Current Addiction Reports
https://doi.org/10.1007/s40429-018-0202-2

ADOLESCENT/YOUNG ADULT ADDICTION (T CHUNG, SECTION EDITOR)

Neurobiology of Craving: Current Findings and New Directions

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Abstract

Purpose of the Review This review seeks to provide an update on the current literature on craving and its underlying neurobiology, as it pertains to alcohol and drug addiction.

Recent Findings Studies on craving neurobiology suggest that the brain networks activated by conditioned cues in alcohol- and drug-dependent populations extend far beyond the traditional mesolimbic dopamine system and suggest that the early neurobiological theories of addiction, which heavily relied on dopamine release into the nucleus accumbens as the primary mechanism driving cue-induced craving and drug-seeking behavior, are incomplete. Ongoing studies will advance our understanding of the neurobiological underpinnings of addiction and drug craving by identifying novel brain regions associated with responses to conditioned cues that may be specific to humans, or at least primates, due to these brain areas' involvement in higher cognitive processes.

Summary This review highlights recent advances and future directions in leveraging the neurobiology of craving as a translational phenotype for understanding addiction etiology and informing treatment development. The complexity of craving and its underlying neurocircuitry is evident and divergent methods of eliciting craving (i.e., cues, stress, and alcohol administration) may produce divergent findings.

Keywords Craving · Addiction · Neurobiology · fMRI · Cue reactivity · Alcohol · Drug

Introduction

The notion of craving and its association with addiction has been the purview of scientific study for the past 60 years [1]. Craving for a substance is defined as a strong desire to consume that substance, which in turn has been associated with the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criterion of loss of control over substance use, one of the seven criteria for substance dependence in DSM-IV [2]. As the diagnostic system evolved, craving itself represents a criterion for substance disorder in the current version of the DSM-5 [3]. A longitudinal study of alcoholism course and chronicity found that craving was associated with the highest relative risk of all other diagnostic criteria for alcoholism [4]. Furthermore, recent studies have advanced our understanding of the neurobiological and genetic bases of craving. Many of these studies use one or a combination of the following: self-report data in family-based designs (e.g., [5]), experimental laboratory paradigms (e.g., [6]), and neuroimaging techniques (e.g., [7]). Pharmacological studies have also leveraged craving paradigms to screen [8] and to establish the initial efficacy [9, 10] of promising medications for alcoholism. In short, the construct of craving has been successfully applied to the study of addiction etiology and treatment. This review of the scientific study of craving and substance use will begin with a discussion of the phenomenology and assessment of craving, followed by a review of studies on craving neurobiology. We will then conclude by providing directions for future inquiry in the field.

This article is part of the Topical Collection on *Adolescent/Young Adult Addiction*

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Phenomenology and Assessment

Although the operational definition of craving has been debated over the years, craving is inherently a subjective experience, best described as a state of desire or wanting [11]. Individuals trying to abstain from alcohol or drugs often

Published online: 04 May 2018

describe craving as an unpleasant state that challenges their commitment to abstinence and is often associated with relapse (e.g., [12]). Furthermore, subjective craving assessed in the laboratory and in the natural environment is positively correlated with negative mood [13, 14]. In fact, while in a craving state, individuals frequently show impaired cognitive processing. For example, Monti and colleagues have shown craving to both increase reaction time [15] and interfere with cognitive resource allocation [16]. Further, while experiencing craving, individuals often overestimate the duration and intensity of their own future urges [17]. This is consistent with Marlatt's conceptualization of cravings as ocean waves that gradually build, peak, and then subside [18]. To that end, scientists and practitioners alike are interested in helping individuals surf those waves of craving without consuming substances of abuse. Importantly, craving has been shown to impair working memory which is a cognitive process related to effective decision-making [19].

It is also of interest that imagery is emerging as an important variable in the study of craving. The work of Kavanagh and colleagues suggests that imagery across sensory channels is critical to the experience of craving [20]. For example, a study showed that visualizations and other forms of sensory imagery were observed in cravings across a range of substances, including food [21, 22]. This line of work makes a case for intensive thoughts forming a "gateway" to episodes of craving and convincing data are presented across substances of abuse. Clearly, identifying the psychological and neurobiological underpinnings of craving has vast implications for addiction etiology and treatment development.

The assessment of craving has received a great deal of attention in the addiction literature over the past three decades (for a review, see [23]). Although a number of self-report paper and pencil measures have been developed to assess craving for substances of abuse (e.g., [24] and [25]), the cue exposure paradigm represents the gold standard in the experimental assessment of craving. This paradigm consists of systematically exposing individuals to alcohol or drug cues and assessing their associated urge to drink/use. For example, during alcohol cue exposure, participants are asked to hold and smell a glass of water as a standard procedure to control for the effects of simple exposure to any potable liquid.

Participants are then presented their preferred alcoholic beverage and asked to hold and smell the beverage for the same number of trials [26]. Experimenter observation and prerecorded instructions further standardize the procedure. In addition to recording self-reported urge to drink, this protocol measures physiological reactivity to cues, such as heart rate, blood pressure, and salivation. These procedures have been found to elicit craving among heavy drinkers and alcohol-dependent individuals [26] and to yield valid and reliable measures of cue-induced craving [27] that are predictive of treatment outcome (e.g., [28]). The cue exposure approach to eliciting craving has been validated for other substances of abuse, including cannabis [29], methamphetamine [30], and even food [31].

Variations of these procedures include the presentation of alcohol/drug stimuli via pictures, imagery, and small taste cues. Different modes of cue presentation and methodological approaches may be more or less suited for different research questions and scientific designs, including brain imaging studies, and may be uniquely informative in experimental and clinical settings. For instance, a treatment study comparing two measures of craving (cue-elicited versus self-reported tonic craving) found that cued craving was uniquely and positively associated with a total number of drinks per drinking occasion, suggesting that cue-elicited craving may capture loss of control over drinking during recovery [32].

From a theoretical standpoint, the cue reactivity paradigm is largely predicated on Pavlovian conditioned responses. Specifically, repeated pairing of alcohol/drug cues (e.g., sight, smell, and taste of the alcoholic beverage or drug) with alcohol/drug consumption over time produced a conditioned reinforcement such that over time, alcohol/drug cues become conditioned stimuli which in turn elicit craving for that substance. These learned processes have been well documented in both human [33] and animal [34] models. The argument can also be made that a variety of stimuli, including external and internal states, may become conditioned stimuli and therefore elicit craving. This is consistent with both the theoretical framework and the clinical phenomenology of craving as well as clinical anecdotes from individuals in recovery [1].

The study of craving has been advanced by ecological momentary assessment (EMA), the near real-time assessment of experiences and behavior in the natural environment using, for example, smart phones. While EMA has been predominately used in the assessment of smoking and smoking relapse (e.g., [35]), it is increasingly being used in the study of alcohol and cannabis use. For example, Litt et al. showed that the magnitude and frequency of craving in the natural environment were associated with consumption in alcohol-dependent individuals [36]. Monti and colleagues have used EMA as an adjunct to laboratory-based procedures such as cue reactivity and alcohol challenge procedures (e.g., [37] and [38]).

While lab-based procedures offer a measure of control that is not possible in the real world (for example, the careful study of blood alcohol concentration and the biphasic effects of alcohol), EMA allows us to capture more general contextual factors, such as the presence of others in the drinking environment [39]. This approach is particularly useful with adolescent populations. For example, Ramirez and Miranda Jr. combined cue reactivity assessment in the laboratory with EMA assessment of craving in the real world in a sample of non-treatment-seeking adolescent drinkers and found that cue-induced craving in the laboratory predicted subsequent alcohol use in the natural environment [40].

In short, the selection of assessment instrument should be driven by the experimental question of interest, including the use of cue exposure paradigms in the context of neuroimaging in order to elucidate the neural underpinnings of craving and craving suppression [41••]. Importantly, the neural underpinnings of craving may vary as a function of the methods used to elicit craving, such as alcohol/drug-induced craving, cue-induced craving, and stress-induced craving. A recent review of neuroimaging studies by Seo and Sinha concluded that neuroadaptations in the cortico-striatal-limbic circuit including the medial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, striatum, and amygdala contribute to alcohol craving and subsequent relapse [42].

Neurobiology

Cue-induced craving is essentially the result of associative learning. The neural basis of this learned association is supported and highlighted in the most prominent neurobiological theories of addiction [43, 44]. Specifically, the neurobiology of addiction focuses primarily on three brain regions: the amygdala, prefrontal cortex, and nucleus accumbens. The activation of dopaminergic pathways through this circuitry is thought to be essential to alcohol/drug seeking, and recent research has shown that conditioned stimuli, such as alcohol or drug cues that predict substance availability and use, will independently trigger the release of dopamine in these brain areas [45]. Dopamine release into the core of the nucleus accumbens in response to stimuli that predict a biologically rewarding event, such as substance use, is thought to modulate the expression of adaptive behaviors, contribute to the assignment of salience to cues, and facilitate the development of learned associations [43].

The concept of incentive sensitization, emphasized in the theoretical work of Robinson and Berridge, has focused on neuroadaptations in the brain reward circuitry, leading to brain sensitization to drugs or drug-associated stimuli [46]. In this model, craving is best described as "wanting," or in other words, as a measure of incentive salience that is distinct from "liking" of a substance and consistent with the neural dissociation of the reward [47]. The assignment of incentive salience at the neural level, in turn, represents an essential determinant of compulsive and disordered patterns of drug-seeking behavior [48]. One of the remarkable features of the neuroadaptation and resulting incentive sensitization processes is their persistence over time. This is consistent with the phenomenology of craving and with individuals' reports of strong ("spontaneous") craving response to alcohol/drug-related stimuli even after years of recovery. This is also in line with the increasing recognition that permanent changes in brain function take place as a result of addiction, and that these neuroadaptations render individuals vulnerable to relapse for extended periods of time [43].

Neurobiological theories of addiction have consistently emphasized the role of dopamine in the assignment of incentive value to alcohol or drug cues. In later stages of addiction, glutamatergic projections from the orbitofrontal cortex to the nucleus accumbens are seen as essential to the maintenance of addictive disorders [43]. Neuroimaging studies of craving have been informed by these neurobiological theories and as a result have focused on these neural pathways. For instance, studies have reported greater neural activation of the brain reward circuitry in response to smoking [49], alcohol [7], and methamphetamine [50] cues, as compared to control cues. These findings underscore the utility of the craving phenotype in addictions research, particularly by advancing inquiries into learning, as well as the neurobiological and genetic underpinnings of addiction.

Furthermore, the most prominent neurobiological theories of addiction have identified dysfunction in diffuse brain systems underling motivated, goal-directed behavior, learning and memory, stress reactivity, decision-making, and executive control [43, 48, 51, 52, 53••]. While each of these models has distinct tenets that set them apart from their counterparts, as a whole, they support drug-induced changes in a neural network, which includes the ventral tegmental area, ventral and dorsal striatum, ventromedial prefrontal cortex, globus pallidus, thalamus, amygdala, lateral hypothalamus, and hippocampus, that is responsible for the integration of motivationally salient corticolimbic information and learned associations in order to produce a situationally appropriate behavioral output [43, 54, 55]. Accordingly, components of this "motivation/reward" network are thought to regulate the acute reinforcing effects of drugs of abuse [56, 57], the goal-directed behavior and exertion of effort in attaining these drugs after repeated use, particularly in response to conditioned stimuli [58], and, after chronic drug use, the development of incentive sensitization or hyper-responsiveness to drug-related stimuli [43, 48, 56] that are present at various stages of addiction. Recent studies have characterized dysfunction in higher cortical areas, such as the orbitofrontal cortex, inferior frontal gyrus, dorsolateral prefrontal cortex, insular cortex, and anterior cingulate cortex [53••, 59–62], that may facilitate the progression from voluntary drug use to compulsive and habitual drug-seeking behavior by further modulating the already altered signaling of the aforementioned motivation/reward network [51, 52, 60, 63].

Animal models of addiction have provided the majority of the evidence for this well-defined translational and neurobiological framework of the various pathologies underlying substance use disorder in humans. Although craving is one such hallmark symptom of addiction, it is an inherently human subjective experience and has therefore relied predominantly on human neuroimaging to identify potential neurobiological

correlates. With that caveat in mind, nearly two decades of neuroimaging research has identified a broad, albeit relatively poorly understood, neurocircuitry associated with the phenomena of craving that only overlaps in part with motivation/reward network described above.

As part of human neuroimaging studies, craving can be measured as tonic, unprovoked state (often termed "spontaneous" craving) or assessed during a phasic psychophysiological state that reliably generalizes to real-world situations in which an addicted individual is at high risk for use, such as after a period of forced or voluntary abstinence that invokes withdrawal symptoms, in response to a physical or psychosocial stressor, after exposure to drug-related stimuli (aka "cues"), after drug priming, or using a combination of these induction techniques. As discussed above, exposure to drug-related cues is the most commonly used method to study craving in humans as part of neuroimaging paradigms due to the ease of incorporating visual and gustatory drug cues with functional neuroimaging protocols. Because response to conditioned drug cues requires Pavlovian learning and is due to the highly subjective nature of experiencing craving, visual cue exposure paradigms activate not only brain areas of the motivation/reward network but also brain regions associated with learning and memory, emotion regulation, interoception, sense of self, visual perception, and salience/attention. For example, several meta-analyses and recent studies in populations with substance use disorder have typically, but not always, observed that drug cues (as compared with control cues) activate areas associated with motivation/reward and learning/memory circuitry (i.e., ventral and dorsal striatum, globus pallidus, ventral tegmental area, hippocampus, anterior cingulate cortex, thalamus, amygdala, inferior frontal gyrus, insula, and orbitofrontal cortex) as well as regions not traditionally associated with addiction, such as the medial frontal gyrus, middle frontal gyrus, superior frontal gyrus, posterior cingulate cortex, precuneus, cingulate gyrus, claustrum, middle temporal gyrus, fusiform gyrus, inferior occipital gyrus, parahippocampal gyrus, brainstem, cuneus, lingual gyrus, and primary and secondary visual cortices [50, 62, 64–67, 68••].

That the brain networks activated by conditioned cues in drug-dependent populations extend far beyond the traditional mesolimbic dopamine system suggests that the early neurobiological theories of addiction, which heavily relied on dopamine release into the nucleus accumbens as the primary mechanism driving cue-induced craving and drug-seeking behavior [48, 69], are incomplete. Indeed, while dopamine transmission from the ventral tegmental area to the nucleus accumbens is still viewed as critical for behaviors that require high effort demands, Pavlovian conditioning, and the assignment of salience and value to environmental stimuli [58, 70], recent animal models have established the critical roles of other brain areas and signaling molecules in addictive behaviors [51, 53]. For example, glutamatergic projections from the orbitofrontal cortex to the nucleus accumbens have been posited to be the final pathway to initiate cue-induced drug-seeking behavior [52], and multiple studies across various drugs of abuse suggest that brain regions associated with self-consciousness and self-related mental representations (e.g., precuneus and posterior cingulate cortex) are reliably activated by drug-related cues [50, 65, 68••, 71]. Therefore, in at least one respect, neuroimaging has been an effective tool to further our knowledge of the neurobiological underpinnings of addiction and drug craving by identifying novel brain regions associated with responses to conditioned cues that may be specific to humans, or at least primates, due to these brain areas' involvement in higher cognitive processes.

Chronic drug abuse produces long-lasting and robust changes in numerous brain areas [72, 73], and these resilient neuroadaptations have been theorized to underlie the heightened cue-induced craving in dependent individuals that has been observed several months into abstinence [74–76]. Theoretically, greater cue-induced craving in the laboratory should predict greater risk for relapse when similar cues are faced in the natural environment, and, transitively, the brain areas associated with heightened cue reactivity in the laboratory should also predict risk for relapse in the real world. If such relationships were to be observed, neuroimaging cue reactivity paradigms would offer a unique and highly effective translational platform to screen novel pharmacological and psychosocial treatments or even predict treatment outcomes with established pharmacotherapies. Unfortunately, as recently reviewed elsewhere [41••], there is presently limited experimental support for such utility. There is little consilience between neuroimaging studies as to what neural responses to conditioned cues predict relapse or predict beneficial treatment responses to psychosocial or pharmacological interventions. Recent meta-analyses and laboratory studies have identified several potential factors which may be contributing to this lack of convergence and that need to be addressed in future neuroimaging studies of craving [41••]. Few studies have reported a significant relationship between neural response to drug cues and subjective reports of craving [77–80], which may also be related to conceptual limitations of measuring self-reported craving [81, 82]. In fact, recent meta-analyses suggested that many of such studies do not actually induce pathological levels of cue-induced craving [83]. Thus, it is plausible that neural response to cue exposure paradigms could not be reliably capturing craving, per se, but some other multi-dimensional, biological phenomena related to the subjective perception of conditioned stimuli.

Conclusions and Future Directions

While it is clear that the scientific study of craving has advanced substantially over the past two decades, it is equally true that we have a long road ahead. Advances in assessment, neurobiology, genetics, and contributions from learning theory and pharmacotherapy have been exciting, indeed.

However, treatment approaches have been only moderately effective. If we are to enhance the treatment for craving, we must emphasize the application of scientific findings.

Several important factors have yet to be fully integrated into the understanding of craving neurobiology and its role in addiction maintenance and recovery. First, the role of brain development in the expression and maintenance of craving is an important area of investigation. A recent study of adolescent heavy drinkers found that increased brain responses to alcohol cues (measured using fMRI) decreased over a 1-month abstinence period [84], thus highlighting the malleability of adolescent brain function. To that end, much will be learned from the Adolescent Brain Cognitive Development (ABCD) Study, which is the largest long-term study of brain development and child health in the USA [85]. The ABCD Study will inform our understanding of the biological and behavioral development through adolescence and into young adulthood, including neurobiological changes that may predispose youth to engage in substance use and misuse. Second, it is critical that studies of craving neurobiology integrate multimodal assessments of craving (e.g., cue-induced, stress-induced, alcohol/drug-induced, basal or tonic, and phasic craving) in order to address their conceptual and neural overlap. Third, the application of craving to treatment development also warrants significant attention. To date, cue-elicited craving has been widely used as a tool for screening pharmacotherapies for addiction [86, 87]. Nonetheless, studies have called into question whether cue-induced craving response in the laboratory reliably predicts clinical outcomes [88]. It is plausible that medications and behavioral treatments that do not reduce craving directly provide clinical benefit to patients in real-world settings. This may be particularly true of novel compounds addressing new molecular targets for addiction [89]. Conversely, a single assessment of cue-induced craving in the laboratory may not be sufficiently reliable for capturing medication effects, and instead, ongoing assessments of craving in the real work may offer a more useful probe of initial efficacy for novel treatments [90].

In summary, there is renewed enthusiasm for the concept of craving as evidenced by its inclusion in DSM-5 as a symptom of substance use disorder. This enthusiasm is in part due to its potential as a translational phenotype with identifiable underlying neurobiology in humans. The present review of the literature on craving neurobiology suggests that the brain networks activated by conditioned cues in drug-dependent populations extend far beyond the traditional mesolimbic dopamine system and suggest that the early neurobiological theories of addiction, which heavily relied on dopamine release into the nucleus accumbens as the primary mechanism driving cue-induced craving and drug-seeking behavior, are incomplete. While dopamine transmission from the ventral tegmental area to the nucleus accumbens is still viewed as critical for behaviors that require high effort demands, Pavlovian conditioning, and the assignment of salience and value to environmental stimuli, recent animal models have established the critical roles of other brain areas and signaling molecules in addictive behaviors [51, 53••]. Ongoing studies will advance our understanding of the neurobiological underpinnings of addiction and drug craving by identifying novel brain regions associated with responses to conditioned cues that may be specific to humans, or at least primates, due to these brain areas' involvement in higher cognitive processes. These findings in turn can be translated into a more complete understanding of addiction as a brain disorder and uncover tractable avenues for intervention that can, in turn, bolster the overall efficacy of addiction treatment.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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