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Clinical Neuroscience of Addiction: What Clinical Psychologists Need to Know and Why

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Abstract

The last three decades in psychological research have been marked by interdisciplinary science. Addiction represents a prime example of a disorder marked by a complex interaction among psychosocial and biological factors. This review highlights critical findings in the basic neuroscience of addiction and translates them into clinical language that can inform clinical psychologists in their research, teaching, and practice. From mechanisms of reward processing, learning and memory, allostasis, incentive-sensitization, withdrawal, tolerance, goal-directed decision making, habit learning, genetics, inflammation, and the microbiome, the common theme of this review is to illustrate the clinical utility of basic neuroscience research and to identify opportunities for clinical science. The thoughtful integration of basic and clinical science provides a powerful tool to fulfill the scientific mission of improving health care. Clinical psychologists have a crucial role to play in the translational science of addiction.

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INTRODUCTION

The last three decades in psychological research have been marked by interdisciplinary science, a shift driven in part by the increased accessibility of novel tools for quantifying biomarkers, including neuroimaging, genetics, epigenetics, inflammation, and the gut microbiome, to name a few. The accessibility of biologically based assays has been matched by a general excitement for biologically based research of clinical phenomena. In 1989, then President George H.W. Bush declared the 1990s the Decade of the Brain. In 2005, Thomas R. Insel, then director of the National Institute of Mental Health (NIMH), declared psychiatry and psychology to be neuroscience disciplines (Insel & Quirion 2005). NIMH continues to emphasize as a chief goal "advancing basic science of brain, genomics, and behavior to understand mental illnesses" (**https://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml**) while maintaining a focus on interdisciplinary science (Gordon 2019, van Dorn 2017). The role of psychological research in achieving NIMH's goal of reducing the burden of mental illness has been nicely articulated with an eye toward balancing institute investments in both psychosocial and biomedical approaches (Teachman et al. 2019). Clearly, the role of psychological science, and of clinical psychological science in particular, in interdisciplinary research continues to evolve and is a source of frequent debate.

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 among psychosocial and biological factors, including genetic predisposition and brain adaption to the pharmacological effects of substances of abuse. Increasingly, the field of addiction science conceptualizes addiction as a chronic and relapsing disorder of the brain. This conceptualization stands in stark contrast to that found in 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, and a compelling argument for treating addiction within the framework of chronic disorders, such as high blood pressure, diabetes, and asthma, has been

articulated (McLellan 2002). The definition of addiction as a brain disease places significant emphasis on the biological component of the biopsychosocial model. As originally articulated, the biopsychosocial model highlights the complex interplay among the biological (e.g., genetic, pharmacological, 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 of addiction and other forms of psychopathology.

The argument for addiction as a brain disease is not without disagreement and debate (Bedi et al. 2017, Grifell & Hart 2018). Nevertheless, the notion of addiction as a brain disease helps explain why so many patients sincerely wish to stop using a substance but simply cannot. Relatedly, 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 (e.g., pharmacotherapy), psychological (e.g., psychotherapy), and social (e.g., lifestyle changes) components remain key ingredients 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 and to look to preclinical and clinical neuroscience findings to elucidate the neurobiological mechanisms of this disorder. It is equally important for clinical psychologists to articulate the crucial role of clinical science and patient-oriented research in addressing the burden of addiction on individuals and on society as a whole.

This framework has informed our research program for the past 15 years and has been articulated in an earlier article aimed at clinical psychologists (Ray 2012). Since the publication of that review nearly 10 years ago, much has changed regarding the interplay of basic and clinical science of addiction in translational science models (Ray et al. 2021). Arguably, neuroscientists have become increasingly focused on the translational impact of their work (Heilig & Leggio 2016). Clinical scientists have emphasized the role of patient-oriented research as crucial to the endgame of promoting mental health and recovery from addiction (Ray et al. 2019a). There is also an argument against the push to speed scientific translation in addiction science (Ostergren et al. 2014). All of this has happened in the context of increased attention to addiction science through major developments such as the rise of nicotine vaping products, legalization of marijuana, and the opioid epidemic.

Given these developments and debates over the past decade, this review seeks to highlight important findings in the clinical neuroscience of addiction and to translate them into clinical language that may be useful to clinical psychologists in their research, teaching, and, importantly, clinical practice with patients suffering from addictive disorders. We also discuss how clinical science is needed to reverse-translate key findings in addiction science. To that end, we review key concepts in addiction neuroscience and discuss how these concepts may be integrated into clinical research and practice (and vice versa). 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. Likewise, such knowledge will empower clinical scientists to engage in cross-disciplinary dialogue and highlight the ways in which clinical science is needed to inform the interpretation of and reverse-translate clinically meaningful findings. This review covers key findings in addiction neurobiology that can be followed with more in-depth analyses of specific theories and mechanisms. It largely updates some early theorizing (Ray 2012), which was prescient about the integration of basic and clinical science in a translational framework. The broad scope is intentional and seeks to lay out a framework for integrating neuroscience and clinical psychology in a more harmonious, clinically relevant fashion.

ALCOHOL AND DRUG REWARD: FROM NEUROBIOLOGICAL MODELS TO CRAVING AND ADDICTION

Extensive preclinical research has shown that alcohol and drugs of abuse activate the same neural circuitry involved in 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, a fact that has 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 (VTA) to the nucleus accumbens and the prefrontal cortex (Koob 1992). As dopamine is released in the striatum, individuals experience subjective reinforcement—in the case of alcohol and drugs, as 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. The impact of one's first high from alcohol and/or drugs is so powerful that, from anecdotal evidence to studies of the neurobiology of learning and memory (Bornstein & Pickard 2020), scientists have sought to understand the implications of drug experience memories on subsequent use. For instance, a recent review of the literature emphasized that instead of breaking learned associations between drug cues and drug rewards, treatment may be better suited to strengthening existing and/or creating new associations between drug cues and rewards that are drug-inconsistent (Bornstein & Pickard 2020). As one of our patients recently said: "It is like watching your own life in a movie and knowing how that movie is going to end. I will sit on the couch after the kids go to bed, I will feel bored, and I will open a beer" (L.A. Ray, unpublished observation). While discussing problem-solving around this high-risk scenario, we talked about creating "new endings to his movie," such as getting up from the couch and inviting his wife for a walk instead. For such a patient, once enough "new movies" have been played, the story is not quite as predictable, and therefore, outside of his control. A possible translational application of the memory and learning paradigms in the context of clinical practice may be to behaviorally and pharmacologically enhance (Hofmann et al. 2014) the development and consolidation of these new and therapeutic memories, in which drug cues and rewards are drug-inconsistent. From a clinical perspective, too much work has focused on decoupling drug cues and responses and even on trying to literally "erase memories" (Han et al. 2009), whereas the current neuroscientific understanding of learning and memory processes suggests that building new, therapeutic memories may be more fruitful.

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 the (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 (Volkow et al. 2016). In other words, over time, patients experience the urge to use drugs 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 same brain structures responsible for driving the organism toward basic survival needs. While studying the role of alcohol and drug rewards and how animals begin to direct their behavior toward the goal of obtaining and consuming alcohol and drugs, a critical piece of reverse translation has been notable in influential animal models. Specifically, the human phenomenology of addiction recognizes that humans begin to prefer alcohol and drugs over natural rewards while traditional animal models failed to present their "subjects" with alternative rewards. Interestingly, a recent study by Venniro et al. (2018) showed that when presented with an alternative social reward (e.g., social interaction

with another rat) or access to a drug (heroin or methamphetamine), animals consistently chose social interaction. Similarly, another recent study of alcohol self-administration in rats found that when presented with an alternative high-value reward (i.e., sugar), only 10–15% of the animals showed a preference for alcohol and developed "alcohol-related problems" (Augier et al. 2018). In other words, when the human condition fully informed animal models and alternative rewards were presented to animals, the threshold for alcohol and drug preference changed dramatically, comparable to that seen in behavioral assays without competing rewards. In essence, the results of these high-profile preclinical studies only confirm what clinicians have known for years: that social reinforcement is key to recovery (Archer et al. 2020) and that it takes time to transition from a preference for natural rewards to alcohol and other drugs, something that only a subset of individuals do (Wagner & Anthony 2002). These studies highlight (more than ever) the need for reverse translation and for clinical science to inform translational research.

In clinical terms, while the decision to use alcohol and/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 patients' struggles with addiction and their reports that despite their sincere desire to quit using substances, they feel as though they cannot. This framework may also be useful for psychoeducation because a considerable amount of blame is often placed on the patient by himself or herself as well as by the patient's loved ones. This model effectively distinguishes the initiation of substance use from its continuation 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. The model does not suggest that individuals should give up their sense of agency or self-efficacy (Snoek 2017) because chronic substance use alters the brain's neurocircuitry. Instead, it recognizes that what makes addiction chronic and relapsing is the inherent loss of control and that certain steps are necessary to remediate these neuroadaptive processes.

Perhaps one reason why it is hard to recognize that chronic substance use may lead to such a loss of control over voluntary behavior is that preclinical and clinical models of addiction are often not well aligned. While animal models of addiction typically produce very high alcohol and drug exposure and are often accompanied by significant withdrawal and alcohol and/or drug seeking, the current DSM-5 criteria for substance use disorder (SUD) are broad and include mild-to-severe presentation. In simple terms, addiction in a translational sense is not equivalent to alcohol use disorder (AUD)/SUD, especially mild-to-moderate AUD/SUD. If a patient presents with mild AUD/SUD, the case conceptualization will not include such severe dysregulation in volitional decision making and self-control and will largely consist of outpatient models of care. For AUD, we may go even further to suggest that controlled drinking may be a suitable goal in mild-to-moderate cases (Mann et al. 2017). The field of addiction does itself a disservice by using terms like AUD/SUD and addiction interchangeably, which contributes to the disconnect between a brain-based conceptualization of addiction (Volkow & Morales 2015, Volkow et al. 2016) and one that frames addiction as a pathology of choice (Bickel et al. 2014). For example, it has been argued that the brain disease model is "neurocentric" and ignores the fact that people use drugs and sustain their addiction because substances temporarily relieve their pain (Satel & Lilienfeld 2017). This is a valid argument but is not incompatible with the brain disease model if one considers that

addiction is represented by the end stage of the disease progression. In other words, both can be true. Substance use can be driven by the relief of pain at its early stages and lead to a stage of neural dysregulation that is so severe as to cause major impairments in inhibitory control. It is important to emphasize that this review is not about espousing a neurocentric view of addiction as a brain disease. Instead, we recognize that progress in addiction science occurs with both neuroscience and behavioral science methods and theories. However, for these discoveries to become clinically useful, an integration of both basic and clinical science is sorely needed. To that end, we are less concerned with being right in terms of what addiction really is and are more focused on effective ways of thinking about how scientific discoveries, both basic and applied in nature, can be leveraged to improve patient care.

Toward understanding how the brain changes in response to chronic substance use, recent theorizing has argued for a dissociation of mechanisms of reward based on the incentive-sensitization theory of addiction. In particular, the basic neuroscience of addiction suggests that reward may be parsed into the "liking" of a drug and the "wanting" of it (Robinson & Berridge 1993). The opioidergic system in the brain is thought to underlie mechanisms of drug liking, while the dopaminergic pathway is primarily responsible for the wanting of the drug—that is, 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, are 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. This should not be at the expense of the psychosocial aspects of addiction. To the contrary, understanding of the psychosocial components of addiction has been most fruitful in informing treatments to date, while the translation of neuroscientific knowledge to addiction therapeutics has been slow to materialize (Egli 2018, Heilig et al. 2016). The key tenet of this review is that integrating clinical and neuroscientific knowledge of addiction is a worthwhile endeavor that can elevate both disciplines and, ultimately, patient care.

PHENOMENOLOGY AND NEURAL BASES FOR WITHDRAWAL, TOLERANCE, AND POSITIVE AND NEGATIVE REINFORCEMENT

Tolerance and withdrawal are two important symptoms of substance dependence and are recognized in DSM-5 as indices of physiological dependence. These symptoms represent physical consequences of repeated substance use on acute intoxication (i.e., tolerance) and on an organism's response to the substance being taken away (i.e., withdrawal) after chronic use. Through repeated alcohol or drug use, the brain becomes desensitized to the same amount of the substance, 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, resulting in a sudden shift in the homeostatic set point and the onset of physiological symptoms that are the opposite of intoxication. In other words, withdrawal is a counteradaptive process to the removal of the drug after heavy chronic use. 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 because the organism is trying to reestablish homeostasis.

The allostatic model of addiction seeks to explain the intricate balance between positive and negative reinforcement in addiction (Koob & Le Moal 1997, Koob & Schulkin 2019). This neurobiological model of addiction is informed by the Opponent Process Theory, which was developed by Solomon & 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, i.e., the *a*-process) and more about negative reinforcement (the counteradaptive opponent process, i.e., the *b*-process) (Ahmed & Koob 2005). This theory seeks to capture the dynamic nature of addiction neurobiology as the brain continuously adapts to large amounts of a given substance 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 & Schulkin 2019). During the reinforcing effects of alcohol intoxication (*a*-process), there are increases in GABAergic activity, opioid peptides, and dopamine output in the ventral striatum, which represent the neural substrates of alcohol reward. During the counteradaptive opponent process marked by negative affect and withdrawal, there is an increase in corticotropin-releasing factor (CRF) activity and a decrease in neuropeptide Y, both of which are key neuromodulators of stress reactivity (Koob & Kreek 2007, Koob & Schulkin 2019).

Together, these processes provide the neural basis of reward and negative reinforcement associated with alcohol intoxication and withdrawal, respectively. Over time, the shift in the balance from positive to negative reinforcement is thought to explain what many patients describe in their experiences with alcohol and other drugs—namely, that their reason for using these substances is no longer to feel good but, instead, to avoid feeling sick. In other words, patients often describe using drugs and/or alcohol to feel normal—a description that is consistent with the allostatic model hypothesis that neuroadaptation in the brain reward circuitry leads to chronic deviation in the brain's reward set point (Koob & Le Moal 1997). In this context, it may be useful for clinicians and patients alike to recognize that from a biological standpoint, chronic and heavy alcohol use causes individuals to drink primarily to alleviate withdrawal and its associated unpleasant affective and physical symptoms.

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 have demonstrated that dopaminergic function is compromised during acute withdrawal (Weiss et al. 1996). Animal models have also emphasized the role of dysregulation in the brain stress system, including CRF-mediated processes, resulting in changes to reward function leading to negative reinforcement (Koob & Kreek 2007, Koob & Schulkin 2019). Ethanol is a powerful modulator of stress systems, and when it is removed from the brain, through abstinence, powerful anxiogenic-like effects 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 can be traced to the neurobiology of neuroadaptations to chronic and heavy substance use.

Clinical research, including ours, has sought to characterize reward and relief processes in clinical samples. In a host of laboratory studies in which individuals received standard doses of alcohol, we found that the positive reinforcing effects of alcohol (i.e., stimulation and positive mood) were associated with alcohol craving in heavy drinkers without AUD but not in individuals with AUD (Bujarski & Ray 2014). These findings were extended in an independent sample, and it was

demonstrated that the reinforcing effects of alcohol were salient determinants of subjective craving in lagged models of subjective response to alcohol and subsequent subjective craving across a range of light drinkers, heavy drinkers, and drinkers with AUD (Bujarski et al. 2017). In a study combining an intravenous alcohol challenge with alcohol self-administration using a progressive ratio model, we did not observe a relationship between AUD severity and subjective response (Bujarski et al. 2018). AUD severity was associated with greater baseline negative mood, sedation, and craving but did not moderate the relationship between subjective response and subsequent self-administration. This finding did not support our prediction based on the allostatic model that higher-severity individuals would show self-administration of alcohol driven by negative reinforcement while lower-severity individuals would self-administer for positive reinforcement. A longitudinal study including alcohol administration in the laboratory found support for the early-stage phase of the allostatic model, such that heavy drinkers who exhibited heightened reward sensitivity and stimulation in response to alcohol were more likely to progress to AUD (King et al. 2016). In brief, experimental psychopathology studies of the subjective rewarding effects of alcohol and negative affect relief have generally provided support for predictions from the allostatic model but only for the early stage of the model. The "dark side of addiction" proposed by the model has not been reliably supported, in large part because experimental studies rely heavily on healthier and younger individuals with more mild AUD presentations (Ray et al. 2017b, Rohn et al. 2017). The disconnect between AUD severity in experimental psychopathology research samples and treatment research samples has been identified as a crucial opportunity for more efficient translation, whereby clinical samples ought to express the pathology severity necessary to fully access the target constructs described in neurobiological models (Ray et al. 2021).

Translation of the allostatic model to clinical samples with AUD has received increased attention. In the treatment domain, it has been argued that clinical response to naltrexone, an opioid antagonist, may be stronger among individuals who report more positive reinforcement for alcohol (Roche & Ray 2015). This line of inquiry overlapped with efforts to identify genetic markers of susceptibility for alcohol reward and for naltrexone responsivity in the lab (Ray & Hutchison 2004, 2007) and in the clinic (Anton et al. 2008, Oslin et al. 2015). While this research did not produce the reliable effects required to predict naltrexone response based on the reward drinking genotype, recent studies using self-report measures of drinking motives have shown that the effect size for treatment with naltrexone is significantly higher among individuals who report drinking for positive reinforcement compared with individuals who drink to alleviate negative feelings or for normalization (Mann et al. 2018). Collectively, these findings suggest a potential convergence of neurobiologically informed phenotypes and clinical phenotypes that can effectively improve treatment for AUD in a meaningful fashion.

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) that considers 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 an ability 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 to refine human models that can effectively translate insights from basic neuroscience. Reverse translation is equally important, as highlighted throughout this review. A combination of novel experimental methods with clinical populations, such as progressive ratio models of alcohol self-administration in humans, along with novel data analytic methods (e.g., machine learning), may ultimately prove useful, as was recently demonstrated (Grodin et al. 2020). Nevertheless, a key feature of any model, data-driven or otherwise, is the opportunity to investigate clinically meaningful phenomena with high potential for discoveries that can affect patient care.

HABIT, COMPULSION, OR GOAL-DIRECTED CHOICE

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 and/or drugs to be highly reinforcing and even memorable (Bornstein & Pickard 2020). But while alcohol and drug use is goal-directed during the initiation and escalation of substance use, it is thought to become habitual as addiction ensues and progresses. The transition from goal-directed to habitual behavior is critical, and evidence suggests that even when the reward is no longer valued, it will be sought out and consumed (Everitt & Robbins 2016). This transition has been documented in preclinical models (Everitt & Robbins 2016) that provide a potential parallel to the phenomenology of addiction in humans, which is marked by continued use despite consequences and recognition that although the drug reward is no longer valued at the psychological level, its consumption has become habitual and through neuroadaptive processes has produced physiological dependence (i.e., tolerance and/or withdrawal).

Habit-driven behaviors are executed automatically without careful consideration of their consequences (Graybiel 2008) and are marked by an absence of goal-directed behavior (Vandaele & Janak 2018). Thus, habits are typically defined as insensitive to manipulations of the outcome or action–outcome contingency. There has been much interest in understanding the brain's habit networks and its implications for a host of behavioral disorders, including addiction (Dolan & Dayan 2013, Malvaez & Wassum 2018, Smith & Graybiel 2016). An overreliance on habit learning strategies may be phenotypically expressed in individuals with addiction (Sjoerds et al. 2013). In the context of addiction, overreliance on habit may account for the continued substance use despite a host of negative consequences.

Basic neuroscience has implicated homologous brain regions across species in neural circuits that subserve goal-directed and habitual actions (Balleine & O'Doherty 2010), with the putamen and dorsolateral striatum playing a large role in the habitual control of behavior (Malvaez & Wassum 2018). Further, the difficulty of breaking habits in addiction may be due in part to maladaptive alterations in goal-directed brain systems (i.e., higher-order prefrontal regions) (Morris et al. 2018), such that the individual can no longer revert to goal-directed strategies in the face of adverse consequences. While habits may play a critical role in addiction, this role may not be uniformly salient across stages of the addiction cycle. In other words, while habits represent a possible strategy for acting, such a strategy may become more prominent at higher levels of addiction severity. For instance, it has been postulated that compulsive alcohol use is characterized by a shift of cue processing from the ventral to the dorsal striatum (Vollstädt-Klein et al. 2010). In our own work, we have sought to dissociate ventral-to-dorsal striatal functional connectivity by focusing on a genetic marker associated with reward drinking (Ray et al. 2014). This notion of a shift in the processing of alcohol/drug cues from the ventral to the dorsal striatum is consistent with the incentive-sensitization model of addiction, whereby compulsive alcohol use is under the control of the dorsal striatum (Everitt & Robbins 2005). The transition to habit-driven behavior

may be seen as compatible with the allostatic model of addiction, whereby later stages of addiction are characterized by compulsivity (Koob & Volkow 2010). Compulsive use is thought to reflect the use of a substance despite the negative consequences associated with such use, which can be considered habitual use or the result of poor goal-directed decision making.

As the neuroscientific understanding of goals and habits in the brain has expanded significantly, the translation of these findings to clinical populations remains a high-priority area. Habit learning, and its underlying neurocircuitry, has been recently investigated in clinical samples using neuroimaging tools (Grodin et al. 2018, Sebold et al. 2017, Sjoerds et al. 2013). Neuroimaging is well suited to provide a mechanistic understanding of habit circuits in clinical populations. Additional work has examined the behavioral correlates of habit in substance-using populations (Luijten et al. 2020, Voon et al. 2015), indicating that this phenomenon can be studied using task-based behavioral assessments. The neuroscientific literature published thus far suggests that insights into habitual actions from clinical and behavioral observations may help uncover translatable assessments that are cost-effective and clinically useful. To that end, our group has examined habit through patterns of daily drinking and cigarette smoking across a 30-day period (Ray et al. 2020). Self-report measures of habit were robustly positively associated with clinical severity of drinking and smoking. However, interclass correlation and autocorrelation AR(7) coefficients, the behavioral measures of "patterness" and putative habit, were not associated with scores on the self-report habit index. In a related effort, we sought to characterize individuals as reward, relief, or habit drinkers according to clinically derived scales, and our validation efforts showed that habit drinking was not distinguishable from relief drinking in our sample (Grodin et al. 2019). In sum, these studies suggest that habit-driven substance use remains a difficult phenotype to reliably access in clinical samples, and this challenge thus hinders the potential for a meaningful translation. Empirical support for habit-based addiction models is limited in the preclinical literature (Hogarth 2020), and instead addiction may be better characterized as a poor goal-directed choice than as a habit-driven response.

A key element of habitual behavior is that it can be elicited and even controlled by cues. Through Pavlovian learning mechanisms, stimuli associated with a given 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 et al. 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 delivery of the drug itself. Interestingly, when cues are not followed by the reward [i.e., prediction error (PE)], there is a dip in dopamine firing as though the system were responding to the absence of the reinforcer with below-normal levels of dopaminergic activity. These fascinating animal findings are closely tied to clinical presentation of addiction in humans, which is marked by intense cue-induced craving and drug seeking—cues that patients often describe as beyond their conscious awareness. In our studies, we have used functional neuroimaging to approximate a clinically relevant reward PE task in humans. We trained participants to expect that they would see a cue for water and receive a taste of water and that they would see a cue for alcohol and receive a taste of alcohol. We then violated those assumptions to evoke positive (expect water and receive alcohol) and negative (expect alcohol and receive water) PEs (Cservenka et al. 2017). Across the entire sample of participants, positive PE-related brain activation was found in a large cluster comprising frontal lobe regions, the insular cortex, and motor and sensory cortices. Compared with social drinking subjects, alcohol-dependent subjects had greater positive PE-related brain activity in the left superior parietal lobule, lateral occipital cortex, and postcentral gyrus. Beyond

the patterns of activation, this study found that the PE signal was sparse and temporally distinct, such that it was detectable only in a few "early" trials. Once individuals began to expect violations of their predictions, the signal faded. This finding highlights the complexity of capturing neuroscientific phenomena in a clinically meaningful fashion. The challenges underscore the need for clinical science to inform the translation of neuroscientific findings.

In a recent paper, Hogarth (2020) reviewed the evidence for three neurobiological theories of addiction: addiction as an overlearned habit (not sensitive to the consequences), addiction as a compulsion that is not sensitive to punishment, and addiction as a goal-directed (but poor) choice. He concluded that goal-directed theory encompasses situations in which the goal of substance use is driven by expectations that it will relieve unpleasant feelings, and he suggested that there is more support for addiction as a goal-directed choice than for addiction as a habit or compulsion. In a thoughtful response to Hogarth's (2020) paper, Epstein suggested that these theories are not so competing (Epstein 2020). In an argument akin to what is laid out in this review, Epstein suggested that rather than a winner-take-all approach to competing theories, cross-level explanations should be considered in which many theories of addiction can be true, and the goal should instead be to determine when, for whom, and to what extent these theories apply. These considerations align with the overarching goal of this review to consider heterogeneous clinical phenomena, such as addiction, from multiple perspectives and with an emphasis on their clinical application (the "when," "for whom," and "to what extent" questions).

INCENTIVE-SENSITIZATION: THE WANTING AND THE LIKING

One prominent theory of addiction is the incentive-sensitization model. The basic tenets of this theory are that drugs of abuse share the ability to alter brain organization (i.e., produce neuroadaptation) in the brain reward systems and thus render the systems 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 demonstrated that sensitization operates primarily at the reward subcomponent termed incentive salience, which is marked by drug craving (i.e., 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 et al. 2009). Importantly, Berridge et al. (2009) have argued that sensitization is not simply an inevitable pharmacological consequence of repeated drug use but instead is modulated by environmental factors associated with alcohol and drug intake. 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.

The treatment implications of 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 has not been 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 overgeneralizability of the conditioned response. It is plausible that alcohol and drug use is accompanied by a wide variety of cues, both internal (e.g., affective states such as negative mood) and external (e.g., places, people, things). To that end, it is simply not feasible to devise exposure exercises that effectively target all such triggers. Nevertheless, functional analysis of behavior is often effective in identifying 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 these effective interventions is the conceptualization of triggers as learned processes that are biologically based and that may evoke the unwanted, yet learned, behavioral response of alcohol or drug use leading to relapse.

Learning theory is particularly useful for 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 often studied in the form of long-term potentiation, 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. Just as the rewarding properties of alcohol and drugs operate within the same neurocircuits responsible for normal reward functions in the brain, Pavlovian (or associative) learning during addiction operates through the same signaling pathways that subserve nonpathological forms of learning (Robinson & Berridge 2008). In basic terms, individuals with AUD/SUD have learned to form associations between triggers and alcohol/drugs through the same biological mechanisms that allow people to associate their favorite restaurants with food.

Neuroimaging studies have shown that the presentation of alcohol or drug cues, compared with control cues, reliably produces increases in blood flow in brain areas associated with reward (nucleus accumbens, VTA, insula) (Filbey et al. 2008) and affect regulation (amygdala) (Childress et al. 1999). A meta-analysis by Schacht et al. (2013) summarized the neural circuitry known to be involved in cue reactivity. Specifically, it has been shown that alcohol cues elicit robust activation of limbic and prefrontal regions, including the ventral striatum, anterior cingulate cortex, and ventromedial prefrontal cortex, in individuals with AUD. Compared with controls, individuals with AUD showed greater activation of parietal and temporal regions, including the posterior cingulate cortex, precuneus, and superior temporal gyrus. Cue-elicited activation of the ventral striatum was most frequently correlated with behavioral measures and reduced by treatment (Courtney et al. 2016). Importantly, while brain activation has been correlated with the subjective experience of craving, captured via self-reports, the correlation is far from perfect and, in some cases, is not present at all (Filbey et al. 2009). This finding suggests that while craving is under conscious awareness, some of it may be subcortical in nature and perhaps inaccessible to patients. That suggestion is consistent with patient reports of being on "autopilot" and having little awareness of their craving levels during a lapse. The use of functional magnetic resonance imaging–based cue reactivity holds promise for screening AUD/SUD treatments and provides a proof-of-mechanism for treatments thought to reduce the incentive salience of alcohol and drugs (Grodin & Ray 2019).

In addition to the learning mechanisms discussed above, protracted withdrawal represents another biologically based response to the removal of a given drug 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 longer-lasting physical and psychological symptoms (Heilig et al. 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 longer-lasting disruption in excitatory and inhibitory neurotransmission resulting from chronic alcohol and/or drug 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 effects 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, such as spending time with loved ones. 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 (Volkow et al. 2001).

The process of brain recovery from addiction is gradual. And while clinical neuroscience cannot effectively estimate how much one's brain will recover and over what period of time, 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 (the use of which can lead to "dopamine leakages"), were damaged (relative to controls) in the brains of patients who died of methamphetamine overdose. Seminal work using positron emission tomography 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. 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 major implication is the notion that sustained recovery is required to fully experience the benefits of abstinence. Patients and their families should adopt a long-term perspective with regard to the behavioral aspects of the recovery process (e.g., building a life worth living, repairing relationships) but also with regard to the neurocognitive and affective benefits of sustained abstinence. The debate about what constitutes recovery and the need to include functional outcomes in addition to alcohol/drug use outcomes has become increasingly salient in the field (Kiluk et al. 2019, Ray et al. 2019b), and there is clearly a need for heavy involvement from clinical psychologists. For example, evidence suggests 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 low in potency compared with drug rewards. 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, the neuroscience of addiction has elucidated several neural circuits that underlie the behavioral expression of tolerance, craving, and withdrawal, which are critical to understanding patients' 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. This also requires a significant involvement of clinical psychologists in the field of addiction. As recently articulated by Dimoff et al. (2017), the field of clinical psychology has not kept up with the rising substance use epidemic, and the workforce of clinical psychologists receives only modest training in the AUD/SUD domains. Thus, building a workforce of clinical psychologists who are prepared to address addiction issues in science and practice is a critical first step, followed by scientific and clinical training that is as interdisciplinary as addiction itself.

THE ROLE OF GENETIC FACTORS IN ADDICTION ETIOLOGY AND TREATMENT

Behavioral genetic research has convincingly demonstrated that a sizable proportion of the risk for 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 et al. 2000). Research studies have also demonstrated that the genetic loading for SUDs is largely shared across disorders, as opposed to being substance specific. For example, a twin study found that the genetic liability for SUDs 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 et al. 2003). Studies of adolescent samples have found strong shared genetic loading across SUDs and conduct disorder (Button et al. 2007). More broadly, studies have found that multiple SUDs and conduct disorder/antisocial personality disorder may cluster into externalizing disorders, which share a large proportion of genetic risk factors (Amstadter et al. 2016). In short, genetic research has supported the heritability of SUDs and has suggested that most of the genetic risk is shared across substances of abuse and even across other forms of externalizing psychopathology.

Despite rapid advances in genetic sequencing technologies, 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, numerous studies have examined candidate genes for AUD and SUD (Bierut 2011, Gelernter & Kranzler 2009). While some reliable candidate genes have emerged (e.g., alcohol dehydrogenase polymorphisms) (Kranzler et al. 2019), the vast majority of the candidate genes studied to date have produced mixed and inconclusive results (Ducci & Goldman 2008), and the same is true for gene × environment interactions (Duncan & Keller 2011). There is increasing recognition in the field that common psychiatric disorders, such as addiction, may result from the interplay among multiple genes of relatively small effect.

The field of genetics has moved from a hypothesis-driven candidate-gene approach to a data-driven hypothesis-generating method—namely, genomewide association studies (GWASs) (Cichon et al. 2009). In fact, the transition to GWASs has been so sharp that it has been argued that GWASs have made candidate-gene studies obsolete (Duncan et al. 2019). GWASs represent a discovery-based approach that analyzes an array of common single-nucleotide polymorphisms (SNPs) across the entire genome without an a priori hypothesis about a specific gene or pathway. Theoretically, GWASs can identify all the common genetic variants associated with a state or disease. Over the last several years, GWASs have found that variations in the genes encoding the alcohol-metabolizing enzymes are among the common variants with the largest effect on AUD risk (Reilly et al. 2017). GWAS sample sizes tend to increase with recency of publication, and yet the alcohol-metabolizing enzyme genes account for the most consistent overall findings for GWASs of AUD to date (Edenberg et al. 2019), replicating findings from candidate-gene and linkage studies. However, these recent results were somewhat discouraging because it was expected that GWASs would identify novel and unexpected variants that would enhance our understanding of the genetics of complex traits including AUD. In reality, large sample sizes are required to achieve statistical power to detect small effects, especially for complex diseases such as psychiatric disorders and addiction. In addition, very conservative statistical corrections are required to control for multiple testing of the more than one million SNPs that are typically investigated in a

single GWAS. A Bonferroni-corrected genomewide significance threshold set at $p < 10^{-8}$ is typically required. Furthermore, the heritability explained by SNP associations is less than estimates of heritability derived from family studies. The variants that reach statistical significance typically explain only a small fraction of the heritability, a phenomenon commonly referred to as "missing heritability" (Manolio et al. 2009). Several hypotheses have been put forward to explain missing heritability, such as undetected rare variants of large effect, epistatic interactions, and the notion that heritability estimates from family studies may be overinflated (Golan et al. 2014, Zuk et al. 2012).

It is well established that AUD risk is the result of multiple genes, environmental factors, and interactions across genes and gene × environment. To account for multiple genetic markers simultaneously, polygenic risk scores can be estimated from GWAS data to provide a quantitative measure of the cumulative effects of common genetic variance across the entire genome on risk for a disorder. Risk scores are calculated as a weighted sum of the number of risk alleles at the selected SNPs carried by a person. The weight is obtained from the effect size associated with the SNPs. These scores can be compared between persons and phenotypes. Polygenic risk scores have had some success in predicting AUD risk in individuals (Kos et al. 2013); however, a recent genomewide meta-analysis of AUD showed that these scores explained only 0.3–1.7% of the variance in alcohol use and misuse phenotypes (Walters et al. 2018).

In sum, the GWAS approach is beginning to uncover novel biology that subserves AUD/SUD but will require further testing and confirmation, especially functional validation. To some extent, the field of psychiatric genetics has moved toward even larger sample sizes leading to meta-analyses of GWASs in hopes of detecting reliable markers of risk for complex phenotypes (Gershon et al. 2011). A comprehensive understanding of the genetic aspect of AUD may reveal potential targets for new pharmacotherapies and may also open avenues for personalized medicine. To that end, an 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 (Jones et al. 2015). While there is enthusiasm for predicting treatment response based on genetic factors, as well as pitfalls (Tate & Goldstein 2004), the consensus is that precision medicine approaches based on genetic markers are not yet ready for clinical implementation for AUD (Hartwell & Kranzler 2019, Nieto et al. 2020).

NOVEL BIOLOGICAL MECHANISMS

Inflammation and Neuroinflammation

Over the past decade, evidence has accumulated implicating the interplay of the brain, behavior, and the immune system in the development and maintenance of addiction. Alcohol is theorized to increase neuroinflammation through two pathways: (*a*) a peripheral pathway through which gut microbes activate innate immune cells, resulting in the production of proinflammatory cytokines that cross the blood–brain barrier; and (*b*) actions directly in the brain, where proinflammatory immune molecules are released through cross talk between neurons and glia (Mayfield & Harris 2017).

The first evidence for the involvement of the immune system in AUD came from the identification of changes in expression of neuroimmune genes and microglial transcripts in postmortem brains of individuals with AUD (He & Crews 2008, Liu et al. 2006). These findings were reverse-translated to rodent models, in which chronic ethanol exposure altered glial and immune gene expression (McBride et al. 2013, Qin et al. 2008). Moreover, mice lacking immune genes demonstrated reduced alcohol intake across ethanol intake paradigms (Blednov et al. 2012), whereas activation of the immune system through lipopolysaccharide promoted ethanol

consumption and preference (Blednov et al. 2011). Support for the role of neuroinflammation in AUD in humans has been largely correlational. Individuals with AUD have elevated serum levels of proinflammatory cytokines (Heberlein et al. 2014, Leclercq et al. 2014a), and levels of the proinflammatory cytokine interleukin-6 were correlated with breath alcohol concentration.

The immune system is also thought to play a role in the withdrawal and negative reinforcement stages of addiction. There is a substantial literature implicating inflammatory factors in depression (Roman & Irwin 2020). In animal models, alcohol withdrawal results in the rapid induction of proinflammatory cytokines in the central nucleus of the amygdala (Freeman et al. 2012) and in the striatum (Pascual et al. 2015), the latter of which has been associated with an increase in anxiogenic-like behavior (Pascual et al. 2015). These data suggest that neuroinflammation is involved in withdrawal and may contribute to the anxiogenic processes that drive negative reinforcement.

Given the accumulating evidence for alcohol-neuroimmune signaling, significant efforts have been made to develop and refine pharmacotherapies with neuroimmune targets. Many preclinical studies have investigated the modulation of the neuroimmune system through various mechanisms including inhibition of toll-like receptors (TLRs), disruption of the TLR signaling cascade, inhibition of phosphodiesterases (PDEs), and activation of peroxisome proliferator-activated receptors (for a recent review, see Erickson et al. 2019). The translation of this work to clinical samples has begun, but the obstacles of moving preclinical findings to human testing—a transition known as the "valley of death" in medications development—still remain (Ray et al. 2018). Despite the substantial obstacles, there are several pharmacotherapies with neuroimmune targets that have shown promising early-stage clinical results. Ibudilast, a nonselective PDE inhibitor, decreased tonic craving and improved mood following stress and alcohol cue exposure in a human laboratory study of individuals with AUD (Ray et al. 2017a). Ibudilast has also shown promise in the treatment of opioid use disorder (Cooper et al. 2016) and methamphetamine use disorder (Worley et al. 2016). Minocycline, a tetracycline antibiotic with independent immune actions, decreased the positive subjective effects of a stimulant in a small study of healthy volunteers (Sofuoglu et al. 2011). Many clinical trials are underway investigating neuroimmune-related compounds (Erickson et al. 2019), further demonstrating the field's enthusiasm for the potential therapeutic benefit of neuroimmune modulation.

The Microbiome and the Gut–Brain Axis

Another emerging area of considerable interest is the impact of the gut microbiome and the gut–brain axis on AUD and SUD. The gut microbiome consists of approximately 10 million genes—about 150 times the number of genes found in the human genome (Gilbert et al. 2018). Within an individual's gut, an estimated 500–1,000 species of bacteria exist at any one time. The gut microbiome supports intestinal homeostasis, producing beneficial metabolites while protecting the host from colonization by pathogenic bacteria (Belkaid & Hand 2014). Similar to allostasis, dysbiosis arises when the normal gut microbiota are imbalanced, and this condition can lead to the development of disease (Rogers et al. 2016). Critically, alterations to the microbiome can have significant effects on the brain and behavior (Heijtz et al. 2011, Kiraly et al. 2016).

Although clinical research will be crucial for the understanding of the gut–brain axis, preclinical animal models provide invaluable tools to develop a mechanistic understanding of gut–brain signaling. There are two prominent animal model paradigms for this purpose: germ-free animals and antibiotic-induced microbiome depletion. Germ-free animals lack an internal microbiome and are raised in a sterile environment; these animals can then be colonized with microbial communities to investigate whether the donor microbiome contributes to a behavior of interest (Luczynski et al.

2016). The antibiotic–depletion paradigm uses broad-spectrum antibiotics to reduce gut bacteria (Zarrinpar et al. 2018). Both paradigms have been used to demonstrate the role of the microbiome in depression- and anxiety-like behavior (Wong et al. 2016), which can be altered through fecal microbial transplants (Heijtz et al. 2011). Mechanistic studies interrogating the role of the microbiome in AUD and SUD have been more limited; however, emerging evidence implicates dysbiosis in AUD/SUD (Meckel & Kiraly 2019). Dysbiosis has been found in response to alcohol, opioids, and psychostimulants in animal models (Kiraly et al. 2016, Lee et al. 2018, Peterson et al. 2017). Jadhav et al. (2018), using a mouse model, attempted to replicate the clinical diagnostic criteria for AUD and found associations between the composition of the gut microbiome and vulnerability to AUD. This type of reverse-translational research is critical to understanding developmental risk factors for AUD and SUD.

Gut dysbiosis has been found in clinical samples with AUD and SUD, although the pattern of changes does not appear to be consistent within and across drug classes. Studies of AUD have shown that the type of alcohol consumed influences the effect of the microbiome (Engen et al. 2015), and there are known interactions between the gut microbiome and liver disease (Tripathi et al. 2018), indicating that the presence or absence of alcoholic liver disease will also affect microbiome profiles. Despite these caveats, there is growing preclinical and clinical evidence that alcohol increases intestinal permeability (Leclercq et al. 2014a,b), thereby allowing gut bacteria to translocate into the circulatory system and sometimes cross the blood–brain barrier to induce neuroinflammation. As preclinical and clinical studies have found gut dysbiosis in individuals with AUD and SUD, there is increased interest in the development and refinement of therapeutics targeting microbial signaling. Psychobiotics, which are defined as both probiotics (beneficial bacteria) and prebiotics (support for these beneficial bacteria) that influence bacteria–brain behavior, have been proposed as a treatment for AUD (de Timary et al. 2017). However, clinical trials need to be conducted to evaluate whether psychobiotics are beneficial to the treatment of AUD and SUD.

MULTIFINALITY OF COMPLEX PHENOTYPES AND TRANSDIAGNOSTIC RISK FACTORS

Inherent in the concept of a complex phenotype is the recognition that there is not a single path into this disorder, nor is there is 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—in this case, disorder—may result from different mechanisms. This notion is consistent with the recognition that addiction is rather heterogeneous and that multiple efforts are needed to further parse out this clinical phenotype using typologies, age of onset, family history, and other variables of high etiological (Leggio et al. 2009) and clinical (Grodin et al. 2019) significance. 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. More recently, we have compelling evidence that delayed reward discounting may not be a risk factor unique to addiction (Amlung et al. 2019). The bifurcation in a multifinality 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, such sharing is often seen in the context of a common liability model operating across a host of psychological disorders (e.g., Røysamb 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 for these disorders as well as

for other forms of psychopathology (i.e., multifinality). Transdiagnostic models of psychopathology cannot easily account for multifinality, an issue that can be overcome through sound clinical psychological science and careful theoretical consideration (Nolen-Hoeksema & Watkins 2011).

So how does the neurobiology of addiction account for these multiple pathways leading to considerable phenotypic heterogeneity? To allow for different paths in and out of a psychopathological outcome, there has been an emphasis on intermediate phenotypes (i.e., endophenotypes) for addiction as well as for other neuropsychiatric disorders (Gottesman & Gould 2003). These phenotypes represent more narrow and 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) (Ray et al. 2016), delayed reward discounting (MacKillop et al. 2011), craving, stress reactivity, and neural response to alcohol or drug cues (Ray et al. 2010). This conceptualization resonates with the Research Domain Criteria (RDoC) approach (Insel et al. 2010) and has been described as a heuristic for the integration of behavioral neuroscience with the study of psychopathology (Sanislow et al. 2010).

The Addictions Neuroclinical Assessment (ANA) was recently proposed as a novel framework for neuroscience-informed assessment that captures three functional domains: incentive salience, negative emotionality, and executive (dys)function (Kwako et al. 2017). This framework aims to understand the heterogeneity in AUD by leveraging deep phenotyping profiles coupled with factor analytic methods (Kwako et al. 2019). While these domains have received initial empirical support (Kwako et al. 2019), validation of the ANA framework in independent clinical samples is needed. The heuristic framework offered in ANA presents new opportunities whereby dysfunctions in these domains may serve as treatment targets. For instance, the ANA can be used to identify novel addiction biomarkers and to refine existing ones (Kwako et al. 2018). To do so would entail filling the translational gaps between behavioral and biological phenotypes, an ongoing challenge in neuroscience and psychology. While there is considerable enthusiasm and potential for an ANA framework, the empirical research on the core constructs of incentive salience, negative emotionality, and executive dysfunction has been limited. It is likely unsurprising to clinical psychologists that despite the sophisticated clinical neuroscience research conducted to date, individual differences in the expression of psychopathological behavior, including addiction, remain elusive, yet so central to optimizing patient care.

SUMMARY AND CONCLUSIONS

The field of clinical psychology, much like the field of psychiatry, has seen a marked increase in biologically oriented research. This is both a result of technological advances and a pendulum swing favoring biologically based explanations to psychopathology, addiction included. By covering a host of prominent theories and models of addiction from neurobiological viewpoints, this review has sought to identify opportunities for translation and, in particular, to argue for the role of clinical psychological science in informing those efforts. From mechanisms of reward processing, learning and memory, allostasis, incentive-sensitization, reward PE, withdrawal, tolerance, goal-directed decision making, habit learning, genetics, inflammation, and the microbiome, the common theme has been to highlight the potential clinical utility of basic neuroscience research and to identify opportunities for clinical science. These efforts are not isolated but rather comprise a set of experiments in which insights from addiction neuroscience are translated to clinical populations through scientific hypotheses and methods that support such inquiry. By systematically testing hypotheses informed by the basic neuroscience of addiction and programmatically translating and reverse-translating their findings, clinical scientists stand to make critical

contributions to the translational science of addiction. While one may rightfully argue that the current state of the field is neurocentric, it is up to clinical scientists to demonstrate the unique utility of a scientific approach that puts clinical translation first and that is grounded in real-world addiction phenomenology in humans. While rats and mice are often the preferred "addiction patients" in the neuroscientific literature, there is renewed effort from our basic science colleagues to make their findings more translatable. One of the chief arguments for clinical neuroscience is that by meeting these efforts halfway with clinically relevant insights and methods, clinical scientists can make unique and transformative contributions to the field of addiction science.

Informed by a previous article (Ray 2012) that outlined a program of research on the clinical neuroscience of addiction and its significance, this review expands considerably on earlier work by providing a host of insights from clinical neuroscience studies undertaken in our laboratory over the past decade. While we continue to move our research forward with a keen interest in translatable neurobiological insights, we clearly recognize the limitations of the neuroscience approaches. The first, most obvious one is that preclinical models have not been fully translated to human samples, and therefore ongoing research is needed to support or refute the applicability of these basic findings to clinical samples. To that end, reverse translation is key and is already underway to a significant degree (Augier et al. 2018, Venniro et al. 2018). It is also critical to recognize that a mechanism is not the same as a cause and that, while the neuroscience of addiction has elucidated a number of important mechanisms related to the expression and maintenance of the addiction phenotype, the cause of addiction that calls the mechanism(s) into action remains elusive (Kalant 2010).

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. The concept of multifinality comes to mind when aligning multiple risk pathways for complex behaviors. Rather than a winner-take-all approach to comparing theories, a more integrative approach that allows for multiple theoretical insights to coexist provides a refreshing and sobering framework (Epstein 2020). In many cases, patients are more interested in the "how-to's" of recovery than in the "whys" of addiction. Clearly, one can inform the other. Recognizing the relative importance and the limitations of all scientific approaches and keeping in mind the common goal of ameliorating the suffering caused by addiction can keep us focused on the end point of scientific inquiry. That is not necessarily to be "right" but, rather, to be helpful and clinically effective. To that end, the thoughtful integration of basic and clinical science provides a powerful tool to fulfill the scientific mission of improving health care. Clinical psychologists have an important role to play in fulfilling this tall order. Training the next generation of clinical scientists and practitioners to integrate their expertise in psychopathology with the underlying neural mechanisms of addiction represents both a challenge and a tremendous opportunity.

SUMMARY POINTS

1. The last three decades in psychological research have been marked by interdisciplinary science, a shift driven in part by the increased accessibility of novel tools for quantifying biomarkers.
2. Addiction represents a prime example of a disorder marked by a complex interaction among psychosocial and biological factors, including genetic predisposition and brain adaption to the pharmacological effects of alcohol and drugs.

3. The field of addiction science often conceptualizes addiction as a chronic and relapsing disorder of the brain, but the notion of addiction as a brain disease is debated.
4. Addiction neuroscientists have become increasingly focused on the translational impact of their work, and this is a unique opportunity for clinical scientists to inform translational efforts.
5. Research has focused on decoupling drug cues and responses, whereas new insights into learning and memory processes suggest that building new and therapeutic memories may be more fruitful.
6. In studies informed by reverse translation, when alternative rewards were presented to animals, the threshold for alcohol and drug preference changed dramatically compared with the outcomes of behavioral assays without competing rewards.
7. The field of addiction science does itself a disservice by using terms like alcohol use disorder (AUD)/substance use disorder (SUD) and addiction interchangeably, which undermines a brain-based conceptualization of addiction.
8. This review does not espouse a neurocentric view of addiction. We recognize that progress in addiction science occurs with both neuroscience and behavioral science and that for these discoveries to become clinically useful, an integration of both is sorely needed.
9. Addiction may be better characterized as a poor goal-directed choice than as a habit-driven choice, as clinical support for the transition to habit-based models of addiction is lacking.
10. Multifinality explains how a common transdiagnostic risk factor may bifurcate into multiple outcomes based on unique genetic and environmental factors.
11. We have reviewed prominent neurobiological models of addiction, identified opportunities for clinical translation, and argued for the key role of clinical psychologists in translational science of addiction.

FUTURE ISSUES

1. Which constructs in addiction neuroscience are translatable to clinical populations? And which are not, thus calling for reverse translation?
2. How can addiction neuroscience constructs be reliably translated to clinical populations?
3. What is the clinical significance of neuroscience-informed assessment and treatment?
4. How can the clinical neuroscience of addiction help close the knowledge gap and allow more evidence-based practices for addiction treatment?
5. How does a brain disease conceptualization of addiction affect the delivery of clinical services and their efficacy?
6. How can clinicians best support self-efficacy in the context of a brain disease conceptualization of addiction?
7. Why have advances in the basic neuroscience of addiction failed to materialize into better treatments for addictive disorders?

8. How can we reliably identify a subset of individuals displaying addiction within the broader range of AUD/SUD diagnoses?

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LITERATURE CITED

Ahmed SH, Koob GF. 2005. Transition to drug addiction: a negative reinforcement model based on an allostatic decrease in reward function. *Psychopharmacology* 180(3):473–90. **https://doi.org/10.1007/s00213-005-2180-z**

Amlung M, Marsden E, Holshausen K, Morris V, Patel H, et al. 2019. Delay discounting as a transdiagnostic process in psychiatric disorders: a meta-analysis. *JAMA Psychiatry* 76(11):1176–86

Amstadter AB, Maes HH, Sheerin CM, Myers JM, Kendler KS. 2016. The relationship between genetic and environmental influences on resilience and on common internalizing and externalizing psychiatric disorders. *Soc. Psychiatry Psychiatr. Epidemiol.* 51(5):669–78. **https://doi.org/10.1007/s00127-015-1163-6**

Anton RF, Oroszi G, O'Malley S, Couper D, Swift R, et al. 2008. An evaluation of μ-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. *Arch. Gen. Psychiatry* 65(2):135–44. **https://doi.org/10.1001/archpsyc.65.2.135**

Archer M, Harwood H, Stevelink S, Rafferty L, Greenberg N. 2020. Community reinforcement and family training and rates of treatment entry: a systematic review. *Addiction* 115(6):1024–37. **https://doi.org/10.1111/add.14901**

Augier E, Barbier E, Dulman RS, Licheri V, Augier G, et al. 2018. A molecular mechanism for choosing alcohol over an alternative reward. *Science* 360(6395):1321–26. **https://doi.org/10.1126/science.aao1157**

Balleine BW, O'Doherty JP. 2010. Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology* 35(1):48–69. **https://doi.org/10.1038/npp.2009.131**

Bedi G, Martinez D, Levin FR, Comer S, Haney M. 2017. Addiction as a brain disease does not promote injustice. *Nat. Hum. Behav.* 1(9):610. **https://doi.org/10.1038/s41562-017-0203-5**

Belkaid Y, Hand TW. 2014. Role of the microbiota in immunity and inflammation. *Cell* 157(1):121–41. **https://doi.org/10.1016/j.cell.2014.03.011**

Berridge KC, Robinson TE. 2003. Parsing reward. *Trends Neurosci.* 26(9):507–13. **https://doi.org/10.1016/S0166-2236(03)00233-9**

Berridge KC, Robinson TE, Aldridge JW. 2009. Dissecting components of reward: 'liking', 'wanting', and learning. *Curr. Opin. Pharmacol.* 9(1):65–73. **https://doi.org/10.1016/j.coph.2008.12.014**

Bickel WK, Johnson MW, Koffarnus MN, MacKillop J, Murphy JG. 2014. The behavioral economics of substance use disorders: reinforcement pathologies and their repair. *Annu. Rev. Clin. Psychol.* 10:641–77. **https://doi.org/10.1146/annurev-clinpsy-032813-153724**

Bierut LJ. 2011. Genetic vulnerability and susceptibility to substance dependence. *Neuron* 69(4):618–27. **https://doi.org/10.1016/j.neuron.2011.02.015**

Blednov YA, Benavidez JM, Geil C, Perra S, Morikawa H, Harris RA. 2011. Activation of inflammatory signaling by lipopolysaccharide produces a prolonged increase of voluntary alcohol intake in mice. *Brain Behav. Immun.* 25(Suppl. 1):S92–105. **https://doi.org/10.1016/j.bbi.2011.01.008**

Blednov YA, Ponomarev I, Geil C, Bergeson S, Koob GF, Harris RA. 2012. Neuroimmune regulation of alcohol consumption: behavioral validation of genes obtained from genomic studies. *Addict. Biol.* 17(1):108–20. **https://doi.org/10.1111/j.1369-1600.2010.00284.x**

Bornstein AM, Pickard H. 2020. "Chasing the first high": memory sampling in drug choice. *Neuropsychopharmacology* 45(6):907–15

Bujarski S, Hutchison KE, Prause N, Ray LA. 2017. Functional significance of subjective response to alcohol across levels of alcohol exposure. *Addict. Biol.* 22(1):235–45. **https://doi.org/10.1111/adb.12293**

Bujarski S, Jentsch JD, Roche DJO, Ramchandani VA, Miotto K, Ray LA. 2018. Differences in the subjective and motivational properties of alcohol across alcohol use severity: application of a novel translational human laboratory paradigm. *Neuropsychopharmacology* 43(9):1891–99. **https://doi.org/10.1038/s41386-018-0086-9**

Bujarski S, Ray LA. 2014. Subjective response to alcohol and associated craving in heavy drinkers versus alcohol dependents: an examination of Koob's allostatic model in humans. *Drug Alcohol Depend.* 140:161–67. **https://doi.org/10.1016/j.drugalcdep.2014.04.015**

Button TM, Rhee SH, Hewitt JK, Young SE, Corley RP, Stallings MC. 2007. The role of conduct disorder in explaining the comorbidity between alcohol and illicit drug dependence in adolescence. *Drug Alcohol Depend.* 87(1):46–53. **https://doi.org/10.1016/j.drugalcdep.2006.07.012**

Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. 1999. Limbic activation during cue-induced cocaine craving. *Am. J. Psychiatry* 156(1):11–18

Cichon S, Craddock N, Daly M, Faraone SV, Gejman PV, et al. 2009. Genomewide association studies: history, rationale, and prospects for psychiatric disorders. *Am. J. Psychiatry* 166(5):540–56. **https://doi.org/10.1176/appi.ajp.2008.08091354**

Conklin CA, Tiffany ST. 2002. Applying extinction research and theory to cue-exposure addiction treatments. *Addiction* 97(2):155–67

Cooper ZD, Johnson KW, Pavlicova M, Glass A, Vosburg SK, et al. 2016. The effects of ibudilast, a glial activation inhibitor, on opioid withdrawal symptoms in opioid-dependent volunteers. *Addict. Biol.* 21(4):895–903

Courtney KE, Schacht JP, Hutchison K, Roche DJ, Ray LA. 2016. Neural substrates of cue reactivity: association with treatment outcomes and relapse. *Addict. Biol.* 21(1):3–22. **https://doi.org/10.1111/adb.12314**

Cservenka A, Courtney KE, Ghahremani DG, Hutchison KE, Ray LA. 2017. Development, initial testing and challenges of an ecologically valid reward prediction error fMRI task for alcoholism. *Alcohol Alcohol.* 52(5):617–24. **https://doi.org/10.1093/alcalc/agx037**

de Timary P, Stärkel P, Delzenne NM, Leclercq S. 2017. A role for the peripheral immune system in the development of alcohol use disorders? *Neuropharmacology* 122:148–60. **https://doi.org/10.1016/j.neuropharm.2017.04.013**

Dimoff JD, Sayette MA, Norcross JC. 2017. Addiction training in clinical psychology: Are we keeping up with the rising epidemic? *Am. Psychol.* 72(7):689–95

Dolan RJ, Dayan P. 2013. Goals and habits in the brain. *Neuron* 80(2):312–25. **https://doi.org/10.1016/j.neuron.2013.09.007**

Ducci F, Goldman D. 2008. Genetic approaches to addiction: genes and alcohol. *Addiction* 103(9):1414–28. **https://doi.org/10.1111/j.1360-0443.2008.02203.x**

Duncan LE, Keller MC. 2011. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am. J. Psychiatry* 168(10):1041–49

Duncan LE, Ostacher M, Ballon J. 2019. How genome-wide association studies (GWAS) made traditional candidate gene studies obsolete. *Neuropsychopharmacology* 44(9):1518–23. **https://doi.org/10.1038/s41386-019-0389-5**

Edenberg HJ, Gelernter J, Agrawal A. 2019. Genetics of alcoholism. *Curr. Psychiatry Rep.* 21(4):26. **https://doi.org/10.1007/s11920-019-1008-1**

Egli M. 2018. Advancing pharmacotherapy development from preclinical animal studies. In *Handbook of Experimental Pharmacology*, Vol. 248: *The Neuropharmacology of Alcohol*, ed. KA Grant, DM Lovinger, pp. 537–78. Cham, Switz.: Springer. **https://doi.org/10.1007/164_2017_85**

Engen PA, Green SJ, Voigt RM, Forsyth CB, Keshavarzian A. 2015. The gastrointestinal microbiome: alcohol effects on the composition of intestinal microbiota. *Alcohol Res. Curr. Rev.* 37(2):223–36

Epstein DH. 2020. Let's agree to agree: a comment on Hogarth (2020), with a plea for not-so-competing theories of addiction. *Neuropsychopharmacology* 45(5):715–16

Erickson EK, Grantham EK, Warden AS, Harris RA. 2019. Neuroimmune signaling in alcohol use disorder. *Pharmacol. Biochem. Behav.* 177:34–60. **https://doi.org/10.1016/j.pbb.2018.12.007**

Everitt BJ, Robbins TW. 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat. Neurosci.* 8(11):1481–89. **https://doi.org/10.1038/nn1579**

Everitt BJ, Robbins TW. 2016. Drug addiction: updating actions to habits to compulsions ten years on. *Annu. Rev. Psychol.* 67:23–50. **https://doi.org/10.1146/annurev-psych-122414-033457**

Filbey FM, Claus E, Audette AR, Niculescu M, Banich MT, et al. 2008. Exposure to the taste of alcohol elicits activation of the mesocorticolimbic neurocircuitry. *Neuropsychopharmacology* 33(6):1391–401. **https://doi.org/10.1038/sj.npp.1301513**

Filbey FM, Schacht JP, Myers US, Chavez RS, Hutchison KE. 2009. Marijuana craving in the brain. *PNAS* 106(31):13016–21. **https://doi.org/10.1073/pnas.0903863106**

Freeman K, Brureau A, Vadigepalli R, Staehle MM, Brureau MM, et al. 2012. Temporal changes in innate immune signals in a rat model of alcohol withdrawal in emotional and cardiorespiratory homeostatic nuclei. *J. Neuroinflammation* 9(1):97. **https://doi.org/10.1186/1742-2094-9-97**

Gelernter J, Kranzler HR. 2009. Genetics of alcohol dependence. *Hum. Genet.* 126(1):91–99. **https://doi.org/10.1007/s00439-009-0701-2**

Gershon ES, Alliey-Rodriguez N, Liu C. 2011. After GWAS: searching for genetic risk for schizophrenia and bipolar disorder. *Am. J. Psychiatry* 168(3):253–56. **https://doi.org/10.1176/appi.ajp.2010.10091340**

Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. 2018. Current understanding of the human microbiome. *Nat. Med.* 24(4):392–400. **https://doi.org/10.1038/nm.4517**

Golan D, Lander ES, Rosset S. 2014. Measuring missing heritability: inferring the contribution of common variants. *PNAS* 111(49):E5272–81. **https://doi.org/10.1073/pnas.1419064111**

Gordon JA. 2019. From neurobiology to novel medications: a principled approach to translation. *Am. J. Psychiatry* 176(6):425–27

Gottesman I, Gould TD. 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am. J. Psychiatry* 160(4):636–45

Graybiel AM. 2008. Habits, rituals, and the evaluative brain. *Annu. Rev. Neurosci.* 31:359–87. **https://doi.org/10.1146/annurev.neuro.29.051605.112851**

Grifell M, Hart C. 2018. Is drug addiction a brain disease? *Am. Sci.* 106(3):160–67

Grodin EN, Bujarski S, Venegas A, Baskerville WA, Nieto SJ, et al. 2019. Reward, relief and habit drinking: initial validation of a brief assessment tool. *Alcohol Alcohol.* 54(6):574–83. **https://doi.org/10.1093/alcalc/agz075**

Grodin EN, Montoya AK, Bujarski S, Ray LA. 2020. Modeling motivation for alcohol in humans using traditional and machine learning approaches. *Addict. Biol.* In press. **https://doi.org/10.1111/adb.12949**

Grodin EN, Ray LA. 2019. The use of functional magnetic resonance imaging to test pharmacotherapies for alcohol use disorder: a systematic review. *Alcohol. Clin. Exp. Res.* 43(10):2038–56. **https://doi.org/10.1111/acer.14167**

Grodin EN, Sussman L, Sundby K, Brennan GM, Diazgranados N, et al. 2018. Neural correlates of compulsive alcohol seeking in heavy drinkers. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 3(12):1022–31. **https://doi.org/10.1016/j.bpsc.2018.06.009**

Han JH, Kushner SA, Yiu AP, Hsiang HLL, Buch T, et al. 2009. Selective erasure of a fear memory. *Science* 323(5920):1492–96

Hartwell EE, Kranzler HR. 2019. Pharmacogenetics of alcohol use disorder treatments: an update. *Expert Opin. Drug Metab. Toxicol.* 15(7):553–64. **https://doi.org/10.1080/17425255.2019.1628218**

He J, Crews FT. 2008. Increased MCP-1 and microglia in various regions of the human alcoholic brain. *Exp. Neurol.* 210(2):349–58

Heberlein A, Käser M, Lichtinghagen R, Rhein M, Lenz B, et al. 2014. TNF-α and IL-6 serum levels: neurobiological markers of alcohol consumption in alcohol-dependent patients? *Alcohol* 48(7):671–76. **https://doi.org/10.1016/j.alcohol.2014.08.003**

Heijtz RD, Wang S, Anuar F, Qian Y, Björkholm B, et al. 2011. Normal gut microbiota modulates brain development and behavior. *PNAS* 108(7):3047–52

Heilig M, Egli M, Crabbe JC, Becker HC. 2010. Acute withdrawal, protracted abstinence and negative affect in alcoholism: Are they linked? *Addict. Biol.* 15(2):169–84. **https://doi.org/10.1111/j.1369-1600.2009.00194.x**

Heilig M, Leggio L. 2016. What the alcohol doctor ordered from the neuroscientist: theragnostic biomarkers for personalized treatments. In *Progress in Brain Research*, Vol. 224: *Neuroscience for Addiction Medicine: From Prevention to Rehabilitation—Methods and Interventions*, ed. H Ekhtiari, MP Paulus, pp. 401–18. Amsterdam: Elsevier. **https://doi.org/10.1016/bs.pbr.2015.07.023**

Heilig M, Sommer WH, Spanagel R. 2016. The need for treatment responsive translational biomarkers in alcoholism research. *Curr. Top. Behav. Neurosci.* 28:151–71. **https://doi.org/10.1007/7854_2015_5006**

Hofmann SG, Fang A, Gutner CA. 2014. Cognitive enhancers for the treatment of anxiety disorders. *Restor. Neurol. Neurosci.* 32(1):183–95. **https://doi.org/10.3233/rnn-139002**

Hogarth L. 2020. Addiction is driven by excessive goal-directed drug choice under negative affect: translational critique of habit and compulsion theory. *Neuropsychopharmacology* 45(5):720–35. **https://doi.org/10.1038/s41386-020-0600-8**

Insel TR, Cuthbert B, Garvey M, Heinssen R, Pine DS, et al. 2010. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* 167(7):748–51. **https://doi.org/10.1176/appi.ajp.2010.09091379**

Insel TR, Quirion R. 2005. Psychiatry as a clinical neuroscience discipline. *JAMA* 294(17):2221–24. **https://doi.org/10.1001/jama.294.17.2221**

Jadhav KS, Peterson VL, Halfon O, Ahern G, Fouhy F, et al. 2018. Gut microbiome correlates with altered striatal dopamine receptor expression in a model of compulsive alcohol seeking. *Neuropharmacology* 141:249–59. **https://doi.org/10.1016/j.neuropharm.2018.08.026**

Jones JD, Comer SD, Kranzler HR. 2015. The pharmacogenetics of alcohol use disorder. *Alcohol. Clin. Exp. Res.* 39(3):391–402. **https://doi.org/10.1111/acer.12643**

Kalant H. 2010. What neurobiology cannot tell us about addiction. *Addiction* 105(5):780–89. **https://doi.org/10.1111/j.1360-0443.2009.02739.x**

Kalivas PW, Volkow ND. 2005. The neural basis of addiction: a pathology of motivation and choice. *Am. J. Psychiatry* 162(8):1403–13. **https://doi.org/10.1176/appi.ajp.162.8.1403**

Kendler KS, Karkowski LM, Neale MC, Prescott CA. 2000. Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. *Arch. Gen. Psychiatry* 57(3):261–69

Kendler KS, Prescott CA, Myers J, Neale MC. 2003. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch. Gen. Psychiatry* 60(9):929–37. **https://doi.org/10.1001/archpsyc.60.9.929**

Kiluk BD, Fitzmaurice GM, Strain EC, Weiss RD. 2019. What defines a clinically meaningful outcome in the treatment of substance use disorders: reductions in direct consequences of drug use or improvement in overall functioning? *Addiction* 114(1):9–15. **https://doi.org/10.1111/add.14289**

King AC, Hasin D, O'Connor SJ, McNamara PJ, Cao D. 2016. A prospective 5-year re-examination of alcohol response in heavy drinkers progressing in alcohol use disorder. *Biol. Psychiatry* 79(6):489–98. **https://doi.org/10.1016/j.biopsych.2015.05.007**

Kiraly DD, Walker DM, Calipari ES, Labonte B, Issler O, et al. 2016. Alterations of the host microbiome affect behavioral responses to cocaine. *Sci. Rep.* 6:35455. **https://doi.org/10.1038/srep35455**

Koob GF. 1992. Neural mechanisms of drug reinforcement. *Ann. N.Y. Acad. Sci.* 654:171–91

Koob GF. 2003. Alcoholism: allostasis and beyond. *Alcohol. Clin. Exp. Res.* 27(2):232–43. **https://doi.org/10.1097/01.ALC.0000057122.36127.C2**

Koob GF, Kreek MJ. 2007. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *Am. J. Psychiatry* 164(8):1149–59. **https://doi.org/10.1176/appi.ajp.2007.05030503**

Koob GF, Le Moal M. 1997. Drug abuse: hedonic homeostatic dysregulation. *Science* 278(5335):52–58

Koob GF, Schulkin J. 2019. Addiction and stress: an allostatic view. *Neurosci. Biobehav. Rev.* 106:245–62. **https://doi.org/10.1016/j.neubiorev.2018.09.008**

Koob GF, Volkow ND. 2010. Neurocircuitry of addiction. *Neuropsychopharmacology* 35(1):217–38. **https://doi.org/10.1038/npp.2009.110**

Kos MZ, Yan J, Dick DM, Agrawal A, Bucholz KK, et al. 2013. Common biological networks underlie genetic risk for alcoholism in African- and European-American populations. *Genes Brain Behav.* 12(5):532–42. **https://doi.org/10.1111/gbb.12043**

Kranzler HR, Zhou H, Kember RL, Vickers Smith R, Justice AC, et al. 2019. Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. *Nat. Commun.* 10(1):1499. **https://doi.org/10.1038/s41467-019-09480-8**

Kwako LE, Bickel WK, Goldman D. 2018. Addiction biomarkers: dimensional approaches to understanding addiction. *Trends Mol. Med.* 24(2):121–28. **https://doi.org/10.1016/j.molmed.2017.12.007**

Kwako LE, Momenan R, Grodin EN, Litten RZ, Koob GF, Goldman D. 2017. Addictions Neuroclinical Assessment: a reverse translational approach. *Neuropharmacology* 122:254–64. **https://doi.org/10.1016/j.neuropharm.2017.03.006**

Kwako LE, Schwandt ML, Ramchandani VA, Diazgranados N, Koob GF, et al. 2019. Neurofunctional domains derived from deep behavioral phenotyping in alcohol use disorder. *Am. J. Psychiatry* 176(9):744–53. **https://doi.org/10.1176/appi.ajp.2018.18030357**

Leclercq S, De Saeger C, Delzenne N, de Timary P, Stärkel P. 2014a. Role of inflammatory pathways, blood mononuclear cells, and gut-derived bacterial products in alcohol dependence. *Biol. Psychiatry* 76(9):725–33. **https://doi.org/10.1016/j.biopsych.2014.02.003**

Leclercq S, Matamoros S, Cani PD, Neyrinck AM, Jamar F, et al. 2014b. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. *PNAS* 111(42):E4485–93

Lee K, Vuong HE, Nusbaum DJ, Hsiao EY, Evans CJ, Taylor AM. 2018. The gut microbiota mediates reward and sensory responses associated with regimen-selective morphine dependence. *Neuropsychopharmacology* 43(13):2606–14

Leggio L, Kenna GA, Fenton M, Bonenfant E, Swift RM. 2009. Typologies of alcohol dependence. From Jellinek to genetics and beyond. *Neuropsychol. Rev.* 19(1):115–29. **https://doi.org/10.1007/s11065-008-9080-z**

Liu J, Lewohl JM, Harris RA, Iyer VR, Dodd PR, et al. 2006. Patterns of gene expression in the frontal cortex discriminate alcoholic from nonalcoholic individuals. *Neuropsychopharmacology* 31(7):1574–82

Luczynski P, McVey Neufeld KA, Oriach CS, Clarke G, Dinan TG, Cryan JF. 2016. Growing up in a bubble: using germ-free animals to assess the influence of the gut microbiota on brain and behavior. *Int. J. Neuropsychopharmacol.* 19(8):pyw020. **https://doi.org/10.1093/ijnp/pyw020**

Luijten M, Gillan CM, de Wit S, Franken IHA, Robbins TW, Ersche KD. 2020. Goal-directed and habitual control in smokers. *Nicotine Tob. Res.* 22(2):188–95. **https://doi.org/10.1093/ntr/ntz001**

MacKillop J, Amlung MT, Few LR, Ray LA, Sweet LH, Munafo MR. 2011. Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology* 216(3):305–21. **https://doi.org/10.1007/s00213-011-2229-0**

Malvaez M, Wassum KM. 2018. Regulation of habit formation in the dorsal striatum. *Curr. Opin. Behav. Sci.* 20:67–74. **https://doi.org/10.1016/j.cobeha.2017.11.005**

Mann K, Aubin HJ, Witkiewitz K. 2017. Reduced drinking in alcohol dependence treatment, what is the evidence? *Eur. Addict. Res.* 23(5):219–30

Mann K, Roos CR, Hoffmann S, Nakovics H, Lemenager T, et al. 2018. Precision medicine in alcohol dependence: a controlled trial testing pharmacotherapy response among reward and relief drinking phenotypes. *Neuropsychopharmacology* 43(4):891–99. **https://doi.org/10.1038/npp.2017.282**

Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, et al. 2009. Finding the missing heritability of complex diseases. *Nature* 461(7265):747–53. **https://doi.org/10.1038/nature08494**

Mayfield J, Harris RA. 2017. The neuroimmune basis of excessive alcohol consumption. *Neuropsychopharmacology* 42(1):376. **https://doi.org/10.1038/npp.2016.177**

McBride WJ, Kimpel MW, McClintick JN, Ding ZM, Hauser SR, et al. 2013. Changes in gene expression within the ventral tegmental area following repeated excessive binge-like alcohol drinking by alcohol-preferring (P) rats. *Alcohol* 47(5):367–80

McLellan AT. 2002. Have we evaluated addiction treatment correctly? Implications from a chronic care perspective. *Addiction* 97(3):249–52

Meckel KR, Kiraly DD. 2019. A potential role for the gut microbiome in substance use disorders. *Psychopharmacology* 236(5):1513–30. **https://doi.org/10.1007/s00213-019-05232-0**

Meehl PE. 1972. Specific genetic etiology, psychodynamics, and therapeutic nihilism. *Int. J. Ment. Health* 1(1–2):10–27

Monti PM, Tidey J, Czachowski CL, Grant KA, Rohsenow DJ, et al. 2004. Building bridges: the transdisciplinary study of craving from the animal laboratory to the lamppost. *Alcohol. Clin. Exp. Res.* 28(2):279–87

Morris LS, Dowell NG, Cercignani M, Harrison NA, Voon V. 2018. Binge drinking differentially affects cortical and subcortical microstructure. *Addict. Biol.* 23(1):403–11

Nieto SJ, Grodin EN, Ray LA. 2020. On the path toward personalized medicine: implications of pharmacogenetic studies of alcohol use disorder medications. *Expert Rev. Precis. Med. Drug Dev.* 5(1):43–54

Nolen-Hoeksema S, Watkins ER. 2011. A heuristic for developing transdiagnostic models of psychopathology: explaining multifinality and divergent trajectories. *Perspect. Psychol. Sci.* 6(6):589–609

Oslin DW, Leong SH, Lynch KG, Berrettini W, O'Brien CP, et al. 2015. Naltrexone versus placebo for the treatment of alcohol dependence: a randomized clinical trial. *JAMA Psychiatry* 72(5):430–37. **https://doi.org/10.1001/jamapsychiatry.2014.3053**

Ostergren JE, Hammer RR, Dingel MJ, Koenig BA, McCormick JB. 2014. Challenges in translational research: the views of addiction scientists. *PLOS ONE* 9(4):e93482. **https://doi.org/10.1371/journal.pone.0093482**

Pascual M, Baliño P, Aragón CM, Guerri C. 2015. Cytokines and chemokines as biomarkers of ethanol-induced neuroinflammation and anxiety-related behavior: role of TLR4 and TLR2. *Neuropharmacology* 89:352–59

Peterson VL, Jury NJ, Cabrera-Rubio R, Draper LA, Crispie F, et al. 2017. Drunk bugs: Chronic vapour alcohol exposure induces marked changes in the gut microbiome in mice. *Behav. Brain Res.* 323:172–76

Prescott CA, Kendler KS. 1999. Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. *Am. J. Psychiatry* 156(1):34–40

Qin L, He J, Hanes RN, Pluzarev O, Hong JS, Crews FT. 2008. Increased systemic and brain cytokine production and neuroinflammation by endotoxin following ethanol treatment. *J. Neuroinflammation* 5(1):10. **https://doi.org/10.1186/1742-2094-5-10**

Ray LA. 2012. Clinical neuroscience of addiction: applications to psychological science and practice. *Clin. Psychol. Sci. Pract.* 19(2):154–66

Ray LA, Bujarski S, Grodin E, Hartwell E, Green R, et al. 2019a. State-of-the-art behavioral and pharmacological treatments for alcohol use disorder. *Am. J. Drug Alcohol Abuse* 45(2):124–40. **https://doi.org/10.1080/00952990.2018.1528265**

Ray LA, Bujarski S, Roche DJO. 2016. Subjective response to alcohol as a research domain criterion. *Alcohol. Clin. Exp. Res.* 40(1):6–17. **https://doi.org/10.1111/acer.12927**

Ray LA, Bujarski S, Roche DJO, Magill M. 2018. Overcoming the "valley of death" in medications development for alcohol use disorder. *Alcohol. Clin. Exp. Res.* 42(9):1612–22

Ray LA, Bujarski S, Shoptaw S, Roche DJO, Heinzerling K, Miotto K. 2017a. Development of the neuroimmune modulator ibudilast for the treatment of alcoholism: a randomized, placebo-controlled, human laboratory trial. *Neuropsychopharmacology* 42(9):1776–88. **https://doi.org/10.1038/npp.2017.10**

Ray LA, Bujarski S, Yardley MM, Roche DJO, Hartwell EE. 2017b. Differences between treatment-seeking and non-treatment-seeking participants in medication studies for alcoholism: Do they matter? *Am. J. Drug Alcohol Abuse* 43(6):703–10. **https://doi.org/10.1080/00952990.2017.1312423**

Ray LA, Courtney KE, Hutchison KE, MacKillop J, Galvan A, Ghahremani DG. 2014. Initial evidence that OPRM1 genotype moderates ventral and dorsal striatum functional connectivity during alcohol cues. *Alcohol. Clin. Exp. Res.* 38(1):78–89. **https://doi.org/10.1111/acer.12136**

Ray LA, Du H, Grodin E, Bujarski S, Meredith L, et al. 2020. Capturing habitualness of drinking and smoking behavior in humans. *Drug Alcohol Depend.* 207:107738. **https://doi.org/10.1016/j.drugalcdep.2019.107738**

Ray LA, Grodin EN, Leggio L, Bechtholt AJ, Becker H, et al. 2021. The future of translational research on alcohol use disorder. *Addict. Biol.* 26(2):e12903

Ray LA, Hutchison KE. 2004. A polymorphism of the μ-opioid receptor gene (*OPRM1*) and sensitivity to the effects of alcohol in humans. *Alcohol. Clin. Exp. Res.* 28(12):1789–95. **https://doi.org/10.1097/01.ALC.0000148114.34000.B9**

Ray LA, Hutchison KE. 2007. Effects of naltrexone on alcohol sensitivity and genetic moderators of medication response: a double-blind placebo-controlled study. *Arch. Gen. Psychiatry* 64(9):1069–77. **https://doi.org/10.1001/archpsyc.64.9.1069**

Ray LA, Lim AC, Shoptaw S. 2019b. What defines a clinically meaningful outcome in the treatment of substance use disorders: 'Getting your life back.' *Addiction* 114(1):18–20. **https://doi.org/10.1111/add.14455**

Ray LA, MacKillop J, Monti PM. 2010. Subjective responses to alcohol consumption as endophenotypes: advancing behavioral genetics in etiological and treatment models of alcoholism. *Subst. Use Misuse* 45(11):1742–65. **https://doi.org/10.3109/10826084.2010.482427**

Reilly MT, Noronha A, Goldman D, Koob GF. 2017. Genetic studies of alcohol dependence in the context of the addiction cycle. *Neuropharmacology* 122:3–21. **https://doi.org/10.1016/j.neuropharm.2017.01.017**

Robinson TE, Berridge KC. 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Brain Res. Rev.* 18(3):247–91

Robinson TE, Berridge KC. 2001. Incentive-sensitization and addiction. *Addiction* 96(1):103–14

Robinson TE, Berridge KC. 2008. The incentive sensitization theory of addiction: some current issues. *Philos. Trans. R. Soc. B* 363(1507):3137–46. **https://doi.org/10.1098/rstb.2008.0093**

Roche DJ, Ray LA. 2015. Subjective response as a consideration in the pharmacogenetics of alcoholism treatment. *Pharmacogenomics* 16(7):721–36

Rogers G, Keating D, Young R, Wong M, Licinio J, Wesselingh S. 2016. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Mol. Psychiatry* 21(6):738–48

Rohn MC, Lee MR, Kleuter SB, Schwandt ML, Falk DE, Leggio L. 2017. Differences between treatment-seeking and nontreatment-seeking alcohol-dependent research participants: an exploratory analysis. *Alcohol. Clin. Exp. Res.* 41(2):414–20. **https://doi.org/10.1111/acer.13304**

Roman M, Irwin MR. 2020. Novel neuroimmunologic therapeutics in depression: a clinical perspective on what we know so far. *Brain Behav. Immun.* 83:7–21. **https://doi.org/10.1016/j.bbi.2019.09.016**

Røysamb E, Kendler KS, Tambs K, Ørstavik RE, Neale MC, et al. 2011. The joint structure of *DSM-IV* Axis I and Axis II disorders. *J. Abnorm. Psychol.* 120(1):198–209. **https://doi.org/10.1037/a0021660**

Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, et al. 2010. Developing constructs for psychopathology research: Research Domain Criteria. *J. Abnorm. Psychol.* 119(4):631–39. **https://doi.org/10.1037/a0020909**

Satel SL, Lilienfeld SO. 2017. If addiction is not best conceptualized a brain disease, then what kind of disease is it? *Neuroethics* 10(1):19–24

Schacht JP, Anton RF, Myrick H. 2013. Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. *Addict. Biol.* 18(1):121–33. **https://doi.org/10.1111/j.1369-1600.2012.00464.x**

Schultz W, Dayan P, Montague PR. 1997. A neural substrate of prediction and reward. *Science* 275(5306):1593–99

Sebold M, Nebe S, Garbusow M, Guggenmos M, Schad DJ, et al. 2017. When habits are dangerous: Alcohol expectancies and habitual decision making predict relapse in alcohol dependence. *Biol. Psychiatry* 82(11):847–56. **https://doi.org/10.1016/j.biopsych.2017.04.019**

Sjoerds Z, de Wit S, van den Brink W, Robbins TW, Beekman ATF, et al. 2013. Behavioral and neuroimaging evidence for overreliance on habit learning in alcohol-dependent patients. *Transl. Psychiatry* 3:e337. **https://doi.org/10.1038/tp.2013.107**

Smith KS, Graybiel AM. 2016. Habit formation. *Dialogues Clin. Neurosci.* 18(1):33–43

Snoek A. 2017. How to recover from a brain disease: Is addiction a disease, or is there a disease-like stage in addiction? *Neuroethics* 10(1):185–94

Sofuoglu M, Mooney M, Kosten T, Waters A, Hashimoto K. 2011. Minocycline attenuates subjective rewarding effects of dextroamphetamine in humans. *Psychopharmacology* 213(1):61–68. **https://doi.org/10.1007/s00213-010-2014-5**

Solomon RL, Corbit JD. 1974. An opponent-process theory of motivation. I. Temporal dynamics of affect. *Psychol. Rev.* 81(2):119–45

Tate SK, Goldstein DB. 2004. Will tomorrow's medicines work for everyone? *Nat. Genet.* 36(11 Suppl.):S34–42

Teachman BA, McKay D, Barch DM, Prinstein MJ, Hollon SD, Chambless DL. 2019. How psychosocial research can help the National Institute of Mental Health achieve its grand challenge to reduce the burden of mental illnesses and psychological disorders. *Am. Psychol.* 74(4):415–31

Tripathi A, Debelius J, Brenner DA, Karin M, Loomba R, et al. 2018. The gut–liver axis and the intersection with the microbiome. *Nat. Rev. Gastroenterol. Hepatol.* 15(7):397–411

van Dorn A. 2017. Joshua Gordon: an interdisciplinary approach to mental health. *Lancet Psychiatry* 4(4):279. **https://doi.org/10.1016/S2215-0366(17)30093-7**

Vandaele Y, Janak PH. 2018. Defining the place of habit in substance use disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 87(Part A):22–32. **https://doi.org/10.1016/j.pnpbp.2017.06.029**

Venniro M, Zhang M, Caprioli D, Hoots JK, Golden SA, et al. 2018. Volitional social interaction prevents drug addiction in rat models. *Nat. Neurosci.* 21(11):1520–29. **https://doi.org/10.1038/s41593-018-0246-6**

Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, et al. 2001. Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *J. Neurosci.* 21(23):9414–18

Volkow ND, Koob GF, McLellan AT. 2016. Neurobiologic advances from the brain disease model of addiction. *N. Engl. J. Med.* 374(4):363–71

Volkow ND, Li TK. 2005. The neuroscience of addiction. *Nat. Neurosci.* 8(11):1429–30. **https://doi.org/10.1038/nn1105-1429**

Volkow ND, Morales M. 2015. The brain on drugs: from reward to addiction. *Cell* 162(4):712–25. **https://doi.org/10.1016/j.cell.2015.07.046**

Vollstädt-Klein S, Wichert S, Rabinstein J, Bühler M, Klein O, et al. 2010. Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. *Addiction* 105(10):1741–49. **https://doi.org/10.1111/j.1360-0443.2010.03022.x**

Voon V, Derbyshire K, Rück C, Irvine MA, Worbe Y, et al. 2015. Disorders of compulsivity: a common bias towards learning habits. *Mol. Psychiatry* 20(3):345–52. **https://doi.org/10.1038/mp.2014.44**

Wagner FA, Anthony JC. 2002. From first drug use to drug dependence: developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology* 26(4):479–88. **https://doi.org/10.1016/s0893-133x(01)00367-0**

Walters RK, Polimanti R, Johnson EC, McClintick JN, Adams MJ, et al. 2018. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nat. Neurosci.* 21(12):1656–69. **https://doi.org/10.1038/s41593-018-0275-1**

Weiss F, Martin-Fardon R, Ciccocioppo R, Kerr TM, Smith DL, Ben-Shahar O. 2001. Enduring resistance to extinction of cocaine-seeking behavior induced by drug-related cues. *Neuropsychopharmacology* 25(3):361–72. **https://doi.org/10.1016/S0893-133X(01)00238-X**

Weiss F, Parsons LH, Schulteis G, Hyytia P, Lorang MT, et al. 1996. Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats. *J. Neurosci.* 16(10):3474–85

Wilson JM, Kalasinsky KS, Levey AI, Bergeron C, Reiber G, et al. 1996. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. *Nat. Med.* 2(6):699–703

Wise RA. 2008. Dopamine and reward: the anhedonia hypothesis 30 years on. *Neurotox. Res.* 14(2–3):169–83. **https://doi.org/10.1007/BF03033808**

Wong M, Inserra A, Lewis M, Mastronardi CA, Leong L, et al. 2016. Inflammasome signaling affects anxiety- and depressive-like behavior and gut microbiome composition. *Mol. Psychiatry* 21(6):797–805

Worley MJ, Heinzerling KG, Roche DJ, Shoptaw S. 2016. Ibudilast attenuates subjective effects of methamphetamine in a placebo-controlled inpatient study. *Drug Alcohol Depend*. 162:245–50

Zarrinpar A, Chaix A, Xu ZZ, Chang MW, Marotz CA, et al. 2018. Antibiotic-induced microbiome depletion alters metabolic homeostasis by affecting gut signaling and colonic metabolism. *Nat. Commun*. 9(1):2872. **https://doi.org/10.1038/s41467-018-05336-9**

Zuk O, Hechter E, Sunyaev SR, Lander ES. 2012. The mystery of missing heritability: Genetic interactions create phantom heritability. *PNAS* 109(4):1193–98. **https://doi.org/10.1073/pnas.1119675109**

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Errata

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