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Clinical Neuroscience of Addiction: Applications to Psychological Science and Practice

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Addiction is a chronic and relapsing psychiatric disorder affecting a large number of patients worldwide. Ample evidence from basic and clinical neuroscience has demonstrated that addiction is a brain disease marked by compulsive substance use despite a host of negative consequences. Although extensive preclinical research has elucidated some of the key neurobiological underpinnings of addiction, these findings have yet to be translated into clinical practice. This article provides a review of addiction neurobiology while applying these insights to the understanding of the clinical phenomenology and treatment of this disorder. Recent progress in the fields of psychology and psychiatry suggests that clinical neuroscience will become increasingly important in clinical psychology science and practice. This review provides a framework for integrating neuroscience and clinical psychology while considering its limitations and opportunities.

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INTRODUCTION

The last decade has seen a large increase in interdisciplinary research. In particular, the accessibility of genetic and neuroimaging technologies has allowed for clinical research to become increasingly focused on the biological bases of psychopathology. Sharing the general excitement for biologically based research of clinical phenomena, the director of the National Institute on Mental Health declared psychiatry, and psychology, as neuroscience disciplines (Insel & Quirion, 2005). And while the increasing focus on biologically based research can be seen across psychological disorders, addiction represents a prime example of a disorder marked by a complex interaction between psychosocial and biological factors, including genetic predisposition and brain adaption to the pharmacological effects of substances of abuse. Increasingly, the field recognizes addiction as a chronic and relapsing disorder of the brain. This conceptualization stands in stark contrast to earlier versions of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), in which alcoholism was classified as a character disorder.

The chronic nature of addiction has been recognized in light of the high relapse rates observed across treatment modalities. McLellan (2002) presented a compelling argument for treating addiction within the framework of chronic disorders, such as high blood pressure, diabetes, and asthma. The shift to a chronic model of care may be instrumental in more adequately addressing the needs of patients suffering from addictive disorders. Moreover, the definition of addiction as a brain disease remains consistent with a biopsychosocial model that emphasizes biological (e.g., genetic, pharmacological, and neural), psychological (e.g., feeling loss of control and intense craving for the substance), and social (e.g., peer influences, access to substances of abuse) components to psychopathology. The notion of

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addiction as a brain disease helps explain why so many patients sincerely wish to stop using a substance, and yet they simply cannot do it. Nevertheless, the attribution of neural causes to addiction etiology and maintenance is not cause for therapeutic nihilism (Meehl, 1972). To the contrary, personal responsibility for treatment compliance and active engagement with recovery activities involving biological (i.e., pharmacotherapy), psychological (i.e., psychotherapy), and social (i.e., lifestyle changes) components remains a key ingredient to managing this chronic condition, akin to the treatment for diabetes or hypertension. Within this framework, it becomes increasingly important for clinical psychologists to recognize the relative contribution of biological factors to addiction, relying on preclinical and clinical neuroscience findings to elucidate the neurobiological mechanisms of this disorder.

This review seeks to highlight important findings in clinical neuroscience of addiction and to translate them into clinical language that may be useful to clinical psychologists in their research, their teaching, and, importantly, their clinical practice with patients suffering from addictive disorders. Specifically, we will review key concepts in addiction neuroscience and discuss how these concepts may be integrated into clinical research and practice. To that end, the terms *alcohol* and *drug* are used interchangeably in providing examples of specific addictive disorders. Recent progress in the fields of neuroscience, psychology, and psychiatry suggests that knowledge of clinical neuroscience will become increasingly important in clinical psychology science and practice. As such, this review covers key findings in addiction neurobiology that can be followed with more in-depth analysis of specific theories and mechanisms. The broad scope is intentional and seeks to lay out a framework for integrating neuroscience and clinical psychology.

GENETICS OF ALCOHOL AND DRUG ADDICTION

Behavioral genetic research has convincingly demonstrated that a sizeable proportion of the risk of developing an addictive disorder is attributable to genetics. Twin and adoption studies have estimated the heritability of alcohol dependence to be approximately 50–60% (Prescott & Kendler, 1999), while the estimate for cocaine dependence may be higher, at approximately 70% (Kendler, Karkowski, Neale, & Prescott, 2000; Tsuang et al., 1998). Research studies have also demonstrated that the genetic loading for substance use disorders is largely shared across disorders, as opposed to being substance specific. For example, a twin study found that the genetic liability for substance use disorders was best accounted for by a two-factor model in which licit and illicit substances formed different latent constructs explained mostly by common genetic and environmental factors (Kendler, Prescott, Myers, & Neale, 2003). In addition, studies of adolescent samples have found strong shared genetic loading across substance use disorders and conduct disorder (Button et al., 2007). More broadly, some studies have found that multiple substance use disorders and conduct disorder/antisocial personality disorder may cluster into externalizing disorders, which share a large proportion of genetic risk factors (Kendler et al., 2003). In short, a wealth of quantitative genetic research has supported the heritability of substance use disorders and has suggested that most of the genetic risk is shared across substances of abuse and even other forms of externalizing psychopathology.

Despite rapid advances in DNA-sequencing technologies, a number of important questions remain about how genetic research may inform prevention and intervention for addiction. While concepts such as heritability and environmentality represent population statistics that are not informative on an individual basis (i.e., cannot be used to inform the treatment of a particular patient), molecular genetic studies can help identify specific genes associated with the liability for the development of addiction. To date, a number of studies have examined candidate genes for alcohol and drug use disorders (Bierut, 2011; Gelernter & Kranzler, 2009). These candidate genes studies typically focus on genetic polymorphisms in genes coding for the neural substrates of addiction, such as endogenous opioids, dopaminergic and GABAergic neurotransmission, and alcohol metabolism. While some reliable candidate genes have emerged (e.g., alcohol dehydrogenase polymorphisms), the vast majority of the candidate genes studied to date have produced mixed and inconclusive results (Ducci & Goldman, 2008). There is increasing recognition in the field that common psychiatric disorders, such as addiction, may result from the

interplay between multiple genes of relatively small effect. Moreover, gene × gene interactions (i.e., epistasis) as well as gene × environment interactions also account for the phenotypic variance (Dick, Riley, & Kendler, 2010).

More recently, the field has moved from a hypothesis-driven, candidate-gene approach to a data-driven, hypothesis-generating method, namely the genome-wide association studies (GWAS; Cichon et al., 2009). These studies rely on large sample sizes of thousands of patients and examine genetic variation covering the entire human genome. While the advantages of this approach are multiple, the phenotypes captured are typically less refined and the threshold for genome-wide significance is quite stringent (10^{-8}) as it controls for multiple comparisons across nearly one million markers. Multiple GWAS in psychiatric genetics, including alcoholism, have produced rather discouraging results. As such, the field of psychiatric genetics has moved toward even sample sizes leading to meta-analysis of GWAS in hopes to detect reliable markers of risk for complex phenotypes (Gershon, Alliey-Rodriguez, & Liu, 2011).

In summary, genetic research in the field of addiction has recognized its heritable etiology and yet has failed to produce reliable risk markers for these disorders. While the field continues to evolve and to a large extent catch up to the technological advances, multiple insights from behavioral genetic research in addiction can be useful in clinical practice. For example, patients often report misguided notions about the genetic bases of addiction, which provides a useful opportunity for psychoeducation. Alcohol and drug use disorders are far from being entirely genetic disorders or else the concordance rate between monozygotic (MZ) twins would be a perfect 1.0. That is certainly not the case for addiction nor is it the case for any other psychiatric disorder. In fact, concordance rates for alcoholism are approximately 47–59% for MZ twins as compared to 31–36% for dizygotic (DZ) twins (Kendler, Heath, Neale, Kessler, & Eaves, 1992). This notion is useful to patients as it highlights the importance of environmental factors. Perhaps this point is even more salient for addictive disorders given that, at a basic level, should patients never be exposed to alcohol or drugs it becomes impossible for them to develop an addiction. The "social" component of the biopsychosocial model may help explain a considerable proportion of risk, such as deviant peer affiliation and low parental monitoring in adolescence as well as the accessibility to alcohol or drugs throughout the life span. Understanding which factors are "tractable" and engaging patients in productive behavior changes toward these controllable variables represents a critical orientation shared by empirically supported interventions for addiction. In essence, patients are dealing with the "set of genetic cards they are dealt" and while assigning blame for their disorder is most often counterproductive, the recognition of which risk and protective factors can be intervened upon helps patients and clinicians target their efforts most effectively.

Finally, a novel area in which genetic research is helping refine treatments is that of pharmacogenetics, which consists of identifying which treatments will be most effective for certain patients on the basis of their genetic makeup (Shastry, 2006). The field of alcoholism has experienced some initial success in this area, as some studies have suggested that naltrexone, an opioid antagonist approved for the treatment of alcohol dependence, may be optimized based on a polymorphism in the gene coding for mu opioid receptors (Anton et al., 2008; Ray & Hutchison, 2007). In short, practicing psychologists are tasked with educating patients and students about the genetic bases of mental disorders and in doing so have the opportunity to communicate the current state of the field while also leveraging the environmentality of the disorder as an opportunity for intervention. Genetic factors also play an important role in determining individual differences associated with the various neurobehavioral risk pathways into the disorder, as discussed in more detail later in this review.

THE NEURAL BASES OF ALCOHOL AND DRUG REWARD

Extensive preclinical research has convincingly demonstrated that alcohol and drugs of abuse activate the same neural circuitry involved in normal responses to natural rewards, such as food and sex. These brain structures serve an important evolutionary task, which is to reinforce behaviors that preserve the species, such as eating and reproducing. These brain structures are therefore highly preserved by evolution, which has in

turn facilitated basic research in addiction as the neural circuitry of reward can be found in several animal models, including rats and mice. Specifically, the reward pathway in the brain consists of dopaminergic projections from the ventral tegmental area to the nucleus accumbens and the prefrontal cortex (Koob, 1992). As dopamine is released in the striatum, individuals experience subjective reinforcement, or in the case of alcohol and drugs, a powerful "high." A key distinction between drugs of abuse and natural rewards is that the former activate the reward pathway much more potently, thereby leading to neuroadaptation and contributing to the disease process in addiction.

Neuroadaptation in the reward pathway is thought to be central to the development and maintenance of addiction, as it renders the patient more vulnerable to (positive and negative) reinforcing effects of substances of abuse (Kalivas & Volkow, 2005). Repeated alcohol and drug use conditions the brain to seek these reinforcers at the expense of natural rewards, which are less potent and over time become less salient to the patient. In other words, over time, patients experience the urge to use the drug of abuse as a very potent biological drive, akin to extreme hunger or thirst. This is consistent with the effects of alcohol and drugs on the very same brain structures responsible for driving the organism toward basic survival needs.

In clinical terms, while the decision to begin using alcohol or drugs is voluntary at first, over time, patients become vulnerable to addiction as drugs of abuse "hijack" the reward circuitry and the drive to obtain and use a drug becomes central to the patient. At that point, when addiction has ensued, drug use is no longer simply a voluntary choice but rather a maladaptive response to brain-based urges that are as potent as the drive for food or water. The process of neuroadaptation can help explain our patients' struggles with addiction and their reports that despite their sincere desire to quit using the substance, they feel as though they cannot. This may also be a useful framework for psychoeducation, as a considerable amount of blame is often placed on the patient by him- or herself as well as by his or her loved ones. This model effectively distinguishes the initiation of substance use from the continuation of drug and alcohol use despite serious health and psychosocial consequences. Specifically, the neuropharmacological effects of drugs of abuse after extensive and repeated use are thought to explain the later process, namely the maintenance of the disorder and its chronic and relapsing nature (Kalivas & Volkow, 2005; Volkow & Li, 2005). Likewise, it is useful for patients to understand that these neuroadaptive processes are present and may render them vulnerable to the effects of drugs of abuse, as well as associated drug cues, long into the recovery process.

Recent theorizing on the role of the reward pathway in addiction has argued for a dissociation of mechanisms of reward based on the incentive-sensitization theory of addiction. In particular, basic neuroscience of addiction has suggested that reward may be parsed into "liking" of a drug and "wanting" it (Robinson & Berridge, 1993). The opioidergic system in the brain is thought to underlie mechanisms of drug liking, while the dopaminergic pathway is primarily responsive for the "wanting" of the drug, or in other words, drug craving (Berridge & Robinson, 2003). This is a clinically meaningful distinction, as patients report drug urges long after the drug "high" becomes a secondary process in their substance use. As patients often describe, their addiction is less about wanting to feel good or "high" given that as the disease progresses, patients report experiencing much less subjective reward from drug use while the very powerful drug urges, or wanting, is maintained and often exacerbated. While there are many gaps in the understanding of how drugs of abuse act on the brain's reward system, the current literature on incentive sensitization and neuroadaptation of these systems has been influential in medication development and may be useful in the psychotherapeutic treatment of addiction as well. Patients and families are likely to benefit from a disorder conceptualization that more effectively incorporates the "bio" component into the biopsychosocial model, by effectively applying clinical neuroscience findings to the understanding of the disorder.

THE NEURAL BASES OF TOLERANCE AND WITHDRAWAL

Tolerance and withdrawal represent two important symptoms of substance dependence and are recognized as indices of physiological dependence by the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association, 1994). *DSM-IV* aptly

recognizes the biological nature of these symptoms as they represent the neuropsychological consequences of repeated substance use on acute intoxication (i.e., tolerance) and on the organism's response to the substance being taken away (i.e., withdrawal). Tolerance is uniformly required before withdrawal can be manifested, while the opposed is not true. Through repeated alcohol or drug use, the brain becomes sensitized to the same amount of the drug, such that higher amounts are required to produce the same neurobehavioral effects. This phenomenon is called tolerance. The reverse process, in turn, occurs when drugs of abuse are no longer present in the system, causing a sudden shift in the homeostatic set point, marked by physiological symptoms that are run the opposite of intoxication (i.e., withdrawal or abstinence syndrome). In other words, withdrawal is a counteradaptive process to the removal of the drug after heavy chronic use. Withdrawal is the result of neuroadaptation because of repeated use leading to the development of tolerance, such that the two processes are mechanistically linked. Once neuroadaptation in the brain occurs, causing behavioral tolerance, the system's new homeostatic (i.e., tolerant) set point is disrupted by the removal of the drug. Although withdrawal is an aversive state, it makes adaptive sense since the organism is trying to reestablish homeostasis.

The allostatic model of addiction explains the intricate balance between positive and negative reinforcement in addiction (Koob, 2003; Koob & Le Moal, 1997). This neurobiological model of addiction is informed by the Opponent Process Theory, developed by Solomon and Corbit (1974) to explain how two opposing processes may occur simultaneously and jointly affect motivation (Solomon & Corbit, 1974). In basic terms, it contends that over time, addiction becomes less about positive reinforcement (the activational process, or the a-process) and more about negative reinforcement (the counteradaptive opponent process, or the b-process; Ahmed & Koob, 2005). This theory seeks to capture the dynamic nature of addiction neurobiology as the brain is continuously adapting to large amounts of alcohol over extended periods of time, thereby causing a shift in the allostatic set point. In addiction, allostasis is defined as the process of maintaining reward function stability through changes in brain reward mechanisms (Koob, 2003). During the reinforcing effects of alcohol intoxication (a-process), there is an increase in GABAergic activity, opioid peptides, and dopamine output in the ventral striatum, which represent the neural substrates of alcohol reward. Conversely, during the counteradaptive opponent process marked by negative affect and withdrawal, there is an increase in corticotropin releasing factor (CRF) activity as well as a decrease in neuropeptide Y (NPY), both of which are key neuromodulators of stress reactivity (Koob & Kreek, 2007; Koob & Le Moal, 2008).

Together, these processes provide the neural basis of reward and punishment associated with alcohol intoxication and withdrawal, respectively. Over time, the shift in the balance from positive to negative reinforcement helps explain what patients describe in their experiences with alcohol or drugs, namely that they no longer use alcohol or drugs to feel good and that instead, alcohol and drug use serves to prevent them from feeling sick. In other words, patients often describe not feeling "normal" unless they are using the drug/alcohol, which is consistent with the neuroadaptation in the brain reward circuitry leading to a chronic deviation of the brain reward set point proposed by the allostatic model (Koob & Le Moal, 1997). In this context, it is critical for clinicians and patients to appreciate that from a biological standpoint, it is only plausible that chronic and heavy drug use over time leads to desensitization to the reinforcing drug effects, while the primary drive to use the drug becomes the alleviation of withdrawal and its associated unpleasant affective and physical symptoms.

Further, the allostatic theory of addiction suggests three stages of the disorder, namely preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect (Koob, 2003). These three stages are thought to be cyclical and to spiral, increasing in their intensity and associated distress, over time. One of the strengths of this theory is that it maps nicely onto *DSM-IV* criteria and the current nosology of addiction. The preoccupation and anticipation stage is marked by cravings and a persistent desire to use the substance. As patients often report, activities related to obtaining and using the drug become increasingly salient to them, requiring more of their emotional and financial resources. The binge/intoxication stage consists of

taking the drug in larger amounts or over longer periods of time than intended. This stage is marked by repeated failure to self-regulate and to "put the brakes on behavior." In other words, patients are unable to resist the urge to use, often leading to a binge or, in the case of treatment seekers, to relapse. The withdrawal and negative affect represent a later stage in the disorder, consistent with the recognition that withdrawal is not a required symptom of substance dependence. However, as convincingly demonstrated in preclinical models, individuals who abuse drugs for extended periods of time are almost certain to develop withdrawal symptoms in the later stages of the disease.

For example, the neurobiological underpinnings of alcohol withdrawal include changes in the neurochemical systems within the extended amygdala, including decreases in neurotransmitter functions subserving the acute reinforcing effects of alcohol (e.g., opioidergic, dopaminergic, GABAergic; Koob, 2003). An increase in alcohol self-administration can be reliably induced in animal models using a withdrawal state, and such models demonstrated that dopaminergic function is compromised during acute withdrawal (Weiss et al., 1996). Recent animal models have also emphasized the role of dysregulation in the brain stress system, including CRF-mediated processes, to changes in reward function leading to negative reinforcement (Koob & Kreek, 2007; Koob & Le Moal, 2008). Ethanol is a powerful modulator of stress systems and when it is removed from the brain, through abstinence, powerful anxiogenic-like effects will ensue. Such effects are critical to drug seeking and relapse, and while patients manifest affective symptoms of agitation and anxiety during withdrawal, the neural bases of those symptoms are reliably traced to the neurobiology of addiction and render them vulnerable to resuming drug use.

In short, the neural mechanisms subserving tolerance and withdrawal provide compelling evidence for the neurobiology of addiction and suggest that neuroadaptation in the brain's reward circuitry leads to a shift in the reward set point. Such changes are critical to the maintenance of the disorder and provide important targets for pharmacological and behavioral interventions. Integrating these concepts in behavioral treatments entails a conceptualization of clinical phenomena, such as tolerance and withdrawal, which takes into account the biological bases of these symptoms. For example, in clinical practice, a careful evaluation of withdrawal symptoms is critical to determining whether a patient is suited to receive treatment on an outpatient versus inpatient basis. Even patients with very high levels of motivation will likely require detoxification prior to outpatient services if their clinical profile is marked by significant withdrawal symptoms. Conversely, patients who show evidence of being able to safely abstain from alcohol or drugs for a period of time are much better candidates for outpatient services. The recognition of the clinical presentation in light of both psychological and neurological factors is critical to effectively targeting addictive disorders. Likewise, from the perspective of clinical science, much work remains to be done in order to develop human models that can effectively translate insights from basic neuroscience. For example, there have been no clinical studies to date effectively testing the stages of addiction proposed by the allostatic model. As such, the development of translational phenotypes for clinical neuroscience of addiction is a top research priority.

NEUROADAPTATION, RELAPSE, AND RECOVERY

Drugs of abuse are by definition unconditioned reinforcers and as such are capable of producing instrumental learning. It is no surprise that patients report their initial experiences with alcohol or drugs to be highly reinforcing, and in fact, their genetic loading may render them vulnerable to experiencing alcohol or drugs as more reinforcing than other individuals. But while alcohol or drug use is goal-directed during the initiation and escalation of substance use, it becomes habitual as addiction ensues and progresses. The transition from goal-directed to habitual behavior is critical and suggests that even when the reward is no longer valued, it will be sought out and consumed. This transition has been well documented in preclinical models (e.g., Barker, Torregrossa, Arnold, & Taylor, 2010) and provides an important parallel to the phenomenology of addiction in humans, which is marked by continued use despite consequences and recognition that the "drug reward" is no longer valued by patients at the psychological level, yet its consumption has become habitual and through neuroadaptive processes

has produced physiological dependence (i.e., tolerance and/or withdrawal).

A key element of habitual behavior is that it can be elicited and even controlled by cues. Through Pavlovian learning mechanisms, stimuli associated with the drug acquire incentive salience. Those conditioned stimuli can then evoke craving and drug-seeking behavior, as demonstrated by preclinical (Weiss et al., 2001) as well as clinical (Monti et al., 2004) models. A series of animal studies quantifying dopaminergic output in the striatum have shown that in the absence of conditioned stimuli (or cues), the "spike" in dopamine firing associated with the neural bases of reward is observed after drug intake (Schultz, Dayan, & Montague, 1997). However, in models where cues precede the availability of the drug, the dopamine spike shifts to the presentation of the cues, rather than the drug itself. Interestingly, when cues are not followed by the reward (i.e., prediction error), there is a "dip" in dopamine firing as though the system is responding to the withdrawal of the reinforcer with below normal levels of dopaminergic activity (Schultz et al., 1997). These fascinating animal findings are closely tied to clinical presentation of addiction in humans, which is marked by intense cue-induced craving and by habitual drug seeking, often described as beyond conscious awareness by patients. Further understanding the neurobiology of drug reward and incentive salience may afford clinical psychologists with a greater appreciation of the neural bases of addiction. It may also be useful as a framework for teaching cognitive-behavioral techniques empirically supported for the treatment of addictive disorders, such as coping with urges and relapse prevention skills.

Learning theory is particularly useful to understanding the neural underpinnings of incentive salience in addiction. It contends that adaptive responses to various types of functional alteration are displayed not only at the level of single neurons but also at the synapses between neurons, hence the term *synaptic plasticity*. This phenomenon has been most studied in the form of long-term potentiation (LTP), which is a process of long-lasting facilitation of neurotransmission across neurons when the synapses between them are used repeatedly under certain conditions. These processes are critical to all learning, both adaptive and maladaptive. Recognizing that much like the rewarding properties of alcohol and drugs that operate within the same neurocircuits responsible for normal reward functions in the brain, Pavlovian (or associative) learning during development of addiction operates through the same signaling pathways subserving all other nonpathological forms of learning (Robinson & Berridge, 2008). In basic terms, patients have learned to form associations between triggers, or in the terms used by 12-Step Facilitation, "people, places, and things," and alcohol or drug consumption through the same biological mechanisms that allow us to associate our favorite restaurant with food, for example. A number of neuroimaging studies have shown that the presentation of alcohol or drug cues, compared with control cues, reliably produces blood flow in the brain areas associated with reward (nucleus accumbens, VTA, insula; Filbey et al., 2008) and affect regulation (amygdala; Childress et al., 1999). Importantly, while brain activation is correlated with the subjective experience of craving, captured via self-reports, the correlation is far from perfect. This suggests that while craving is under conscious awareness, some of it may be subcortical in nature and perhaps accessible to patients. That is consistent with patient reports of being on "auto pilot" and having little awareness of their craving levels during a lapse.

A prominent theory of addiction consists of the incentive-sensitization model. The basic tenets of this theory argue that drugs of abuse share the ability to alter brain organization (i.e., produce neuroadaptation) in the brain reward systems, rendering the system "sensitized" to drugs and associated stimuli (Robinson & Berridge, 2001). A key contribution of this theory is the dissociation between two aspects of incentive-sensitization, namely "liking" and "wanting." Specifically, it has been nicely demonstrated that sensitization operates primarily at the subcomponent of reward-termed incentive salience, which is marked by "drug wanting." While the neural basis of liking is primarily subserved by the endogenous opioid system, the process of wanting has been associated with dopaminergic activity in the brain's reward circuitry (Berridge, Robinson, & Aldridge, 2009). Importantly, the authors argue that sensitization is not simply an inevitable pharmacological consequence of repeated drug use and instead is modulated by environmental factors

associated with alcohol and drug intake (Robinson & Berridge, 2001). The notion of environmental modulation of neuropharmacological experiences has important implications not only for understanding addiction and relapse but also for developing and implementing intervention strategies and relapse prevention.

The treatment implications of the incentive salience are multiple. From a neurobiological standpoint, teaching patients to cope with triggers is akin to training one's brain to unlearn associations, or at a behavioral level, to inhibit a prepotent (learned) response, such as alcohol use in the presence of a drinking buddy. While learning theory has been influential in the development of highly effective treatments for anxiety disorders, such as exposure-based interventions, similar success is not seen in the case of addiction. Cue exposure treatments for alcoholism have produced mixed results (Conklin & Tiffany, 2002). The lack of strong empirical support for exposure-based treatments for addiction is largely explained by the over-generalizability of the conditioned response. In others, it is plausible that alcohol and drug use is accompanied by a wide variety of cues, both internal (e.g., affective states such as stress and negative mood) and external (e.g., places, people, and things). To that end, it is simply not feasible to devise exposure exercises that effectively target all of such triggers. Nevertheless, functional analysis of behavior is commonly used to effectively identify patients' most salient drug use triggers. Likewise, behavioral techniques for coping with triggers, such as avoiding, taking time-outs, and learning refusal skills, represent important components of cognitive-behavioral therapy for addiction. What is often lacking from this effective intervention is the conceptualization of triggers as learned processes that are biologically based and as such may evoke the unwanted, yet learned, behavioral response of alcohol or drug use, leading to relapse.

In addition to learning mechanisms discussed earlier, protracted withdrawal represents another biologically based response to the drug being removed from the system, which in turn threatens recovery, particularly during its early stages. While acute withdrawal is marked by intense feelings of physical discomfort associated with a "rebound effect" from chronic drug use, protracted withdrawal is marked by less severe yet long-lasting physical and psychological symptoms (Heilig, Egli, Crabbe, & Becker, 2010). For example, protracted alcohol withdrawal is marked by feelings of nervousness, agitation, anhedonia, dysphoria, and sleep difficulties. These symptoms are thought to persist for approximately 3 months during early remission. Not surprisingly, these physical and psychological symptoms can be traced to the long-lasting disruption in excitatory and inhibitory neurotransmission resulting from chronic alcohol use. The hyperactive glutamatergic projections from the nucleus accumbens to the prefrontal cortex have been implicated in the process of relapse through mechanisms of protracted withdrawal such as nervousness and agitation (Kalivas & Volkow, 2005). Likewise, longer-term disruptions in the dopamine-mediated reward pathway can be associated with mechanisms such as anhedonia, the inability to experience pleasure from natural rewards (Wise, 2008). Patients in early recovery are often confronted with the fact that despite not using alcohol or drugs, they feel unable to experience reward from activities that used to be reinforcing to them, such as spending time with loved ones. However, it is important to recognize that the neural systems of reward have been subjected to alterations in their organization and that these alterations will not be immediately resolved through short-term abstinence. Conversely, the process of brain recovery from addiction is rather gradual. And while clinical neuroscience cannot effectively estimate how much one's brain will recover and over what period of time, a few recent studies have documented the neural changes associated with recovery.

A study by Wilson et al. (1996) was the first to document that dopamine synaptic terminals, which are the primary targets of methamphetamine, leading to "dopamine leakages," were damaged in the brains of patients who died of methamphetamine overdose relative to controls (Wilson et al., 1996). More recently, a study using positron emission tomography (PET) to visualize dopamine nerve terminals in the human brain found that these terminals were damaged in methamphetamine abusers relative to controls (Volkow et al., 2001). Perhaps most encouraging, when patients were reevaluated after periods of prolonged abstinence, there was clear evidence of recovery of dopamine nerve cells in the brain (Volkow et al., 2001). These human

studies suggest that brain damage occurs as a result of chronic drug use and that recovery can also occur after periods of abstinence.

From a clinical perspective, increasing recognition of recovery as a brain-based process can have important implications for patients and clinicians alike. One of the major implications of this conceptualization is the notion that sustained recovery is required to fully experience the benefits of abstinence. Patients and their families ought to bring a long-term perspective to the recovery process with regard to the behavioral aspects of the process (e.g., building a life worth living, repairing relationships) but also with regard to the neurocognitive and affective benefits of sustained abstinence. For example, this notion would argue that anhedonia commonly associated with initial abstinence may subside over time as the brain's reward system recovers and is better able to process natural rewards, which are relatively minor compared to the potency of drug rewards in those circuits. From a clinical science perspective, human studies that can more accurately capture the neural aspects of recovery with regard to affective and cognitive processes would be valuable in elucidating the nature, and time course, of recovery of such functions as hedonic capacity and cognitive abilities. Clinical neuroimaging studies would also be enhanced by phenotypic classifications that can effectively account for remission stages.

As reviewed in this section, neuroscience of addiction has elucidated several neural circuits underlying the behavioral expression of tolerance, craving, and withdrawal, which are critical constructs to understanding patient vulnerability to relapse as well as their prognosis for long-term recovery. Continued integration of basic and clinical science through translational studies will further the impact of these contributions to clinical care. In addition, well-informed clinicians who can effectively discuss the neural bases of addiction with patients and their families will be well positioned to facilitate the dissemination and optimization of science-based approaches to clinical care.

MULTIPLE PATHWAYS TO A COMMON PSYCHOLOGICAL DISORDER

Inherent in the concept of a complex phenotype is the recognition that there is not a single path into this disorder nor is there a single "way out" through a common intervention that will work well for all patients. In contrast, the developmental psychology constructs of equifinality and multifinality are more applicable to addiction etiology. Equifinality refers to the notion that a common phenomenon, or in this case disorder, may result from different mechanisms. This is consistent with the recognition that addiction is rather heterogeneous, leading to multiple efforts to further parse out this clinical phenotype using typologies, age of onset, family history, and other variables of putatively high etiological significance (Babor & Caetano, 2006). Multifinality, in turn, refers to the notion that a common etiological factor may result in multiple psychopathological outcomes. A classic example is childhood abuse and maltreatment leading to a host of possible forms of psychopathology, both internalizing and externalizing in nature. The bifurcation in this model is provided by environmental factors and unique genetic vulnerabilities. The multifinality concept is highly consistent with the genetic and environmental risk factors shared by multiple psychological disorders. In psychopathology research, that is often seen in the context of a common liability model operating across a host of psychological disorders (e.g., Roysamb et al., 2011). In short, patients may arrive at an addictive disorder through different pathways (i.e., equifinality) and multiple genetic and environmental risk factors may confer risk of these disorders as well as other forms of psychopathology (i.e., multifinality).

So how does the neurobiology of addiction account for these multiple pathways leading to considerable phenotypic heterogeneity? To take into consideration different paths in and out of a psychopathological outcome, there has been increasing emphasis on intermediate phenotypes, or endophenotypes, for addiction, as well as other neuropsychiatric disorders (Gottesman & Gould, 2003; Hines, Ray, Hutchison, & Tabakoff, 2005). These phenotypes represent narrower and more discrete pathways into the disorder of interest. Another important contribution of these narrow phenotypes is that they are purportedly closer to the neurobiology of the disorder. Examples of addiction intermediate phenotypes include subjective intoxication (alcohol or drug "high"), inhibitory control, craving, stress reactivity, and neural response to alcohol or drug cues, to

name a few (Hines et al., 2005; Ray, Mackillop, & Monti, 2010). This conceptualization, in turn, resonates with the recent call for research domain criteria (RDoC), which is thought to advance the field by promoting integrative research on mental disorders through common brain-based mechanisms of risk (Insel et al., 2010). This approach has been described as a heuristic for the integration of behavioral neuroscience to the study of psychopathology (Sanislow et al., 2010).

In this context, it is critical to recognize that drugs alone are not capable of producing addiction. Even highly addictive substances, such as heroin, lead to addiction in only a relatively small subset of users (Anthony, Beddell, Lindon, & Nicholson, 1994). Therefore, individual differences in risk profiles, both genetic and environmental, may predispose some alcohol and drug users to become addicted, while the majority of users never go on to develop an alcohol or drug problem. Genetic factors may account for one's vulnerability through unique pathways such as the hedonic experience of alcohol or drugs, the development of incentive salience, and the experience of alcohol or drugs under conditions of psychological stress, for example.

Additionally, there are numerous examples of environmental factors controlling gene expression, such that individuals with a given genetic makeup may be vulnerable to the development of addiction and to relapse under certain environmental conditions but not under others (e.g., Breese et al., 2005). To that end, understanding the unique vulnerability profile of individual patients has great potential to improve clinical care. While the underlying causes of such vulnerability have yet to be elucidated from a neurobiological standpoint, behavioral markers of risk can be equally useful in informing treatment and developing more targeted interventions. This approach has been influential in medication development for addiction, which now targets more discrete aspects of the pathophysiology of the disorder, such as blocking the rewarding effects of alcohol, or ameliorating protracted withdrawal and stress-induced relapse (Heilig, Thorsell, et al., 2010). This approach also presents unique opportunities for clinical psychologists to develop more targeted behavioral interventions on the bases of individualized risk profiles. It is likely not surprising to clinical psychologists that despite the sophisticated clinical neuroscience research conducted to date, individual differences in the expression of psychopathological behavior remain elusive, yet so central to patient care.

CONCLUSIONS, LIMITATIONS, AND OPPORTUNITIES

Neuroscience of addiction has provided compelling evidence of the neural and behavioral bases of key addiction mechanisms, such as the transition from goal-directed to habitual drug taking, the development of incentive salience, the neuroadaptive process underlying tolerance and withdrawal (including protracted withdrawal), as well as brain damage from drug and recovery from such damage during prolonged abstinence. While considerable research has yet to be performed in order to effectively translate these findings to patients suffering from addictive disorders, insights from neuroscience can be incorporated into clinical research and practice. This review contends that doing so can be highly informative and perhaps therapeutic to patients and their loved ones. Importantly, as highlighted in this article, insights from clinical neuroscience of addiction are rather compatible with several of the clinical approaches used in practice. As the field of psychology increasingly becomes a neuroscience discipline, the important contribution of clinical psychology to understanding addiction etiology and developing more effective interventions rests on our ability to effectively translate basic research into clinical science and practice. Translational efforts remain interdisciplinary in nature, and in the context of such cross-discipline collaborations, clinical psychologists' expertise regarding the clinical phenomenology of addiction, its course and prognosis, as well as treatment recommendations remains highly relevant and informative. The ability to effectively translate and reverse-translate clinical knowledge into basic neuroscience is critically necessary to produce translational models that are relevant to the human experience of psychopathology.

The limitations of the clinical neuroscience approach must be clearly recognized. The first and most obvious one is that preclinical models have not been fully translated to human samples such that further research is needed to support the applicability of these basic findings to clinical samples. Another important limitation, aptly noted by Kalant (2010), is the recognition that a

mechanism is not the same as a cause and that while neuroscience of addiction has elucidated a number of important mechanisms to the expression and maintenance of the addiction phenotype, the cause of addiction, which calls the mechanism into action, remains elusive. The distinction between the why and how of addiction calls into question the extent to which reductionist approaches can effectively elucidate the primary causes of addictive behavior, rather than the mechanisms underlying its expression. While critical reviews of various scientific approaches are central to providing a sobering perspective of the relative strengths and weaknesses of various research methods and their relative contribution, the clinical neuroscience of addiction has undoubtedly produced important insights leading to advances in patient care. The call for more integrative approaches to understanding the underlying causes of addiction, however, is a very important one. To that end, clinical psychologists have an important role to play in fulfilling this rather tall order. Clinical expertise in the phenomenology of addiction is essential to the success of such pursuits. Training the next generation of clinical scientists and practitioners to integrate their expertise in psychopathology with the underlying neural mechanisms of such complex behaviors represents both a challenge and a tremendous opportunity for the field of clinical science.

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