocaine-induced neuroplasticity (which produced the behavioral sensitization effect) was related to neural connection changes in the striatum that allowed ventral striatal (NAC) activation (which encoded the motivation to perform exploratory locomotion) to more efficiently and powerfully instigate and maintain locomotor activity encoded in the dorsal striatum (CA-PU). Based on the resulting animal data from all the rats in the study, it was possible to mathematically model this cocaine-induced behavioral sensitization data as:

Equation 1: Chronic Cocaine History Effect

$$(\textbf{\textit{dorsal striatal}}\ (\textbf{\textit{CA}}-\textbf{\textit{PU}})\ \textbf{\textit{activation}}) \simeq \textbf{\textit{d}}(\textbf{\textit{ventral striatal}}\ (\textbf{\textit{NAC}})\ \textbf{\textit{activation}})$$

where *dorsal striatal (CA-PU) activation* was proportional to (symbolized by "$\simeq$") a coefficient d (that was larger if the animal had a cocaine injection history: e.g., 0.74 with cocaine history versus 0.56 with saline

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history) multiplied by the level of *ventral striatal (NAC) activation*. Again, as mentioned above, the dorsal striatal (CA-PU) activation was also tightly proportional (across all animals) to actual behavior (levels of locomotor activity post cocaine challenge injection in the arena). In essence, this expression shows how, in simple mathematical terms, the cocaine history had a cumulative, sustained neuroplastic effect that increased the ability (or efficiency) of the motivational system to call up and maintain the locomotor codes represented in the dorsal striatum, which generated the extremity of the behavioral sensitization phenotype (the addiction model).

In contrast to the cocaine effects, the NVHL model caused the animals to show a pathological *decrement* in medial prefrontal cortical (PFC) network activation (i.e., they were "**hypofrontal**"), which is a well-known characteristic of human schizophrenia and other forms of severe mental illness that involve PFC dysfunction and related cognitive deficits. Interestingly, this hypofrontality was also associated with a proportional *increase* in *dorsal striatal (CA-PU) activation*, in parallel to what cocaine history could do (in healthy non-NVHL rats), but even without a prior cocaine history being present in the case of the NVHL animal. So, it was also possible to make a simple mathematical statement that reflects this mental illness-based effect:

Equation 2: Mental Illness Effect

$$(\boldsymbol{dorsal\ striatal}(\boldsymbol{CA-PU})\ \boldsymbol{activation}) \simeq (\boldsymbol{secondary\ motor\ cortex}) / (\boldsymbol{medial\ PFC})$$

In this expression, the *secondary motor cortex* activation serves as a control region for ambient neuronal activation levels that are not strongly influenced by either cocaine or NVHL history. So, the ratio of *secondary motor cortex* to *medial PFC* activation gets larger as *medial PFC* activation gets lower. Thus, with greater hypofrontality (e.g., corresponding with more severe mental illness), the quotient (*secondary motor cortex*)/(*medial PFC*) gets larger.

Finally, it was possible to model how Equation 1 (reflecting how the chronic cocaine history changed activation in the network) and Equation 2 (reflecting how the mental illness model changed activation in the network) could interact to generate different levels of *dorsal striatal activation* (and degree of behavioral sensitization) across the entire set of animals in the experiment. Remarkably, it was found that a very simple

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integration of these two equations in the form of a simple multiplication could tightly model all the animals in the experiment:

Equation 3: Integrated Effects of Addiction and Mental Illness= (Equation 1) × (Equation 2)

$$(dorsal\ striatial(CA-PU)activation) = d(ventral\ striatal\ (NAC)\ activation)\ (secondary\ motor\ cortex)/(medial\ PFC).$$

In words, this mathematical expression states that the overall degree of dorsal striatal (CA-PU) neural network activation across the animals (and their corresponding levels of behavioral sensitization, representing the severity of the addiction disease process) was shown to be a simple multiplicative product of (1) the drug-induced neuroplastic effects due to the prior cocaine history within the striatum and (2) the mental illness–based cortical–striatal network alterations present in the NVHL model. Thus, mental illness, in a totally involuntary way, but in a way that is mathematically measurable (and neurobiologically observable), *amplifies* the addiction disease process within cortical–striatal circuits.

In Study #3, **a gene-expression mapping study** (Chambers et al., *Genes, Brain and Behavior*, 2013), NVHL versus healthy control animals had their frontal cortical/ventral and dorsal striatal circuits biologically examined again 2 weeks after a cocaine sensitization (versus a saline injection series), but this time looking at genome-wide **mRNA expression patterns** using **microarrays** that contained >24,000 gene products (probesets). This time, in contrast to Study #2 where acute cocaine-challenge–induced neural activation was the sole biomarker of interest, there was no acute cocaine-challenge injection delivered at the time of the brain examination (sacrifice of rats). So, this design could provide a view on the enduring molecular/cellular changes induced by the prior addictive drug (cocaine) history and the mental illness (NVHL) model, unimpeded or masked by any recent cocaine exposure.

Here, and in patterns that replicated themes observed in Study #2, NVHLs predominantly downregulated gene expression in the *medial PFC*, while causing abnormal upregulation in the *dorsal striatum (CA-PU)*. These data revealed yet another manifestation of the hypofrontality produced by the NVHL model, this time showing up as a relative impoverishment in

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neuronal gene expression (consistent with the loss of cocaine-induced neuronal activation in the medial PFC in NVHLs observed in Study #2). Also, this NVHL-related hypofrontality was associated with an abnormal *increase* in gene expression in the dorsal striatum (CA-PU) consistent with the abnormal *increase* in cocaine-induced neuronal activation in the dorsal striatum of NVHL rats observed in Study #2. At the same time, in terms of drug history–induced effects observed in Study #3, cocaine history had its strongest effect in abnormally upregulating gene expression in the dorsal striatum (CA-PU), which again was consistent with how this drug history pathologically increased acute cocaine-induced neuronal activation in the dorsal striatum, as seen in Study #2.

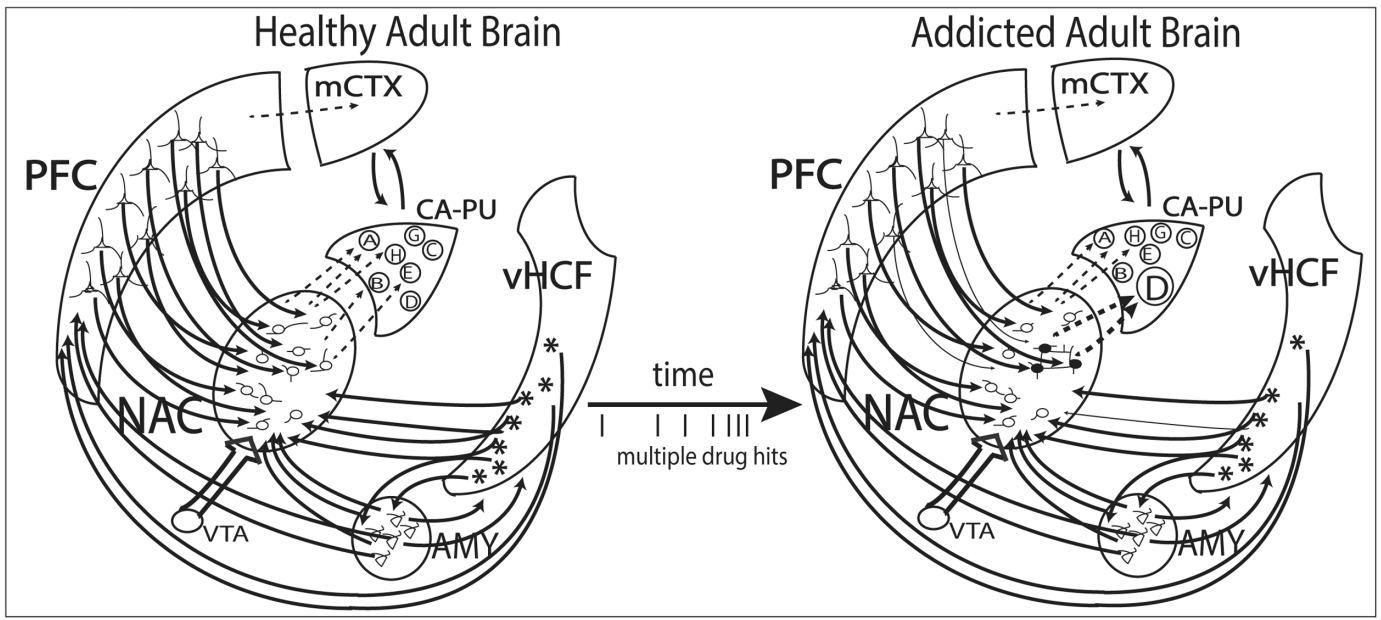
Taken together, these three studies indicate that mental illness–induced acceleration of the addiction disease processes is happening:

(1) *Within cortical–striatal networks* in microcircuits that are postsynaptic to (a) DA projections from the VTA that regulate motivational learning, involving (b) glutamate projections from limbic regions (PFC, AMY, vHCF) that are crucial to generating normal motivational representations in the NAC/ventral striatum, and are pathologically altered in the context of mental illness; and

(2) *Via involuntary biological mechanisms of disease amplification* where mental illness–related abnormalities of cortical–striatal circuity exacerbate and compound with the pathogenic neuroplastic effects of chronic addictive drug delivery in these same circuits that govern motivated behavior.

Addiction is thus installed on neurobiological, neurocomputational, and behavioral levels more efficiently and with greater severity in the context of mental illness. This disease interaction (and major form of addiction vulnerability) occurs neither as a matter of individual choice nor for the medicinal benefit of the individual. Instead, it is a consequence of overlapping neural mechanisms and brain architectures subserving motivational processing, and neuroplasticity, where the pathologies of addiction and mental illness are biophysically convergent and synergistic. Studies 1, 2, and 3, taken together with many other lines of dual-diagnosis–focused neuroscience (spanning animal modeling, neural network simulations, human neuroimaging, and clinical–epidemiological studies), can allow us to succinctly illustrate the integrative neuroscience of addiction pathogenesis (Figure 4.3), and mental illness–based addiction vulnerability and acceleration (Figure 4.4).

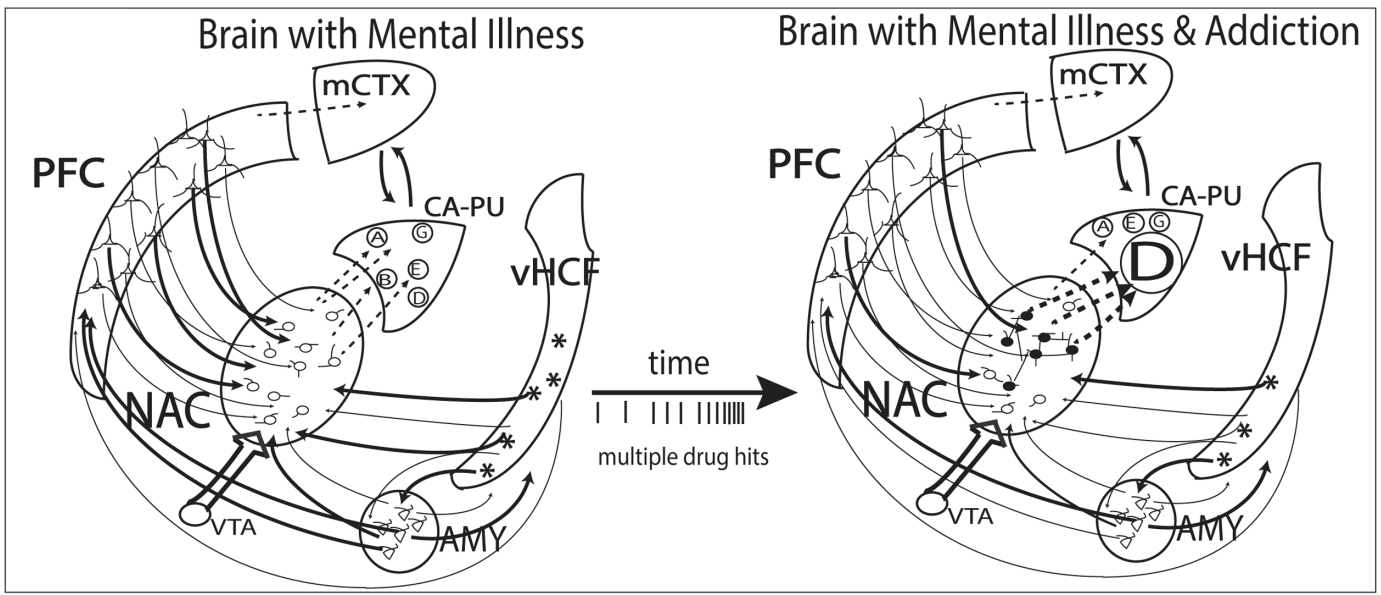
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Figure 4.3 Addiction pathogenesis: healthy adult brain. In the *healthy adult brain*, axonal fibers from the prefrontal cortex (PFC), ventral hippocampus (vHCF), and amygdala (AMY) are convergent into the nucleus accumbens (NAC) where they participate in the generation of motivational representations. Dopamine (DA) signaling (large open arrow) from the ventral tegmental area (VTA) into the NAC facilitates transitions between motivational representations as well as mediating neuroplastic changes within the NAC network, allowing motivations to adapt, grow, or newly form. These motivational representations, via polysynaptic pathways (involving "spiraling" relays; thin, stippled arrows from NAC/PFC into the dorsal striatum/caudate putamen (CA-PU) and motor cortical (mCTX) circuits) influence the selection, prioritization, ordering, and formation of specific motor programs represented and stored in the CA-PU network (e.g., as represented as A, B, C, D, E, H, G neuronal firing ensembles in CA-PU). In the addiction disease process, leading to an *addicted adult brain*, multiple drug hits pharmacologically induce abnormal patterns and levels of DA efflux into the NAC network. These episodes of drug-induced DA release produce abnormal incremental neuroplastic changes in the NAC network, leading to the recruitment of NAC neurons (dark-shaded NAC neurons) that represent (encode) strong motivation to acquire and use the drug again. The introduction and growth of this drug-use motivation increases the selection and prioritization of motor programs (behaviors) that subserve drug use, as represented symbolically by the relative growth in size of the drug use behavioral ensemble (D) in CA-PU. This new bout of drug use, in turn, reintroduces even more drug-induced/DA-invoked neuroplastic change to increase drug-use motivation even further, contributing to an escalating, vicious cycle of drug use behavior (more frequent/higher doses) that occurs increasingly beyond willful control.

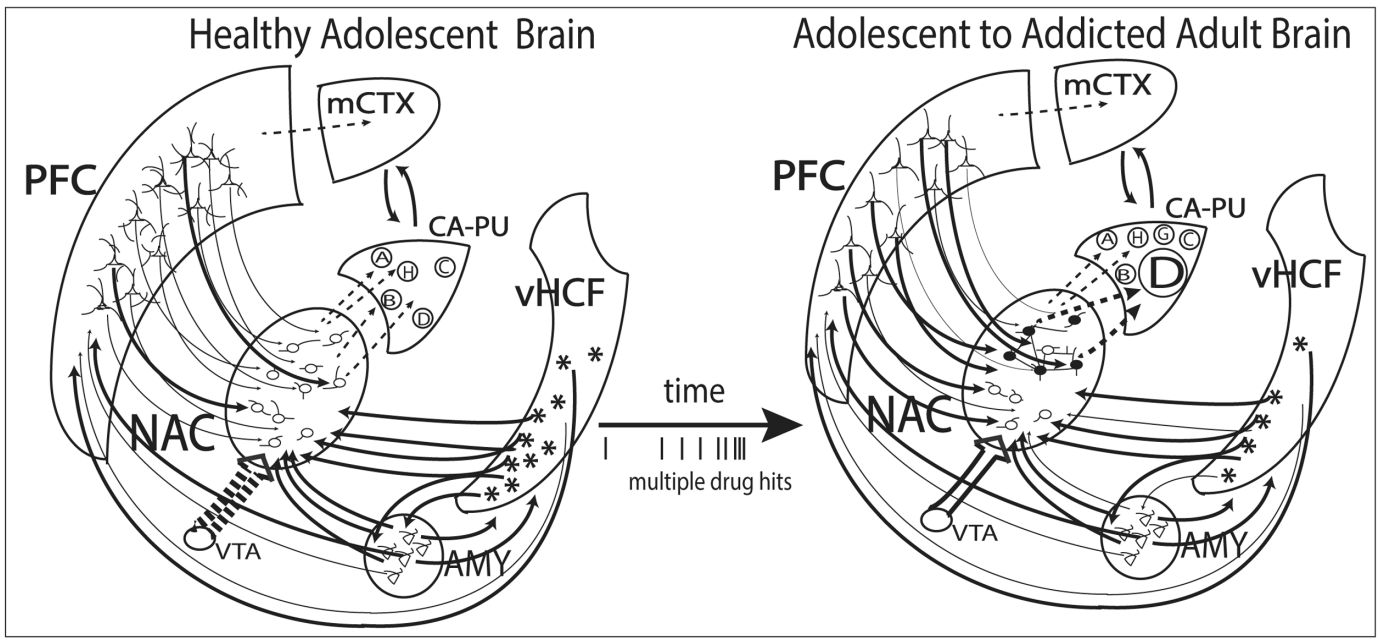
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Figure 4.4 Addiction pathogenesis accelerated: disease acquisition in mental illness. In the *brain with mental illness* prior to addictive drug exposure, there is a relative impoverishment of long-range network connectivity across frontal cortical–striatal and temporal limbic networks. This impoverishment may take the form of impaired functionality or efficiency of information transfer, reception, or representation between and within subnetworks, and/or relative losses in neuroplasticity (i.e., impairments of adaptability of axo-dendritic connection strengths underpinning learning and memory). Depending on the type and severity of mental illness, different interlimbic connection pathways (e.g., connecting PFC, NAC, AMY, vHCF) and their local networks may be differentially altered. Here, a brain with a severe form of mental illness such as schizophrenia, which carries particularly high levels of addiction risk, is depicted. Fewer functional projections from (i) PFC to NAC; (ii) vHCF to PFC; (iii) vHCF to NAC; and (iv) bidirectionally, between AMY and vHCF are depicted as a thinning and attrition of connections through these pathways. In the hippocampus, with severe mental illness, loss of connectivity and capacity for adaptive neuroplastic change may also be reflected in the loss of neurogenic neurons or dysregulated neuronal turnover (depicted by fewer ⁎ symbols in the vHCF). Global connectivity impoverishment also corresponds to thinning of PFC and vHCF layers shown here (which in real brains are detectable by post-mortem or *in vivo* structural neuroimaging studies across most major forms of psychotic, mood, and trauma-related mental illnesses). Note that the NAC network is shown with a subtle loss of intranetwork connectivity, reflecting (and resulting from) the loss of input connectivity from outlying PFC, vHCF, and AMY regions. Accordingly, there are impairments of motivational prioritization, selection or generation of certain motor program sets and sequences stored in the CA-PU (A, B, D, E, G), resulting in a relative loss of storage or functionality of natural adaptative behavioral program representations (shown as loss of C and H motor program sets compared to the healthy brain; Figure 4.3). Note that reflecting these impairments in the motivational-behavioral repertoire, we observe social and occupational dysfunction as hallmark features and criteria for major mental illness diagnoses. Altogether, these conditions are ripe for a more severe and accelerated form of addiction pathogenesis, as shown in the *brain with mental illness and addiction*. In mental illness, the capacity of addictive drug-induced DA release to invoke substantial neuroplastic change within the NAC (needed to install and support drug motivation) is largely preserved, even as the capacity of natural experiences and complex reinforcers to generate and entrain healthy motivation (via natural plasticity) is relatively compromised (as a result of PFC–vHCF, PFC–NAC, and vHCF–NAC connectivity impoverishment). Thus, in mental illness, the balance of motivational entrainment that addictive drugs versus natural reinforcers produce is shifted in the favor of drugs. So, fewer initial drug hits are needed to initiate the addiction cycle, resulting in a more rapidly accelerating and devastatingly compulsive pattern of drug use. Within the NAC of the mentally ill brain, neural ensembles (more interconnected dark neurons) dedicated to representing motivation to acquire and use addictive drugs are more efficiently recruited, further compromising already deficient natural-adaptive motivational representations. At the level of the CA-PU, behavior program sets subserving drug use and taking (D) become so highly prioritized, habitual, and dominating that the already diminished behavioral repertoire (behavioral sets A, B, E, G) are further damaged, even to the point where some adaptive-healthy behavioral sets (e.g., B) are totally lost. In this way, drug-seeking and drug-taking behavior (D) has grown more rapidly, into a more massively oversized, dangerous, and self-reinforcing "tumor" within the behavioral repertoire, compared to what takes place in a brain that is initially relatively free of mental illness. On top of these changes, the various distributed neurotoxic and vascular effects of chronic/heavy drug use in severe addiction cause further deterioration of connectivity and neuroplasticity of the mentally ill brain (as shown by further thinning of PFC–NAC and vHCF–NAC connectivity), and even greater loss of neurogenic neurons (⁎ symbols) in the vHCF. Thus, the heavy addiction comorbidity exacerbates (not self-medicates) the underling mental illness, producing a bidirectional worsening of disease components in dual-diagnosis disorders.

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Figure 4.5 Addiction pathogenesis accelerated: disease acquisition in adolescent neurodevelopment. In the *healthy adolescent brain*, the PFC, one of the last regions of the brain to mature before full adulthood, is still undergoing substantial neurodevelopment remodeling. On a microarchitectural level, there is an overabundance of local connectivity left over from childhood (symbolized as greater dendritic arborization on PFC neurons). As the brain enters adulthood this excess local connectivity is "pruned" out, in the interest of growth and maturation of longer-range connectivity (e.g., PFC–NAC and PFC with vHCF/AMY networks). This pruning is detectible in neuroimaging as maturational thinning of PFC layers relative to white matter thickening (carrying interregional projection axons from the PFC). Cognitively, these changes to PFC systems correspond to acquisition of more abstract thinking and progressive refinements in the capacity to inhibit (deprioritize or deselect) strong motivations. Subcortically, in the NAC, new motivational representational sets are being installed corresponding to cognitive, sexual, and social maturation involving PFC, AMY, vHCF systems (which project directly into the NAC) and many other subcortical centers including the hypothalamus (not shown). The subcortical situation in adolescence also encompasses functional hyperresponsivity and robustness of DA signaling into the NAC (shown as large stippled VTA–DA projection arrow into the NAC), which facilitates more rapid shifting between motivational sets, relatively robust motivational sensitivity to novel stimuli, and relatively greater plasticity within the NAC network. Within the HCF, neurogenic activity is also greater (symbolized by a relative abundance of $_{*}$). In concert, these subcortical circuit dynamics facilitate more efficient learning and memory of a rapidly expanding motivational behavioral repertoire that will equip the individual for a variety of adult roles. However, during adolescence (compared to adulthood) there is an imbalance between PFC versus subcortical maturational events in which strong new motivations represented (and facilitated by DA) in the NAC are inadequately inhibited by PFC network modulation and control. This developmental state is a double-edged sword: it confers increased impulsivity to adolescent motivation (and behavior) while promoting experimental behavior needed to manage new motivations and learn new adult behaviors and roles (note the *healthy adolescent brain,* compared to *the healthy adult brain* (Figure 4.3) does not yet have a normally sized repertoire of motor programs stored in the CA-PU). Because the healthy adolescent brain is more attracted to novelty (trying new things), the adolescent is more likely to initiate experimentation with addictive drugs. At the same time, due to the aforementioned imbalance involving relatively deficient inhibitory control (PFC) in the face of a relatively robust motivational sensitivity to novelty and neuroplastic change (DA-NAC), the healthy adolescent brain is especially primed to acquiring addiction. With an accumulation of drug hits, the *adolescent to adult addicted brain* is especially sensitive to acquiring drug-use motivation and behavioral patterns, as fortified by the ongoing maturation of the PFC–NAC network assembly during drug usage. As symbolized by the formation of the relatively larger ensemble of dark NAC neurons recruited to represent drug motivation, a larger portion of the representational space in the CA-PU subserving motor programs dedicated to acquiring and using drugs (D) is installed, selected for, and prioritized, even as some new motor programs (G) do come online, whereas others (E) never make it due to developmental disruption caused by the addiction.

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Addiction as a Neurodevelopmental Disorder: Adolescent-Brain Amplification of Addiction Vulnerability

Equipped with this neural systems understanding of addiction acceleration by mental illness, it becomes straightforward to understand the neuroscience of addiction vulnerability in another major risk context: *adolescent neurodevelopment*. As in the brain context of mental illness, adolescent neurodevelopment confers heightened vulnerability to the reinforcing effects of addictive drugs so that they are essentially more pharmacologically capable of producing impactful, long-term motivational effects.

Up until about the turn of the century (circa 2000), addiction had been almost exclusively thought of as a disorder of adulthood. This view was reinforced by the fact that by far, most patients in treatment for addiction were older adults, and the chronic accumulating effects of drug addiction on the mind and body (that are part of making an addiction diagnosis) typically take years to fully manifest, well into adulthood. However, a seminal epidemiologic study by Wagner et al. (*Neuropsychopharmacology*, 2002) examining the typical age ranges of drug experimentation and subsequent acquisition of addictions showed that most addictions (regardless of drug type) begin by late adolescence or early adult hood (<age 25). In fact, as a rule of thumb that "averages" the findings across several studies, about 95% of adults with an addiction have their first exposure to the drug before the age of 25, and nearly half of addictions may reach thresholds of becoming clinically diagnosable by the time people reach the age of 20.

Not only are these trends not drug-specific, but they are not human-specific! Rodent models of addiction (variously involving cocaine, nicotine, and alcohol) have also confirmed that when researchers hold the amounts and chronic durations of addictive drug delivery constant, adolescent exposures to the drugs produce greater frequencies and severities of addicted phenotypes in the population compared to adult exposures. Additionally, rodent models of addiction that involve sustained peri-adolescent exposures to drugs have shown that the behavioral expression of the addicted phenotype becomes more robustly expressed as animals progress from adolescence into young adulthood.

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Notably, again, not only are the adolescent developmental trends in addiction vulnerability not drug-specific, but they extend even to the developmental onset of *behavioral addictions (that don't involve substances)* such as pathological gambling. Conversely, we observe in human studies that experimentation with addictive drugs happening later in adult life (>25 years) carries significantly *lower* risk of producing addiction than what similar patterns of exposure can in adolescence. Taken together, these lines of data provide quite overwhelming evidence that brain changes that underline the transformation of a child into an adult impart developmentally specific and quite potent effects, amplifying addiction vulnerability in a way that is not drug-specific. Also, these developmental dynamics of addiction risk are so strong that they rise to clinical relevance even when evaluating individual patients: *one important way of assessing severity of addiction in the initial interview of an adult is to determine how early in adolescence their first experimentation and regular use of various substances took place.*

Similar to how we can understand the involuntary nature of mental illness–induced addiction vulnerability, we can understand adolescence-induced addiction vulnerability by appreciating that (a) addiction is a brain disease, with an anatomical and neuropathological basis, and (b) the risk condition (e.g., adolescent neurodevelopment) is itself a special neurobiological circumstance (a stage of neurobiological and anatomical revision) that involves motivational neurocircuitry where addiction strikes hardest. However, unlike the situation with mental illness, adolescent neurodevelopment is *a normal, necessary, and largely adaptive* phase of brain change that nevertheless makes the individual more vulnerable – at least for a few years – to addiction disease. So, while addiction disease opportunistically exploits the presence of another brain disease in the circumstance of mental illness, it can also exploit an otherwise healthy neurobiological context (or transition) in the situation of adolescence. Interestingly, this happens in large part because of the way this developmental stage transiently mimics, both behaviorally and neurobiologically, certain features of mental illness.

Normal adolescent neurodevelopment involves the transient emergence of (or relatively heightened expression of) two major behavioral motifs: (1) **impulsivity** (i.e., behavioral actions conducted despite heightened risk of adverse consequences of the action), and (2) **novelty seeking** (intense interest in exploring and/or engaging in new adult situations and

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behaviors). The reader will by now, based on what we have covered in this and prior chapters, recognize these two traits as being general risk indicators for addiction (and also representing endophenotypes, as reviewed above, present in several forms of mental illness). However, in adolescence, although these traits may be risky, they are not pathological. In adolescence, these traits are healthy and functionally necessary because they allow the older child to learn how to think, act, and be motivated like an adult, through actual *behavioral experimentation*, where there is actual physical feedback and consequences of their actions rebounding on them from the external world. This contrasts with the learning style (about the adult world) used by younger children that happens via fantasy and imaginative play, where results and consequences of actions are mostly simulated in the mind and play zone through pretending. So, while the 5-year-old is motivated to play with little toy cars, the 15-year-old is motivated to drive real ones that weigh 2 tons and are capable of going 90 miles an hour. In adolescence, the often quite strong motivation to drive a car is there as a necessity, because obviously, without actually trying to drive, one cannot really learn to drive. The desire to drive is necessary to allow the adolescent to acquire the skill of driving, and to acquire the experience needed to make it safer for them. However, this strong desire is there before years of experience driving have accumulated, necessary for making it relatively safe to drive! In other words, adolescence is *necessarily* a relatively dangerous phase of development, in which exuberant risk-taking (behavioral impulsivity) and the desire to experience new behaviors and stimuli (novelty seeking) is particularly intense – all as an unavoidable requirement for learning how to behave and be motivated as a well-functioning adult. In the example of automobile driving, this risk reality is born out in real numbers: although car accidents are among the leading causes of injuries and death for people between the ages of 16 and 26, they are also by far more likely to happen in this age range than in any other decade of life.

So, in adolescence, the brain is undergoing a deliberate and biologically programmed transition in which heightened impulsivity and novelty-seeking traits are conjoined to motivate behaviors that provide "on the job" learning about functioning in the adult world – all in a physically interactive, relatively risky format, that just cannot happen any other

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way. Neurobiologically (returning to an automobile analogy) this developmental epoch can be understood as the brain entering a phase where the ability to put the "brakes on behavior" are relatively weak and underdeveloped or "under construction" (corresponding to heightened impulsivity), while the "accelerator pedal" is operating relatively robustly and in a mode that is tilted toward "go" (corresponding to heightened novelty-seeking). Because we know quite a bit about what parts of the motivational neurocircuitry subserve these somewhat opposing functions of impulse control (in the case of the PFC) versus novelty motivation (in the case of subcortical motivational–limbic systems including VTA–DA, NAC, AMY, and vHCF systems) – we know where to look in the brain to see how adolescent neurodevelopment is producing functional changes in these structures to increase addiction risk. So again, as in the general example of mental illness that encompasses behavioral impulsivity and PFC dysfunction (as per the example of the NVHL modeling discussed above), we see a similar kind of impulsivity–PFC dysfunction motif associating with addiction vulnerability again, but this time in the context of adolescent neurodevelopmental change.

Essentially, in adolescence, the PFC is undergoing a major phase of neurobiological remodeling where local neural connectivity is being significantly reduced while longer-range intercortical and cortical–limbic connections are growing stronger. This corresponds to heightened levels of **synaptic pruning** observable on the cellular level in the PFC, and **PFC volume reductions** observable on the gross/neuroimaging level (and many other microcircuit changes not discussed here). Concurrent with this remodeling, the PFC is not fully able to effectively inhibit or regulate motivations represented in the NAC that are capable of driving behavior. Hence, the adolescent is more impulsive. At the same time, changes in AMY and vHCF subcircuits, and changes in their connectivity and communications with the NAC, are facilitating the emergence of adult motivations in the NAC (e.g., pertaining to sexual behavior, social relationships, and other adult behaviors and occupations). With this subcortical revision of limbic circuits, we also see evidence that the DA neurotransmitter system, which regulates the gating, flow, and neuroplastic revision of the NAC network, is operating in a relatively robust functional state. Evidence for greater pre- and postsynaptic sensitivity and reactivity of the DA system in the NAC emerges alongside a relatively heightened state of neuroplastic flexibility in prefrontal cortical–

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ventral striatal circuits, and capacity for long-term storage of novel neural representations in these systems that will make up the individual's adult motivational-behavioral repertoire. In this way, the adolescent brain is primed with neurobiological attributes that transiently make the brain: (1) more likely to be exposed to (experiment with) a wide variety of addictive drugs (associated with PFC-based structural remodeling and impulsivity); (2) more susceptible to the short-term reinforcing effects of addictive drugs (from DA–NAC system-based hyperreactivity corresponding to heightened novelty sensitivity); and (3) more susceptible to the long-term motivational effects of addictive drugs (from a combination of PFC and NAC network-based elevations in neuroplastic flexibility that is susceptible to DA-mediated neuroplastic revision).

As illustrated in Figure 4.5, which summarizes this neurobiology of adolescent addiction vulnerability, there are certain parallels and themes shared with what's happening in the neurobiology of mental illness–based addiction vulnerability (compare with Figure 4.4). Indeed, in viewing these figures, it should be appreciated that (1) adolescent-age vulnerability to addiction pathogenesis and (2) the emergence of an adolescent-onset mental illness, which also contributes to addiction vulnerability, are not mutually exclusive brain contexts and may happen at the same time in particularly vulnerable individuals. And, consistent with an interactive effect of these two often compounding vulnerability states, we note that many of the major mental illnesses that impart some of the greatest addiction risk (e.g., schizophrenia, bipolar disorder, PTSD, personality disorders, and so on) also tend to be diagnoses that typically show peri-adolescent and/or young adult onset or worsening. When considering that different forms of severe adult mental illnesses can be understood as representing various states of arrested development occurring in certain limbic regions (in the process of the adolescent brain turning into an adult brain), it is also possible to understand mental illness–based addiction vulnerability as being quite similar to that of adolescent neurodevelopment, albeit manifesting in a much longer-lasting and more severe form of vulnerability. Notably, however, it is important to keep in mind that adolescent neurodevelopment is not a mental illness (as much as parents of teenage children may sometimes feel that it is!). Different types of mental illness reflect different patterns and anatomical distributions of neural network abnormalities (spanning PFC, NAC, AMY, vHCF subcircuits and other regions), and these illness forms are generated by differential

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combinations of polygenetic factors and differential timing of adverse environmental experiences. In the case of adolescent neurodevelopment, we are describing a much more orderly, normal, and genetically staged unfolding of cortical–limbic maturation, in which the PFC becomes the last large neural network to wire in as an adult system. But still, because the AMY and vHCF project directly into the PFC (and NAC), mental illness-based abnormalities that are primarily "seated" in the AMY or vHCF may have downstream effects on PFC anatomy and function that only become fully manifest as the individual goes through peri-adolescent maturation of the PFC. So, much as different forms of adult mental illness may represent impaired forms of neuroplasticity in different limbic subcircuits, creating a clinical state of adulthood that is like being stuck in a prolonged adolescence, mental illness and adolescent neurodevelopment can interactively change addiction thresholds and probabilities of acquiring addictions that become quite severe and involve multiple substances. In summary, adolescent neurodevelopment and mental illness both operate as **cross-sensitization** and **brain attractor states** for the acquisition of addictions.

Pathological Rebound of Addiction to Worsen Mental Illness

Adding even greater complexity to these frequently interactive neurobiological dynamics occurring between adolescent neurodevelopment and mental illness (to increase addiction vulnerability) is the concurrent accumulating impact of chronic, heavy substance use (that happens only in addiction) to produce toxic effects on brain neurocircuitry and neuroplasticity. Basically, the addiction itself, even when brought on by adolescent age or mental illness vulnerability factors, also rebounds biologically to (a) prolong or impair adolescent neurodevelopmental change, and (b) compound/worsen the already existing biology of an underlying mental illness. Thus, most addictive drugs including alcohol, nicotine, opioids, cannabinoids, stimulants, and so on, when taken chronically and in heavy doses (in addiction patterns) in the adolescent or adult brain, can exert a range of adverse effects on brain circuits and neuroplasticity that subserves cognition, emotion, social interactions, decision-making, and (of course) motivation. So,

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this rebounding toxicology of addictive patterns of drug use actually worsens mental illness, occurring concurrent with the biological effect of mental illness to increase addiction risk and severity. This biology underpins the **bidirectional causality** between addiction and mental illness. As mentioned in Chapter 2 (*myth-busters*), this bidirectional causality is strong enough (and scientifically well-supported enough) to explain the close clinical and epidemiological associations between mental illness and addiction, so that there is no need to rely on "self-medication hypotheses" for explaining dual diagnosis, which requires accepting the many logical, empirical, and clinical failures that this hypothesis entails. As we will discuss in Chapter 5, the tight neurobiological connectivity and bidirectional causality that exists between mental illness and addiction is a key focus for the field of addiction psychiatry and its *raison d'etre* for providing expert integrated care for co-occurring disorders.

Although chronic heavy drug use in the context of chronic addiction does worsen mental illness as a rule of thumb, it is important to mention some key caveats to this generalization. First, of course, the severity and quality of the effect depends on which addictive drug type, or combination, or route of use, the patient has been exposed to chronically. The different main addictive drug types do have quite diverse psychoactive and neurotoxicological profiles, involving different intoxicating versus withdrawal effects. They have differential liabilities on cognition, and different mechanisms through which they not only impact the brain but alter the function of other body organs that can also impact the brain. Second, there are many biological pathways and mechanisms by which each addictive drug (through chronic/heavy use) can harm the brain. For example, cocaine and nicotine can each cause hemorrhagic strokes, or they can contribute to hypertension and arterial disease that can lead to ischemic hypoperfusion across different brain regions. Opioids, as in the context of opioid overdose, can also cause a global ischemic brain injury, whereas i.v. use of opioids or amphetamines can lead to endocarditis, that can then lead to embolic strokes in the brain. An alcohol overdose can cause an ischemic brain injury too, whereas the chronic toxicological effects of the drug on neurons and neuronal connectivity can cause generalized or focal brain atrophy. Too many bouts of alcohol withdrawal can produce seizures that are also, on some level, neurotoxic. Then there is the capacity of addictive drug intoxication, whether involving stimulants or depressants, to make the individual prone to brain injuries resulting from accidents or assaults.

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On a more subtle level, most of the addictive drug types and classes (when used chronically) exert pathological effects on neuroplasticity (and learning and memory) in different parts of the brain, which can keep patients stuck in thought or behavioral patterns that are not adaptive to their situation. In these patterns of *being stuck*, patients are less able to effectively meet the challenge of normal life stressors or psychosocial change, and they are also *more* **treatment-refractory** (less able to respond) to evidence-based treatments for mental illness, including both psychotherapies and medication treatments.

A third major variable in the capacity of addictive drug use to generate mental illness symptoms or syndromes (that could be long-lasting) is the developmental timing of the chronic addictive drug exposure (e.g., whether it is happening in adolescence, early adulthood, or older age). Each of these brain ages, of course, encompass different neurobiological and neural network attributes, so the brain substrates upon which the toxic or cardiovascular effects of additive drugs exact a cost vary by age. Focusing again on adolescence, we note that although the brain may be more plastic (capable of neural network remodeling associated with learning and memory) compared to older adult ages, it is also more potentially alterable by the long-term neuroplastic effects of addictive drugs, as previously reviewed. Moreover, adolescence and young adulthood are ages when the brain needs to be highly motivated to learn about the world, adult occupations, and social pursuits, in a way that (hopefully) are unimpeded by either the adverse motivational or cognitive effects of addictive drugs. The adolescent brain is highly sensitive to the cognitive effects of addictive drugs to disrupt educational obtainment, their motivational effects to derail academic effort and achievement, and their social-motivational effects in causing preference for friends based on whether they use drugs as well.

Impaired Hippocampal Neurogenesis in the Bidirectional Causality of Mental illness and Addiction

Accumulative neurotoxic damage resulting from additive patterns of chronic drug use can be observed in the brain in several ways, all of which can mimic what endogenous mental illness entails. We have already covered two of these motifs: (1) cortical–limbic atrophy (e.g., subtle shrinkage of PFC, AMY, vHCF, or associated regions, visible in **structural neuroimaging**) and (2)

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microstructural or functional evidence of loss of connectivity within or between these cortical–limbic regions (visible by histopathological analysis and functional neuroimaging). A third neurotoxic motif involved in the bidirectional pathogenesis of dual diagnosis involves **hippocampal neurogenesis**. Neurogenesis is a type of neuroplasticity that occurs at particularly high rates in certain parts of the brain (e.g., in the **dentate gyrus** sector of the HCF), where new neurons are born and "wire in" to the local neural network at particularly high rates. This neuronal regeneration is also accompanied by a removal of older neurons – a death rate – and it persists well into adulthood and older age. As part of a continual process of hippocampal neuronal turnover and population renewal, neurogenesis likely endows the hippocampal network with a more robust mechanism for neuroplastic change compared to that allowed by typical axo-dendritic synaptic plasticity. By analogy, demolishing a whole building and constructing a new one in its place is a more profound change than simply remodeling the interior or adding a room.

Hippocampal neurogenesis appears to be dynamic over time in mammals depending on the degree and durations of environmental changes, stressors, and related cognitive challenges they encounter. Interestingly, although the appropriate regulation of neurogenesis and neuronal turnover may be important to maintaining resilience against a range of stress-exacerbated psychiatric disorders such as major depression and PTSD, it has also been shown that psychiatric treatments including antidepressants, ECT (**electroconvulsive therapy**), and even cardiovascular exercise can upregulate neurogenesis. At the same time, as a rule of thumb, most addictive drug classes have been shown to *suppress hippocampal neurogenesis*, mimicking what endogenous mental illness may do. This evidence, taken alongside animal modeling studies demonstrating the effects of developmental damage to the vHCF (as in the NVHL model) in generating *both mental illness and addiction vulnerability*, suggests that dysregulated or impaired hippocampal neurogenesis is involved in both mental illness and elevated addiction risk. At the same time, the chronic use of addictive drugs, which addiction would create, would in turn further suppress hippocampal neurogenesis and plasticity, worsening the underlying mental illness.

In summary of this chapter, we have reviewed how many causal ingredients and neural mechanisms of addiction risk spanning genetics, adverse environmental experiences, mental illness, and adolescent

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neurodevelopment can operate independently or in concert to elevate addiction risk. In turn, severe chronic addictions can then rebound in very complex ways to intensify all of these risk factors – especially mental illness – within individuals or, intergenerationally, within families. For example, the genetic loading of addiction risk can be concentrated intergenerationally, given the phenomena that people with severe active addictions are more likely to have sexual relations and procreate with others with severe active addictions, thus concentrating genetic risk in their offspring. At the same time, the increased likelihood of both parents suffering with severe addictions when one parent does translates not only into a greater genetic loading for mental illness, but greater probability of exposure to a variety of addictive drugs at a younger age in the offspring, and a greater risk of children suffering from socioeconomic deprivations, educational failures, traumatic experiences, and attachment failures, which all raise the risk of both mental illness and addiction in adulthood (see Figure 1.2). As we will describe in the final chapter of this book, which focuses on diagnosis and treatment, it is for this reason that addiction psychiatry puts a premium on, and is best equipped for, providing expert, integrated prevention and treatment of addiction and co-occurring mental disorders.

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