HHS Public Access

Author manuscript

Alcohol Clin Exp Res. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Alcohol Clin Exp Res. 2019 January ; 43(1): 6–21. doi:10.1111/acer.13912.

"What is addiction? How can animal and human research be used to advance research, diagnosis, and treatment of alcohol and other substance use disorders?

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Abstract

The current article highlights key issues in defining, studying, and treating addiction, a concept related to but distinct from substance use disorders. The discussion is based upon a roundtable discussion at the 2017 annual meeting of the Research Society on Alcoholism (RSA) where Warren Bickel and John Crabbe were charged with answering a range of questions posed by Kenneth Sher. All the presenters highlighted a number of central concerns for those interested in assessing and treating addiction as well as those seeking to conduct basic preclinical research that is amenable to meaningful translation to the human condition. In addition, the discussion illustrated both the power and limitations of using any single theory to explain multiple phenomena subsumed under the rubric of addiction. Among the major issues examined were the important differences between traditional diagnostic approaches and current concepts of addiction, the difficulty of modeling key aspects of human addiction in nonhuman animals, key aspects of addiction that have, to date, received little empirical attention, and the importance of thinking of recovery as a phenomenon that possibly involves processes distinct from those undergirding the development and maintenance of addiction.

Keywords

addiction; substance use disorders; alcohol use disorders; behavioral economics; animal models; compulsive use

In June 2017, at the annual meeting of the Research Society on Alcoholism (RSA), then RSA president, Kenneth Sher, hosted a roundtable with two leading researchers in the area of alcohol and substance use disorders, Warren K. Bickel and John C. Crabbe, with the goal of fostering discussion on how best to define and understand this serious clinical and public

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[1]Note that while major theories of addiction may highlight specific manifestations of addiction that correspond to one or more diagnostic criteria and clinical addiction concepts, most of these theories would argue that the core mechanisms relate to a wide range of phenomena and are not limited to those indicated by an "X" in Table 1. That is, this organizational scheme should be viewed as heuristic and not absolute or exhaustive.

health problem. In particular, the two discussants were charged with addressing the interrelated questions of whether or not there is value to the concept of addiction and, if there is, whether or not there are any specific symptoms that are pathognomic (i.e., necessary and sufficient).

Although widely used by professionals and laymen alike, the term “addiction” is not a formal diagnostic entity in the most widely used diagnostic systems including the Diagnostic and Statistical Manual, version 5 (DSM-5) of the American Psychiatric Association (APA, 2013) or the World Health Organizations (WHO) International Classification of Diseases, Version 10 (ICD-10; WHO; 2007)). However, diagnostic criteria of Substance Use Disorder (SUD) in DSM-5 and Substance Dependence in ICD-10 include what many would consider key features of addiction, for example, craving and compulsive use.

As depicted in Table 1, we can think of key addiction constructs in at least three conceptually overlapping but distinct ways: (1) established diagnostic criteria (e.g., DSM and ICD) based upon signs and symptoms of disorder, (2) clinical addiction concepts that may overlap with one or more diagnostic criteria (e.g., compulsive use is implied by several different SUD criteria), and (3) specific mechanistic processes that are associated with major theories of addiction (e.g., allostasis, incentive sensitization, habit formation)[1]. Further consideration of the differences among diagnostic criteria, the concept of addiction, and theories of addictive behavior bring to the fore a number of considerations for thinking about the relations among these related yet distinct domains. Specifically:

1. Theories of addiction vary with respect to the addiction constructs they are associated with and the specific diagnostic criteria to which they relate.
2. A one-to-one correspondence does not exist between diagnostic criteria of, say, DSM-5 and specific addiction constructs. For example, multiple criteria (e.g., psychological and health problems, interpersonal and social problems) could index the same addiction construct (e.g., compulsive use).
3. Some theories highlight symptoms (e.g., negative affectivity) that are not part of our current diagnostic system for SUDs and overlap considerably with general psychopathology (e.g., Caspi et al., 2014).
4. Not all SUD criteria are fully consistent with clinical notions of addiction nor with specific theories of addiction that have been advanced. As argued elsewhere (Martin et al., 2011) “hazardous use,” (e.g., drinking while driving) although perhaps a secondary indicator of addiction in that it could reflect aspects of compulsive use, may represent little more than general heedlessness and not an acquired symptom for many individuals (although for others it could indicate a pattern of compulsive use). Indeed, the possibility exists that a given diagnostic criterion can be met for a host of reasons. For example, interpretation of specific criteria by clinicians and/or patients (e.g., Chung and Martin, 2005) can lead to false positive reports of a symptom. Further, as is likely the case with respect to hazardous use, the criterion itself could reflect either an addiction construct such as compulsive use or a generalized predisposition to take risks (Martin et al., 2011). More generally, using reported problems from substance use for assessing

diagnostic criteria is potentially problematic because many ostensible substance-related consequences are multidetermined and the attribution of substance causation cannot be made rigorously (Martin et al., 2014). Moreover, a given correlate could be predisposing to addiction, a manifestation or consequence of addiction, or spuriously related due to a common third variable.

5. Related to this last point, two individuals with the same number of SUD criteria may vary greatly in the extent to which they are "addicted" depending upon the specific symptoms manifested (Lane and Sher, 2015), further highlighting the conceptual distinction between addiction and SUDs.

These concerns highlight the potential utility of using basic research on addiction to improve on definitions of substance use disorder and, perhaps, guide the development of new assessment approaches.

Although different theories may focus on different mechanisms and ostensibly relate to different addiction constructs and SUD criteria, this does not preclude the possibility that common mechanisms contribute to phenotypically different constructs, etiological processes and diagnostic criteria. As one example, the development of incentive sensitization is likely with associated craving but, apparently, impulsivity too (Lovic et al., 2011). Thus, the rubric of Table 1 is not only an oversimplification, but it also highlights a challenge in thinking about what distinguishes an addicted human or nonhuman animal from one that is not addicted. Certain premorbid characteristics that may put someone at risk for SUDs and addiction such as impulsivity broadly defined (Dick et al., 2010) or low level of response to alcohol (Moreau and Corbin, 2010) might be further changed in a causal way by addictive overindulgence (e.g., further decreases in self-regulation associated with *chronic* drug use, the development of tolerance). This is not merely an important theoretic concern but presents significant challenges to developing assessments that are able to distinguish acquired, substance-related changes from premorbid traits and, possibly, to developing behavioral and pharmacological treatments that address predispositions versus substance-specific morbidity.

In order to advance a broader discussion of addiction, Professors John Crabbe and Warren Bickel were asked to provide their own perspectives on the nature of addiction and address related questions, including: Can basic research in animals and humans inform diagnostic criteria for alcohol use disorders in humans? Do partial animal models that focus on a single feature versus models that attempt to mimic the totality of AUD provide insights or "red herrings"? And how important is the drug user's increasing focus on their drug of choice, to the exclusion of other naturally occurring reinforcers? Each brings to the discussion a distinguished career of basic research on addiction but a different background as to the phenomena and the species they've studied. Consequently, common and individual questions were posed to each speaker in order to highlight possible areas of consensus and to exploit their areas of individual expertise in genetic and animal models of features of addiction (Crabbe) and behavioral economics (Bickel). Summaries of their presentations follow which, in combination, highlight the value of examining addiction through the lenses of multiple distinct phenomena (Crabbe) as well as a single, overarching perspective (Bickel). In a concluding section we highlight the implications of these perspectives for

advancing basic research on addiction and for developing novel approaches to clinical assessment and treatment.

Translational Perspectives on Addiction: What Can Rodents Tell Us About Addiction in Humans…and What Can't They Tell Us?

John C. Crabbe

The term "addiction" represents a broader concept than that of alcoholism, alcohol use disorders (AUD), or alcohol dependence. Substance-related and addictive disorders (DSM-5, American Psychiatric Association, 2013) encompasses psychiatric diagnoses of AUD and drug use disorders (DUD). Moreover, the addiction construct is sometimes applied to potentially related problems such as Gambling Disorder, and some selective Feeding and Eating Disorders. Additionally, all of these conditions are frequently comorbid with Disruptive, Impulse Control, and Conduct Disorders as well as Depressive Disorders, Anxiety Disorders, Bipolar Disorders, and Personality Disorders. However, the focus here is on substance-related and addictive disorders. I believe that the overarching concept of addiction has value, as basic research clearly indicates some lines of biological evidence that converge across at least some of these multiple ways people find to execute their addictive behaviors [see for example (Ozburn et al., 2015)]. One important task for those seeking more effective therapies for AUD is to try to mine other neurobiological substrates that appear to be relatively restricted to the misuse of alcohol.

Addiction is, however, fundamentally defined by its behavioral expression: ironclad diagnostic biomarkers do not exist. The addicted person must perform the acts related to gaining access to the target (e.g., seeking drugs) and then performing the addictive behavior (e.g., taking those drugs, offering money to a video poker machine). This human instrumentality continues to fuel popular resistance by some to the disease concept of AUD, which traces the beginning of its wide acceptance by the research community to the1950's (Jellinek, 1960). Theoretical explanations of the addictions implicitly assume the basic validity of the disease concept; thus, they all have included psychological constructs related to dysregulated motivation. While a thorough review of theories of addiction is beyond the scope of this commentary, it may be useful to seek commonalities among some of the more widely-known theories. At the risk of vastly oversimplifying complex concepts, I summarize some of these here and refer the reader to more extensive developments of the theories. Probably the most widely invoked at present by preclinical researchers is that proposed by Koob and LeMoal (Koob and LeMoal, 1997; 2006). These authors assert three core features: compulsion, loss of control, and emergence of a negative emotional state when access to the drug is blocked. Robinson and Berridge (Robinson and Berridge, 1993, 2003) propose five key features: compulsion, time devoted to seeking and using, persistence of use despite adverse consequences, inability to quit, and relapse vulnerability. In more colloquial terms, these five concepts can be reduced to two – a shift from liking the drug, to wanting it. For Everitt and Robbins, (2016) the primary single key is the shift from goal-directed behavior to habit-driven behavior. While Piazza and Deroche-Gamonet (2013), emphasize the shift from controlled to uncontrolled use after long-term use in selected (i.e., vulnerable) individuals.

Note here that in human studies, as suggested in Ken Sher's introduction, it cannot easily dissociate any biological-psychological-social factors that predispose to addiction from those that result from excessive substance use. It is here that preclinical animal models for addiction-related behavior have much to offer. In simplest form, the common concepts invoked by these theories are compulsion (or persistence of use) and loss of control over use (e.g., using more of a substance or using it longer than intended). These characteristics have been targeted by animal models at the level of behavior, learning and reinforcement parameters, brain circuits, and/or neural plasticity. Each of the above broad theories of addiction have framed studies in those domains. However, the field is far from in agreement about the face validity of many of the preclinical models – as noted in the next section, "compulsion" and "loss of control" encompass implied self-reflective states not usually attributed to other species.

Lumping versus splitting—Given that some conceptual generality exists across AUD and other addictive disorders, is it reasonable to think that any preclinical animal model can encompass the broad diagnosis of AUD? I confine this discussion to rodent models, which comprise the majority of preclinical animal studies. I believe that it is unrealistic if not impossible to capture the entirety of AUD in any single preclinical model (Crabbe, 2014), though this opinion is certainly not shared by all (Cicero, 1979; Rodd et al., 2004). Rather, I support an initial reductionistic strategy, believing that animal models do better, and can do more, with simpler than more global traits. This strategy first identifies key features of the disorder to model for in depth study (McClearn, 1979) and then seeks better understanding through synthesis from the parts (Crabbe, 2012). In the DSM-5, 11 diagnostic criteria address AUD (American Psychiatric Association, 2013). Of these, two have been modeled extensively in laboratory animals (tolerance and withdrawal). Compulsive use is not a specific criterion in DSM-5 but if one equates it to continued use despite predictable negative consequences, then it is implicit in multiple criteria (e.g., continued use despite social/interpersonal problems attributable to alcohol, continued use despite physical/psychological problems caused or exacerbated by alcohol). Consequently, it is noteworthy that research on use despite concurrent punishment is beginning to attract attention. However, the animal models cannot be viewed as strict translations owing to the fact that they depend crucially on attempting to target internal psychological (interoceptive) states that humans can verbalize (accurately or not, honestly or not) while rodents cannot. For example, using in greater amounts and/or longer than intended; desire, but failure to quit or control use; and craving seem essentially human. Among other limitations to the DSM-5 criteria are that they do not directly reflect either age of onset, or the developmental course of the disease; they do not explicitly consider relapse; nor do they directly reflect either the quantity, frequency or patterning of drinking (Leeman et al., 2010). All of these factors are of high clinical importance, if not to etiology then to treatment.

Are partial models useful?—What then is the track record for preclinical models of the various aspects of AUD? For preclinical research, the behavior of the animal is often the final readout of an experiment. I'd argue that various aspects of cognition (e.g., attention, learning, generalization, memory) are pretty well modeled in rodents. Motoric effects (stimulation, discoordination, ataxia, sedation) are also [e.g., (Crabbe et al., 2010)].

Pavlovian-based models are pretty convincing for self-reported hedonic effects, of which alcohol has both positive and negative (Stephens et al., 2010). Where partial models have had more difficulty have been with things such as “anxiety-like behavior,” depression, and anhedonia.

The two features best modeled have been tolerance and withdrawal (n.b., Alcohol Withdrawal is even a separate diagnostic category in the DSM-5 owing to its clinical importance independent of other symptoms of AUD). These were among the earliest features targeted [e.g., reviews such as (Kalant, 1971; Kalant et al., 1971; Tabakoff and Hoffman, 1988)]. Most studies have concentrated on the early stages of withdrawal, but lately more have explored protracted abstinence (Heilig et al., 2010). The concentration of animal models on these topics was driven in part by ethyl alcohol’s unique features as a drug, including low potency (reflected in the ingestion of huge volumes of alcoholic beverages), ubiquity of targets (ranging from pockets in neural membrane receptor proteins to essentially all organ systems), and the ready production of both functional and metabolic changes with chronic dosing (Kalant, 1971; Samson and Harris, 1992). Besides the two basic types, pharmacodynamic (functional – seen as reduced response or escalated dose) and metabolic (dispositional – seen as changes in absorption, distribution, and elimination), tolerance comes in many forms. These are distinguished mostly by the rate of development and loss, and have been studied in humans, rats, mice, *C. Elegans, Drosophila*, and fish, in addition to other mammalian species (Bettinger et al., 2012; Greizerstein and Smith, 1973; Tran et al., 2016; Samson and Harris, 1992). The many symptoms of withdrawal are, for the most part, ubiquitous across species as well (Friedman, 1980). Systematic studies of tolerance, dependence, and withdrawal over the years have explained much about the effects of ethanol on the brain, so for these diagnostic criteria, the value of partial animal models has been indisputably great.

A recent attempt to relate the human and animal literatures was undertaken after an initial finding appeared to suggest multiple genetic pathways leading to DSM-IV (APA, 1994) human alcohol dependence diagnosis risk, rather than the usually assumed single genetic path of vulnerability (Kendler et al., 2012). In these twin data, three distinguishable paths to human genetic risk were indicated by structural equation modeling, based on the multivariate relationships among specific diagnostic criteria and outcomes. The first genetic factor loaded strongly for tolerance, as well as quantity-frequency measures. The second reflected preoccupation, loss of control, desire to quit, and foregoing other activities. The third factor reflected withdrawal symptoms and continued use despite negative consequences. When we sought parallels in the rodent literature, only two criteria, tolerance and withdrawal, had enough rodent data to seek their apparent genetic relationships. Surprisingly, tolerance and withdrawal appeared independently to predict genetic risk in twins. When we examined the rodent data, however, we found only modest evidence for genetic correlation. That is, rodent genotypes predisposed to severe withdrawal did not appear particularly susceptible to develop tolerance, and *vice versa*. Thus, the rodent data seemed to support the heterogeneity of human genetic risk factors (Crabbe et al., 2013). Note that while genetic factor analyses such as Kendler et al’s (2012) find evidence for multiple factors, genetically non-informative factor analyses fail to reliably show anything

more than a unidimensional structure (Hasin et al., 2013) highlighting how genetics can be a useful tool for characterizing etiologically distinct features.

As noted above, although use despite punishment is not an explicit diagnostic criterion, the concept is implicit in those criteria assessing use despite negative social and personal harms. This implicit feature can be considered to be well-modeled if, for example, a rat will continue to administer cocaine intravenously even after infusions are now paired with electric shock (Vanderschuren and Everitt, 2004). Such insensitivity to concurrent punishment has more recently been documented for ethanol drinking as well (Seif et al., 2013). More frequently invoked procedures have shown that adulteration of alcohol solutions with the presumptively aversive substance quinine can fail to reduce high alcohol drinking (Lesscher et al., 2010). These approaches appear promising, although each demands diligent attention to control issues. Quinine adulteration studies use the oral route of administration and therefore require careful consideration of taste quality, sensory thresholds, and preferences (Crabbe, 2012), while for foot shock-resistant drinking, such features as pain sensitivity thresholds must be considered (Hopf and Lesscher, 2014). On a positive note, these methods avoid requiring that the rats or mice have “knowledge of deleterious consequences.” Warren Bickel proposes delay discounting as a procedural model of continued use despite predictable adverse consequences later in this article. Delay and the value of aversive consequences of shock has rarely been studied in preclinical models, but discounting of preference for a larger food reward in rats (Rodriguez et al, 2018) was titrated by delay of shock, and preference for one of two equal doses of cocaine was discounted by delaying histamine injections in rhesus macaques (Woolverton et al, 2012).

Three criteria seem possibly amenable to rodent modeling.

“A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.” Conceivably, some aspect of this criterion could be addressed if an animal’s living environment could be structured to offer alternative activities that became less frequent or intense as alcohol intake chronically increased.

“Important social, occupational, or recreational activities are given up or reduced because of alcohol use.” Behavioral assays exist where rodents can choose to allocate their time to activities directed at another conspecific.

“Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.” School is out, but “work” might be modeled by having rodents accustomed to gaining access to food through performing an operant behavior.

However, a clear lack of studies exists targeting these diagnostic criteria in the literature. Such studies would not be easy to arrange and perform, and one immediately begins to see alternative explanations that would demand use of sophisticated controls.

Alcohol provides complex interoceptive feedback—Certainly we know that the presumed interoceptive effects of alcohol can be either positive or negative in rodents. Chris Cunningham showed years ago that minor modifications to the timing of administration of ethanol in a Pavlovian conditioned place learning paradigm could yield either a conditioned

place preference (CPP) or avoidance (CPA) for the side of the apparatus paired with alcohol injections. In a series of experiments, his group showed that intraperitoneal or intragastric administration of the same dose of ethanol produced an aversion to a distinctive side of the apparatus if it was paired with the initial, unpleasant effects of the drug, while if pairing was delayed, that side was chosen due to its association with the later, positive effects the animals perceived (Cunningham et al., 2002; Cunningham et al., 2006). Robinson and Berridge (1993) point out that as one progresses to uncontrolled wanting of a drug, liking may no longer be present. And a major feature of the Koobian allostatic dysregulation theory is the progression to a negative affective state, leading to a shift from reward-seeking to aversion for the protracted alcohol withdrawal state. The best this has been modeled thus far is in rats that show anxiety-like behavior in apparatus such as the elevated plus maze (Koob, 2014).

The roles of genetics—The use of genetic strategies is an area where alcohol research and its attempts to develop and utilize preclinical animal models effectively has always concentrated much more than is the case for other drugs of abuse or addictive behaviors more generally. This is mostly due to the belief by prominent investigators that genetic vulnerability was an important aspect of why most of the population experiments with, and even eventually uses alcohol, but only ± 10% of people experience difficulties serious enough to lead to an AUD diagnosis. The role of genetic animal models has frequently been reviewed and I won't recapitulate those studies here. All aspects of alcohol's effects discussed above have been subjected to genetic analyses, and long-standing animal models have been developed for preference drinking (McBride et al., 2014; Ciccocioppo, 2013; McBride et al., 2013; Quintanilla et al., 2012) and binge-like drinking (Crabbe et al., 2014). Increasingly, manipulations of single genes have revealed many differences versus control populations in many different responses to alcohol (Crabbe et al., 2006; Mayfield et al., 2016). For reviews of genetic contributions to the preclinical literature, the reader is referred to the citations above and (Greenberg and Crabbe, 2016; Becker, 2013; Cunningham, 2009; Buck et al., 2012).

Areas of opportunity—I have mentioned several areas where I feel that rodent models are strong, and some where I think they are clearly inapplicable. In this final section, I venture some suggestions for where I think an increased emphasis on rat and mouse research could be very useful. Some of these were discussed in an earlier review that focused specifically on genetics (Crabbe, 2012). Relapse models are commonly used in research on other abused substances [e.g., (Wolf, 2016)] but are used less frequently in alcohol research. Most such studies seem largely focused on studying the initiators of relapse (parallel to studying onset/development of addiction). Medications development and other treatment studies would doubtless be benefitted by better targeting to recovery/relapse. Relatively few animal studies even offer alcohol over long periods of time, but exceptions exist (Vengeliene et al., 2014; Becker and Lopez, 2016; Vendruscolo and Roberts, 2014; Wolffgramm and Heyne, 1995). I feel this is an understudied area in the non-human animal literature, probably because of the difficulty and expense inherent to long-term chronic studies and the unforgiving nature of relatively short US grant funding cycles. On the other hand, since most such models rely on some form of two-bottle preference drinking, it is unusual that rodents

drink in patterns focused enough to exceed the threshold for behavioral intoxication, unlike humans with an AUD.

Another fundamental question is how (but first, whether) alcohol comes to be such a highly valued reinforcer that humans will repeatedly drink to intoxication. Alcohol isn't that strong a reinforcer (as compared to other abused drugs) in standard preclinical studies, which makes this a particularly sensitive issue for our field. On the other hand, not many studies, for example, offer a rodent in a cage much to do to fill the time, and the appearance of an initially novel fluid as a drinking choice will evoke exploration. Modeling the reinforcement value of a drug is time-consuming and generally undertaken with operant schedules of access that require performance of work to gain access. Humans will come to sacrifice many other activities (and in severe cases, nutritional sources) in favor of drinking. Will rodents elect to drink alcohol given the choice of other rewarding activities, or fluids?

Serge Ahmed has done some very interesting research pitting cocaine or heroin vs sweetened solutions as a choice; the underlying theoretical issues, and many papers in this vein, are nicely reviewed by Vandaele et al. (2016). In his studies, rats that have learned to self-administer cocaine intravenously will generally rapidly learn to choose a sweet solution over cocaine once that choice is offered. But, the context of the choice to take drug or not is a powerful moderator of such effects, particularly when that context involves the influence of the abused drug. Alcohol is generally not given intravenously to rodents in part due to low potency (thus large volumes needed), in part due to the physical irritation and pain it causes, and because such studies are ferociously difficult in mice given their tiny veins. Such studies might be very informative, however and some certainly exist (Meisch, 2001). A recent review of intravenous alcohol research highlighted some interesting species differences as well (Le and Kalant, 2017). A major interpretive hurdle to be overcome would be that the contextual presence (interoceptive effects) of one choice could directly influence the reinforcement value of the alternative solution. This is similar to the difficulty of using quinine adulteration to mimic "punishment" in alcohol-experienced animals.

Conclusion—Many features of alcohol-related behavior are amenable to laboratory investigation, in species ranging from invertebrates to non-human primates. A good model system should target a phenomenon carefully. Its goal should be to offer a simpler way to interrogate the basis for the phenomenon. Even when strictly following the guidelines established for the care and use of laboratory animals, we are ethically allowed many invasive procedures with rodent models that lead us to deeper understanding of neurobiology. Translating from rodents to humans is probably most difficult in the domain of psychiatric disease, but the hope of better pharmacotherapies depends on making this effort. I have tried to point out some areas where I think preclinical research could offer hope for increasing our understanding of how AUD is like, yet different from, other addictive behaviors, as the need for better treatments remains acute.

The essential limitation of preclinical studies will always remain: any behavioral construct that is targeted in laboratory animals must be operationally defined. The more complex the construct, the more likely that multiple, possibly related, phenomena represented by any behavioral assay performed (the "lumping/splitting" problem). The example of "anxiety" is

useful to consider. Even 10 years ago, a preclinical investigator who wished to demonstrate the “role of gene X” in “anxiety” could simply produce evidence that an animal with a dysfunctional variant of gene X showed reduced time and entries into the unprotected arms of an elevated plus maze (EPM), the principal industry-standard assay for rodents. More recent publications attempting the same would be more likely to show reduced “anxiety-like behavior” in an EPM, a light-dark box, and an open field arena. But all three of these rodent assays are so-called “conflict” tests. While they may model one aspect of human anxiety disorders, they less clearly model others. For an interesting discussion of the use of specific rodent anxiety assays that putatively selectively model different human anxiety-related disorders (e.g., panic disorder vs obsessive-compulsive disorder) see (Haller et al., 2013). Another example is impulsivity, where different aspects of impulsive behavior are now targeted with specific human instruments, and some assays (e.g. delay discounting) can be assessed in both humans and laboratory animals (Dick et al., 2010).

Situating the DSM-5 Substance Use Disorder Diagnostic Criteria with Behavioral Economics: A Theoretical Translational Proposal

Warren K. Bickel

The question, “What is Addiction?” can be answered in many ways depending on the perspective (e.g., cultural, personal experience, etc.). However, when this question is asked of addiction science, then the answer derives from the conceptual schema that informs the empirical questions that we as a field ask (Bickel et al., 2013). Currently, DSM-5 is among the most widely used ways to diagnose the disorder, and it may be considered a schema that informs our understanding of addiction (American Psychiatric Association, 2013). One of the challenges confronting the DSM-5 schema of addiction comes from the Research Domain Criteria (Insel et al., 2010). The Research Domain Criteria (RDoC) argues that “Diagnostic categories based on clinical consensus fail to align with findings emerging from clinical neuroscience and genetics.” (Insel et al., 2010 p. 748). What may be a central concern of the RDoC initiative is that the symptom clusters of DSM-5 are nominal units (Cohen and Brooke Lea, 2004) and, as a result, are not relatable to the quantitative measurement (e.g., interval scale) used in molecular science. These concerns suggest that the DSM has limited scientific utility in the development of RDoC and the scientific understanding of psychopathology (Cuthbert and Insel, 2013). On the other hand, one challenge to the RDoC initiative is developing an understanding of psychopathology and diagnostic criteria from the ground up which will take considerable effort and time.

An alternative approach may be to explore the correspondence between an analytical level that is still process or mechanistically focused but conceptually closer to the DSM-5 diagnostic criteria. More specifically, could our understanding of addiction be furthered by translating the diagnostic criteria into the terms of quantitative behavioral processes (e.g., Watson, 2005)? Such an effort may allow those interested in molecular processes to have a target that is probably more tractable compared to the current formulation of the diagnostic criteria. In addition, the success in translating the diagnostic criteria in terms of quantitative behavioral processes may help achieve the goals of RDoC sooner while retaining the diagnostic criteria in a translated form.

One candidate behavioral system that may prove useful in translating DSM-5 criteria for substance use disorder is behavioral economics. Behavioral economics refers to the integration of two disciplines, psychology (including operant approaches) and economics, and has a longstanding history of contributions to addiction science (Hursh, 1984; Vuchinich and Tucker, 1988). As applied to addiction science, behavioral economics is the behavioral study of the relatively greater value accorded to alcohol and drug reinforcers compared to pro-social reinforcers, e.g, employment, school, and family (Bickel et al. 1993; Bickel et al. 2014a; Hursh 1984; Vuchinich and Tucker 1988; MacKillop 2016). Behavioral economics provides unique concepts, methods, and terminologies to quantify the value, effects, and interactions between various commodities and reinforcers (Bickel et al., 1992). As such, behavioral economics may comprise a sufficiently rich set of processes along with wide range of corresponding measurements to explore a quantitative translation of the diagnostic criteria.

The purpose of this paper is to take the schema and eight of the 11 diagnostic criteria provided by DSM-5 (See Table 1) and propose how they may be related to two broad categories: (1) specific behavioral economic concepts, principles, processes, and measures; and (2) a model of how some behavioral economic principles interact, referred to here as Reinforcer Pathology. The goal here is to explore the plausibility of translation, not to claim that our current knowledge is sufficient to conclude that translation is assured. Clearly, more studies will be necessary to draw such conclusions. However, future research can prospectively and rigorously test the relationship between behavioral economic processes and current diagnostic criteria. The three remaining diagnostic criteria (tolerance, withdrawal, and craving) are independent and well-studied phenomena that have an extensive profile of effects. These independent phenomena have been shown to also impact behavioral economic measures (Giordano et al., 2002), but reviewing that work is beyond the scope of this paper. Before examining the eight diagnostic criteria from a behavioral economic perspective, I will outline briefly two critical concepts in the behavioral economics of addiction.

Behavioral Economics: A Brief Review—Application of behavioral economics to addiction science has largely focused on two processes: (1) the excessive preference for immediate reinforcers, and (2) the high valuation conferred to abused substances (Bickel et al., 2016; Heinz et al., 2012; MacKillop, 2016). Both processes have been measured with choice for actual and hypothetical outcomes. Comparisons of actual and hypothetical outcomes have been found to be concordant (Amlung et al., 2012; Bickel et al., 2009; Johnson and Bickel, 2002; Madden et al., 2003; Wilson et al., 2016). Moreover, both of these processes have been shown to be stable over time (Kirby, 2009; Murphy et al., 2009; Ohmura et al., 2006). Note that although these processes are generally robust, as will be reviewed below, a few individuals often fall in the range of controls (Bickel et al., 2008, 1993). The processes discussed in this paper are not referring to that minority.

The first process is delay discounting, which refers to the reduction in value of a reinforcer as a function of the delay to its receipt (Mazur, 1987). Certainly, most, if not all, individuals discount delayed rewards to some extent in that most would likely prefer an immediate $1000 relative to receiving a $1000 a year from now. The preference for the immediate

$1000 would indicate that the later identical amount is discounted but would not index exactly how much that later amount is worth. To identify the extent of discounting, the immediate amount is systematically decreased (e.g., $950 now vs $1000 in a year, $900 now vs $1000 in a year, etc.) until preference switches from the immediate to the delayed amount. The point at which preferences switch is referred to as the indifference point. If these series of choices are conducted at several delays (e.g., 1 week, 1 month, 3 months, 6 months, and 1 year), then a curve can be determined that measures the decline in value as a function of delay. These curves are typically observed to be hyperbolic in form. Hyperbolic delay discounting is an empirical observation based on numerous studies, while exponential discounting proposed in traditional economics has been shown to be inconsistent with the observed findings (Frederick et al., 2002; Mazur, 1987). An example of the extent of discounting can be seen in study of delayed monetary discounting curves for opioid-dependent individuals and matched community controls (Madden et al., 1997). In that study, opioid-dependent individuals discounted a hypothetical $1000 substantially more than the matched controls. This observation has been replicated in almost every form of substance use disorder with only conflicting results observed in those with the marijuana-use disorder (Bickel and Marsch, 2001; MacKillop et al., 2011).

Valuation, the second process, can be determined by measurement of behavioral economic demand. Behavioral economic demand, which refers to the quantitative association between purchasing of a commodity and its cost, is widely measured using purchase tasks in which individuals make cost-benefit decisions about how much of a specific commodity to consume at a different range of prices. For example, in the alcohol purchase task (APT), individuals report the number of drinks they would buy at escalating prices (e.g., “How many drinks would you buy if they were $1 each?”; “How many drinks would you buy if they were $2 each?”; etc.). The responses across the different prices are translated into a demand curve with multiple indices including the intensity of demand (i.e., consumption at a near-zero price) and elasticity of demand (i.e., the change in consumption as price increases). For example, demand curves for heavy and light drinkers have been compared (Murphy and MacKillop, 2006). The heavy drinkers value alcohol more than light drinkers which is reflected in the heavy drinkers having a higher intensity of demand and a lower elasticity of demand. These indices of demand have been widely used to assess drug valuation and have demonstrated the ability to predict treatment outcomes.

Behavioral economic concordance with DSM criteria

Continuing to Use Despite Delayed Consequences as Delay Discounting.: DSM-5 includes several diagnostic criteria of dependence that refer to the continuing use of substances despite its consequences. These include (1) “hazardous use” (i.e., repeated use of substances when it puts you in danger); (2) continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by the substance, and (3) continuing to use, even when you know you have a social or interpersonal problem that is caused or made worse by the substance. The first two of these criteria are particularly relevant to the current opioid overdose crisis in that most users are likely aware that highly potent opioid agonist, fentanyl, may be in street opioids and may lead to overdose. However, this knowledge is not sufficient to prevent its use. Indeed, the Center for

Disease Control has recently reported that opioid overdose cases were up approximately 30% from July 2016 to September 2017 (2018).

These diagnostic criteria may be understood from the behavioral economics concept of delay discounting. An empirical body of evidence indicated that individuals with SUDs exhibit substantial discounting of delayed events or outcomes (e.g., money, health, substances) when confronted with the opportunity to use a substance immediately despite being cognizant that later negative consequences may result. They may do so because these later events are devalued. Previous studies demonstrated excessive discounting of monetary reinforcers among populations with substance use disorders, and with problem gambling compared to controls (Amlung et al., 2016; MacKillop et al., 2011). For example, one meta-analysis of non-continuous observations examined 57 comparisons (n=3,329) and found a medium magnitude effect ($d=0.58$; $p<0.0001$), with significantly larger effect sizes for studies using clinical vs. non-clinical samples (MacKillop et al., 2011). Another meta-analysis examining continuous relations found that delay discounting is robustly associated with measures of addiction severity and quantity/frequency of substance use (Amlung et al., 2016). Indeed, another review concluded that delay discounting should be considered a behavioral marker of the entire addiction process (Bickel et al., 2014b).

In addition to evidence obtained by comparing discounting of delayed rewards among individuals with substance use disorder and controls, other evidence from studies investigating the efficacy of current behavioral treatment of addiction (e.g., contingency management) supports this perspective. Contingency management, as often applied, provides a reinforcer to the drug-dependent person for abstinence as measured biochemically. For example, if the person is abstinent on a specific day, he or she may receive a couple dollars for subsequent visits with abstinence during the week. Contingency management is among the most efficacious treatment for various drugs of dependence (Higgins and Rogers, 2009). In a meta-analysis of the contingency management studies (Lussier et al., 2006), greater delay between the target behavior (e.g., presentation of a drug-free urine sample) and the receipt of the reinforcer for that behavior was shown to significantly affect the efficacy of that treatment; that is, greater delay diminished the efficacy of contingency management. An interesting future experiment would investigate delay discounting ability to predict the efficacy of contingency management when reinforcements are delivered at different delays. Overall, these findings from delay discounting and addiction treatment research are consistent with the two previously mentioned DSM criteria (i.e., delayed outcomes are not valued or discounted among those suffering from addiction).

Inability to regulate consumption as preference reversals.: Two diagnostic criteria refer to the inability to regulate consumption. The specific criteria are: (1) “impaired control” (i.e., taking the substance in larger amounts or for longer than intended), and (2) attempts or desire to cut down. These criteria may be familiar to many who have been interested in restricting caloric intake but have succumbed to temptation when the dessert tray arrives. This inability to regulate consumption is perhaps best documented when individuals enter treatment to curtail substance use. For example, despite the fact that 68% of regular smokers would like to quit and 43% have attempted to quit in the past year, only 6% of smokers who

attempt to quit without assistance maintain abstinence for 30 days US Dept of Health and Human Services (2014). Moreover, those who seek assistance with quitting from a variety of efficacious treatments will only experience a success rate of approximately 30% (Cahill et al., 2013).

From a behavioral economics perspective, attempts at abstinence that later result in relapse are conceptualized as preference reversals. Preference reversals refer to switching preference from a larger later reward to a sooner smaller reward as the rewards become temporally proximate (Kirby and Herrnstein, 1995). Preference reversals are derivable from the deeply bowed hyperbolic discounting curves. When viewed from a greater temporal distance, the larger later reward has greater value and is preferred. However, as the temporal distance decreases, the value of the sooner smaller reward increases until it becomes more valued and preference reverses to the smaller more proximal reward.

Although preference reversals have been well recognized as a phenomenon, they are largely understudied in clinical contexts. Recently, two studies have examined the association between preference reversals and delay discounting and have shown that they are significantly correlated in controls, smokers, or both (Pope et al., in press; Yi et al., 2016). However, applications to predicting treatment outcomes have yet to be examined. Given that delay discounting is predictive of intention to quit in cigarette smokers (Athamneh et al., 2017), predictive of many substance use treatment outcomes (Stevens et al., 2014), and is well correlated with preference reversals, delay discounting could be used as a proxy measure to examine treatment outcomes until such time that preference reversals procedures are well studied and applied in this context (Pope et al., in press). However, even though Stevens and colleagues' recent review concluded that there was consistent evidence of delay discounting predicting treatment outcome in tobacco and cocaine dependence (only one study was conducted with alcohol use disorder that reported negative results), the review notes that results can be influenced by the magnitude of delay discounting with higher magnitudes functioning as better predictors (see also Mellis et al. 2017). In addition, the review noted that the relationship between delay discounting and treatment outcomes may be moderated by some treatment elements such as the magnitude of the incentive in contingency management. Stevens et al. (2014, p. 66) concluded, "If replicated, these findings may have important clinical implications, as they suggest that measures of delay discounting can be used to guide treatment allocation". Although considerably more research will be necessary, the conceptual relationship between preference reversal and inability to regulate consumption appears worthy of additional studies as well as its role in relapse.

Interaction between Substance- and Prosocial Reinforcers as Reinforcer Pathology.: Four diagnostic criteria refer to the often observed clinical picture of addiction where substances increase in value, the value of prosocial reinforcers such as employment and relationships show a concomitant decline. Observations such as these have been termed anhedonia. However, the anhedonia we are referring to in this study is a special form found specifically among individuals with addiction. Anhedonia typically refers to the inability to feel pleasure, but for addiction, this is not a loss of pleasure from all rewarding events as often documented in cases of depression, but a loss of pleasure from things other than

substances. This loss in value of normal events is associated with an increase in the value of abused substances. These diagnostic criteria include: (1) spending a lot of time getting, using, or recovering from use of the substance; (2) not managing to do what you should at work, home, or school because of substance use; and (3) continuing to use, even when it causes problems in relationships. Note that a fourth, giving up important social, occupational, or recreational activities because of substance use could also be viewed from this vantage point in addition to, as noted earlier, continued use despite delayed consequences. The latest version of a behavioral economic theory of addiction, Reinforcer Pathology, may provide a potential translation of these criteria.

The initial version of Reinforcer Pathology specified that excessive discounting of delayed outcomes and drug valuation were independent factors that interacted to support an addiction. As such, we could consider Reinforcer Pathology as one cell that results from the 2 by 2 matrix composed minimally vs substantial discounting of delayed outcomes crossed with a low or high valuation for the drug of dependence. From this perspective, the cell representing both substantial discounting of delayed rewards with high valuation constitutes Reinforcer Pathology. To be clear, this perspective is not specifying that all individuals who meet misuse or dependence criteria fall neatly into this cell. Rather, this view indicates that individuals who fall into this cell exhibit these two processes that contribute to the expression of addiction (Lemley et al., 2016). We note that this initial version could be considered an extension of those theories of addiction that were based on the dopamine hypothesis and other related theories (Bickel et al., 2018).

Recently, we extended and elaborated the initial Reinforcer Pathology and a new version has emerged (Kwako et al., 2016). In this new version, we again are referring primarily to those individuals who fall into the cell that exhibit both excessive discounting crossed with excessive reward valuation. However, the key differences between the initial and new version are that the new version specifies that reinforcers are integrated over a temporal window and the length of that window determines the relative value of different reinforcers. The temporal window of integration has been studied previously in neuroscience, auditory-perception, and information sciences (Gupta and Merchant, 2017; Okamoto and Fukai, 2009) but to my knowledge has not been previously addressed in any existing theory of addiction (Bickel et al., 2018; West, 2006).

To see if this temporal window determines the value of different reinforcers consider the intensity, range in valence, and the temporal characteristics of the drug and prosocial reinforcers. Drug reinforcers are immediate, intense, brief and reliable, while prosocial reinforcers are less immediate, less intense, less reliable (e.g., good, bad, or just okay) but may accrue considerable value over time (cf., Heyman, 2009, P. 145). Now consider the relative value of these two types of reinforcers when viewed from a shorter versus longer temporal window. When evaluated over a short temporal frame, the choice is between a brief intense reliable reinforcer vs. lower intensity, less reliable reinforcers. Hence, the substance will likely have greater value. If the short temporal frame is operative and, as a result, prosocial reinforcers have less value, then according to the basic behavioral principle of the Matching Law (Herrnstein, 1974), the remaining reinforcers will exhibit increased strength or value. When evaluated over a longer temporal frame, the prosocial reinforcers would have

higher value compared to substances because the prosocial reinforcers' lower intensity value could be integrated over a longer timeframe. However, this does not mean that the substance-related reinforcers would have no value, but rather would have less value when integrated over a long temporal window compared to when integrated over a short temporal window. This change in preference and valuation depending on the length of the temporal window might be a result of the number of reinforcers present during that timeframe. Thus, Reinforcer Pathology is the condition in which the temporal window is restricted; that, in turn, diminishes the value of temporally extended prosocial reinforcers while enhancing the value of brief intense substances. Importantly, this approach identifies the temporal window as a potential target for intervention.

From the vantage point of the new version of Reinforcer Pathology, the four DSM criteria [(1) spending a lot of time getting, using, or recovering from use of the substance; (2) not managing to do what you should at work, home, or school because of substance use; (3) continuing to use, even when it causes problems in relationships and (4) giving up important social, occupational, or recreational activities because of substance use] could be interpreted to indicate that as an addiction develops, the temporal window decreases. This, in turn, increases the value of substance reinforcers and decreases the value of prosocial reinforcement. One method to test this idea would be to identify an intervention that would lengthen the temporal window and if this version of Reinforcer Pathology were operative, then the value of substances should decline. Episodic Future Thinking (EFT) is an intervention that has been shown previously to result in a greater valuation of future events as measured by delay discounting (Peters and Büchel, 2010). EFT, based on the emerging science of prospection (Gilbert and Wilson, 2007), asks individuals to create several concrete possible future events they might experience. EFT, as applied in our prior studies consists of having participants develop several potential future events that correspond to several future timeframes (e.g., 1 week, 1 month, 3 months, etc.). For each of these timeframes, participants are asked to concretize the events (e.g., What are you doing? Who will be there? What will you see, hear, smell, and feel?). Participants are instructed not to refer to substance use or the goals of abstinence. As such, we note that EFT is different from a variety of other approaches including brief motivational interviewing, cognitive behavior therapy, and implementation intentions.

The effects of EFT on delay discounting and the valuation of substance reinforcers recently has been examined among smokers and alcohol-dependent individuals. For example, EFT increases the valuation of the future and decreases cigarette and alcohol valuation as measured in the purchase task (Snider et al., 2016; Stein et al., 2016). This replicates similar findings with the obese (Daniel et al., 2013). Stein et al. (2016) asked cigarette smokers to come to the study laboratory cigarette deprived and gave them free access to cigarettes for an hour. During that free access to cigarette hour, participants listened to their assigned, self-generated cues (EFT or control) recorded by their own voice. Interestingly, during that hour, the EFT group smoked significantly less number of cigarettes compared to the control group. Symmetrically, interventions that increase the discounting of delayed reinforcers (value the future less) should result in greater valuation of brief intense reinforcers (Sze et al., 2017). Two important questions are: (1) Do all interventions that change the discounting of delayed rewards also change substance valuation among those with substance use

disorder? And (2) Are most of those affected with SUDs susceptible to interventions of time perspective? Nonetheless, the extant results support the Reinforcer Pathology notion and may provide novel insights into the substance-related anhedonia and the corresponding four DSM criteria. Additional observations will determine the breadth and magnitude of these effects. A related consideration is the extent to which the reinforcer pathology concept may be applicable to other conceptually-related phenomena. For example, Epstein and colleagues has applied reinforcer pathology to obesity (Carr et al., 2011) and delay discounting has been proposed as a trans-disease process (Bickel et al., 2012). However, given the recency of reinforcer pathology model, numerous questions remain to be addressed in future research such as whether these phenomena predate and contribute to addiction or are the consequences of consuming substances and how other decision processes such as response inhibition may be related (cf., Bickel et al., 2017).

Addiction is clearly a challenging and multi-faceted phenomenon. If it was easily understood, then surely, we would be able to prevent and treat addiction with greater alacrity than we in fact do. As such, we must continue to find new empirical results and consider new conceptual understandings to see if those new findings and perspectives permit greater prediction and change in the phenomena of addiction. Here I considered how the majority of the 11 DSM-5 criteria may be interpreted from a behavioral economics perspective (See Bickel et al., 2018, for a detailed review and comparision of contemporary theories of addiciton including reinforcer pathology). If new studies support or clarify this interpretation, the field may be able to employ them as quantitative measures of diagnostic criteria and perhaps lead either to a more comprehensive paradigm of addiction or alternatively perhaps clarify that addiction is not a unitary phenomenon.

General Discussion

Crabbe and Bickel's foregoing discussions highlight a number of key issues for advancing research and practice on substance use disorders and provide concrete suggestions for setting the stage for more effective translation between basic science and clinical endeavors. Below we summarize some of the most critical issues highlighted in their responses.

Does addiction entail multiple distinct processes or can a single underlying process explain its myriad manifestations?—The landscapes painted by Crabbe and Bickel, and major theorists noted in Table 1, suggest the possibility that what we term addiction or substance use disorders represent complex phenomena that involve several distinct yet correlated processes. Assuming that such a view is correct, seemingly competing theories may each provide a valuable perspective on how to conceptualize addiction as a disorder of reward evaluation and processing, self-regulatory processes, habit and other automated processes, and drug-induced homeostatic dysregulation. Each process contributes to one or more clinical features of disorder but, by itself, fails to account for the full complement of symptoms observed in patients. Moreover, to the extent that a given symptom (e.g., compulsive use) can arise from multiple processes (e.g., habit, incentive sensitization, Reinforcer Pathology), optimal diagnostic approaches may need to involve resolving those mechanisms that lead to manifest symptoms. As embodied in the Research Domains Criteria (RDoC; Insel et al., 2010), such an endophenotypic assessment strategy

could be more useful than the current approach in providing a more mechanistic and process-oriented view of pathology. The translation of RDoC concepts to the study of addiction has been slow but appears to be gaining in influence in that it provides a tractable strategy for identifying treatment targets (Kwako et al., 2015; Litten et al., 2015) and facilitates the type of translation evident in Bickel and Crabbe's positions. Although perhaps not ready for routine clinical use, a range of laboratory tasks have been developed that map onto addiction constructs (Stacy and Wiers, 2010) and hold potential for not only directly measuring critical processes but being able to do so in a quantitative way as described by Bickel with respect to behavior economic measures.

How many diagnostic criteria are needed to define a disorder? How do you count them?—Bickel highlights the notion that ostensibly phenotypically distinct diagnostic criteria may be endophenotypically similar in that they represent a common underlying core process. Kendler and colleagues' (2012) genetic factor analyses yield results with similar implications. These types of findings raise the question of whether the current diagnostic architecture of DSM-5 artificially "splits" rather than "lumps" various signs and symptoms that may more profitably be viewed as reflecting common underlying mechanisms? Indeed, as is evident in Table 1, ICD "lumps" pairs of distinct DSM AUD/AD criteria into single criteria based on conceptual similarity.

Beyond the conceptual similarity and grouping symptoms by common mechanism, an additional complexity is mapping various alcohol consequences onto diagnostic criteria. As noted by Martin et al. (2014, p. 1776), *"If someone reports that frequent intoxication has led to impairment in their familial role obligations because of reduced social activities with their family, should this count as one symptom or two? Given these quandaries, it is not surprising that some criteria are highly correlated…we found that the association of the AUD symptoms of role impairment and reduced social activities was exceptionally high (tetrachoric r = 0.85)*." Recent studies (Raffo et al., in press; Steinley et al., 2016) have shown that the DSM-IV and 5 criteria sets could be shortened without much if any loss of information. All of these findings suggest that the approach to diagnosis as embodied in the current DSM is, at best, inefficient. Moreover, it suggests that we might want to move beyond the largely deliberative, consensus approach to deriving diagnostic criteria sets without a conceptual core to one informed by theory and characterized by more attention to distinct underlying mechanisms.

Are all acquired changes reflecting neuroadaptation indicative of disorder?—In DSM-III (APA, 1980), the diagnostic category, "substance dependence," the presumed more severe of the of the two AUD subcategories, was defined on the basis of either tolerance or withdrawal. While the DSM-5 working group ultimately decided to include withdrawal among the DSM-5 SUD criteria, the issue appeared to be somewhat contentious in that it was argued that "the adaptations associated with drug withdrawal are distinct from the adaptations that result in addiction, which refers to the loss of control over the intense urges to take the drug even at the expense of adverse consequences" (O'Brien et al., 2006). Verges et al. (2018) recently reported that, among daily drinkers, "the reported mean number of drinks without intoxication is associated with daily drinking quantity but not with AD

diagnosis" (after controlling for quantity) suggesting that tolerance development may be a risk factor for developing other symptoms associated with addiction but is not, itself, a part of this syndrome (and thus, likely distinct from other putative indicators). These tolerance findings are consistent with the multivariate genetic structure described earlier by Crabbe.

This is not to say that tolerance or withdrawal are benign conditions. Greater tolerance facilitates higher levels of consumption which is the prime determinant of most medical consequences of alcoholism (Rehm et al., 2013). Major withdrawal from alcohol (i.e., delirium tremens), although rare, is a serious medical condition associated with nontrivial mortality rates (Schuckit, 2014). Despite the seriousness of both types of drug adaptations for health and the fact that they are correlated with other symptoms of AUD, perhaps by virtue of their association with chronic consumption, the wisdom of "lumping" them with symptoms more clearly associated with addiction deserves further scrutiny as their etiology, course, and treatment implications may differ as suggested by multiple lines of research. This issue highlights a paradox that some reliable indicators of addiction that are medically important may be distinct from addiction itself, at least in some cases.

Can we distinguish vulnerability to addiction from manifest addiction?—As noted in the introduction and in Crabbe's and Bickel's statement, many key features of addiction are observable prior to the onset of addiction. Indeed, they are often observable prior to exposure to the addictive substance. While the problem has been recognized for decades (e.g., Barnes, 1983), how we consider this in our diagnostic formulations has not been a focus of systematic work. Some early typologies of alcoholism implicitly recognized this issue by noting associated characteristics (e.g., personality pathology and mood disorders; e.g., Schuckit, 1985) in distinguishing types of alcoholism on the basis of comorbidty patterns and developmental history. Taking this a step further and determining how to apportion, say, acquired tolerance from initial sensitivity or drug-induced hazardous behavior from a general pattern of risk taking has not been given much attention. Additionally, an RDoC approach doesn't necessarily resolve this issue since this "confound" is likely present at all levels of neurobiological analysis. The distinction may not be merely academic since it may have implications for gauging adequate treatment response and determining what a good clinical outcome is.

How can rodent models advance our understanding of the human condition and how to treat it?—Crabbe highlights the challenges faced by those seeking to model the human condition in animals in that some diagnostic criteria seem uniquely human, such as "using in greater amounts and/or longer *than intended* [emphasis added]; desire, but failure to quit or control use; and craving." However, he goes on to highlight the success of animal models of tolerance and withdrawal, the recent interest in appetitive behavior in the face of punishment, and new areas for research that appear amenable to translation. An important message for those working with animal models is that greater attention to the human condition might provide opportunities for developing new models with greater potential for translation to the clinic. Rather than repeatedly looking under the same streetlight for the same keys, researchers might consider moving on to new streetlights illuminated by clinical description and theory.

Is it time to develop a science of recovery?—Both Bickel and Crabbe highlight the need to consider basic and applied research on recovery processes, which despite increasing attention from clinical researchers (e.g., see Kelly and White, 2010), remains a greatly under-researched area (Humphreys and Bickel, 2018). While as noted by Crabbe, some aspects of the recovery process (e.g., intentions of remaining abstinent) seem uniquely human, much can be done by examining the long-term course of behavior following prolonged periods of heavy substance exposure that could provide basic insights into the course of changes in brain mechanisms relating to drug seeking and self-regulation. Additionally, the term "recovery" may have connotations that mislead us clinically and theoretically in that the term itself implies a return to a prior level, a *restitutio ad integrum,* as opposed to the recruitment and development of new processes that compensate for possible durable changes induced by chronic drug excess. As noted by Bickel, behavioral economic concepts can be flexibly applied to relapse and recovery and perhaps the evaluation of the type of theories listed in Table 1 should be expanded to highlight relevance for recovery.

Concluding Statement

In recent years we've witnessed the continued development of theories of addiction along with a greater understanding of addiction's neurobiological underpinnings. However, major gaps remain in our translation between basic research and clinical application with respect to assessment and to targeting specific, underlying mechanisms therapeutically. Also, there is increasing recognition that no single theory of addiction, at this time, is sufficiently comprehensive to explain addiction in all its manifestations. Developing an integrated framework that explains common and unique mechanisms generating each of these manifestations is a goal that is currently aspirational but does seem within reach. However, in the near term an important consideration for addiction science is to identify concepts that will lead to new questions that, in turn, will result in new answers and will allow us to understand more fully the phenomena of addiction.

Acknowledgments

Preparation of this manuscript was supported by the US Department of Veterans Affairs Grant BX000313 and NIH grantsU01AA13519, and R24AA20245 to John Crabbe, NIH grants K05AA017242 and R01AA024133 to Kenneth J. Sher, and NIH Grant P60AA10760 to Tamara J. Phillips, NIH grants R01 DA039456, R01 DA034755 and R01 AA021529 to Warren K. Bickel

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Table 1.

Distinctions Among Diagnostic Criteria, Clinical Addiction Concepts, and Major Theoretical Concepts

Formal Criteria	Diagnostic Systems			Clinical Addiction Concepts				Major Theoretical Concepts				
	DSM-IV[1]	DSM-5[2]	ICD-10[3]	Compulsive use	Neuro-adaptation	Craving	Addictive Substance Preferred to Other Reinforcers	Incentive Sensitization (Robinson-Berridge[4])	Habit (Everitt-Robbins[5])	Allostasis (Koob-LeMoal[6])	Multi-Step (Piazza-Deroche-Gamonet[7])	Reinforcer Pathology (Bickel et al[8])
Legal Difficulties	**AA**	---	---									
Use in hazardous situations	**AA**	**AUD**	---	X???					X		x	X
Failure to fulfill major role responsibilities	**AA**	**AUD**	**AD**	X			X				X	X
Use despite social or interpersonal problems	**AA**	**AUD**		X				X	X		X	X
Use despite physical or psychological problems	**AD**	**AUD**	**AD**	X				X	X		X	X
Tolerance	**AD**	**AUD**	**AD**		X					X		
Withdrawal	**AD**	**AUD**	**AD**		X					X		
Impaired Control (larger/longer)	**AD**	**AUD**	**AD**	X	X???		X	X	X		X	X
Attempts or desire to “cut down”	**AD**	**AUD**		X				X	X		X	X
Time spent (obtaining, using, recovering)	**AD**	**AUD**		X			X	X	X			X
Important activities given up	**AD**	**AUD**	**AD**	X			X					X
Craving	---	**AUD**	**AD**			X		X			X	
Noncriterial Sx's Implied by Theory												
Negative affectivity	---	---	---							X		
Relapse Vulnerability						X		X		X	X	

Notes; AUD=Alcohol Use Disorder. AA=Alcohol Abuse. AD=Alcohol Dependence. We use the alcohol-specific designations her rather than SUD, SD, and SA

[1]DSM-IV=Diagnostic and Statistical Manual, Version 4 (American Psychiatric Association, 1994)

[2]DSM-5=Diagnostic and Statistical Manual, Version 5(American Psychiatric Association, 2013

[3]ICD-10=International Classification of Diseases, (WHO 2007)

[4]Robinson and Berridge 1993

[5]Everitt and Robbins 2016

[6]Koob and LeMoal 1997, 2006

[7]Piazza and Deroche-Gamonet 2013

[8]Bickel et al., 2014a