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# The Clinical Neurobiology of Drug Craving

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## Abstract

Drug craving has re-emerged as a relevant and important construct in the pathophysiology of addiction with its inclusion in DSM-V as a key clinical symptom of addictive disorders. This renewed focus has been due in part to the recent neurobiological evidence on craving- related neural activation and clinical evidence supporting its association with drug use, relapse and recovery processes. This review covers the neurobiology of drug craving and relapse risk with a primary focus on cocaine addiction and a secondary emphasis on alcohol addiction. A conceptualization of drug craving on the continuum of healthy desire and compulsive seeking, and the associated neurobiological adaptations associated with the development of an increased craving/wanting state is presented. Altered dopamine neurochemistry as well as disrupted prefrontal control and hyperactive striatal-limbic responses in experiencing drug cues, stress, drug intake and in basal relaxed states are identified as neurobiological signatures that predict drug craving and drug use. Thus, the clinical and neurobiological features of the craving/wanting state are presented with specific attention to alterations in these cortico-limbic-striatal and prefrontal self-control circuits that predict drug craving and relapse risk. The methodological challenges that need to be addressed to further develop the evolving conceptual approach in the neuroscience of drug craving is presented, with a focus on identification and validation of biomarkers associated with the craving state and treatment approaches that may be of benefit in reversing the neurobiological adaptations associated with drug craving to improve treatment outcomes in addiction.

## Introduction

The concept of drug craving has had a long and chequered history in the science of addiction. While clinical reports of drug craving among addicted individuals have kept the construct alive and relevant, difficulties in developing reliable ways to provoke craving and assess its relevance to drug use, relapse and treatment outcome led to questions regarding it's utility [1]; [2]. However, a number of scientific developments have led to a renewed emphasis on its relevance to addiction, resulting in the re-emergence of its importance as a



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significant clinical symptom in the pathophysiology of addiction. First, the basic science incentive sensitization model of wanting/craving for drug [3]) and research modeling drug seeking in drug experiences or dependent animals [4]; [5]. Second, clinical research using reliable provocateurs of craving in the laboratory [6]; [7]; [8]; [9], ecological momentary assessment (EMA) approaches to studying craving and drug use episodes in real time in the daily lives of addicted individuals [10]; [11]; [12]) and treatment studies on drug craving predicting treatment outcome and relapse [13]; [14]; [15]; [16], although some negative studies have also been reported. Finally, there are a growing number of neuroimaging studies of the drug craving state and its relevance in drug use and relapse risk [17]; [18]; [19]; [20]; [21]; [22]; [23]. This paper briefly reviews this clinical neurobiological research and presents a renewed conceptualization of drug craving, its clinical relevance and neurobiology, and the challenges that need to be addressed in future research, to both establish the role of drug craving in the pathophysiology of addiction, and to assess its clinical utility as a target of treatment development to improve addiction treatment outcomes.

## Development of Craving and Compulsive Seeking: Relevance to Drug Use and Relapse

Engaging in rewarding and pleasurable behaviors is a natural part of human existence. Exposure and access to hedonic stimuli like addicted drugs results in the pleasurable, positively reinforcing effects of the drug and also “desire” for that which is pleasurable when drug is not present. Indeed, drug-related stimuli and contexts (e.g., drug paraphernalia, passing a favorite bar, buying alcohol) may increase subjective desire for reward. Thus, light to moderate amounts of drug use elicit the rewarding effects of drug, which may increase desire for drug. Clearly small to moderate amounts of drug can be consumed with no signs of addiction, and indeed the majority of individuals using drugs like cocaine or alcohol do not develop addictive disorders. However, chronic and excessive levels of drug intake are associated with increased salience, as proposed by Robinson and Berridge [3], and a more intense, urgent “abnormal desire” characterized by longing, yearning and physiological need for drug which may be defined as “craving”[24].

While the mesolimbic dopaminergic and glutamatergic adaptations associated with high levels of drug intake are linked to a “wanting” or craving state [3]; [25], additional neurobiological adaptations in brain catecholaminergic, CRF and opioid systems have been reported, along with their contribution to the greater longing and physiological need for drug identified here as craving and compulsive seeking [26]; [27]. In human studies, heavy, non-dependent drinkers report higher levels of cue-induced drug craving than light drinkers. Increasing levels of anxiety and arousal are reported with increasing levels of drug craving as blood levels of cocaine decrease in addicted individuals [28]. In addition to anxiety, additional physiological and stress-like symptoms are associated with the drug craving state. For example, the cocaine craving state (distinct from mild, low level increase in subjective desire) is associated with irritability, restlessness, increases in heart rate, butterflies in stomach, nausea and other arousal symptoms that overlap with stress-related arousal [29]. Interestingly, we’ve consistently reported increases in drug craving with personalized stress exposure in different groups of treatment engaged abstinent addicts, that is minimally reported in healthy light social drinkers [9], and stress-induced increases in drug craving as well as drug-cue-induced increases in craving in the laboratory are predictive of future drug relapse risk [30]; [31] (unpublished data with drug cue-induced cocaine craving predictive of future cocaine relapse risk).

Ecological momentary assessment (EMA) approaches have shown acute increases in drug craving in daily life are directly predictive of subsequent episodes of drug use [12]; [10];

[11]; [32]. The research presented in the previous section suggests that phenomenologically, drug craving is a more reliable and measurable state in drug abusing individuals, in which the drug craving state increases with decreasing drug levels during drug taking (clinically characterized in cocaine-taking as “chasing the high”), but also with stress and drug cue exposure. This state is described by patients as mildly aversive, with increases in stress-related arousal, and significant associations between increased anxiety and high craving levels have been reported [9]. However, thus far, clinical studies show that increases in anxiety or distress does not predict drug intake or relapse, but concomitant increases in drug craving predicts subsequent drug taking and relapse [12]; [30]; [31]. Based on these data, it may be speculated that anxiety and distress, while increasing during craving, is not driving drug use in the context of stress, drug cues or falling blood levels of drug, but rather the stronger the craving, the more likely the individual will engage in drug intake. As proposed by Tiffany [1], conscious conflict about engaging in drug use or not would increase craving, and perhaps the strength of the craving modulation may predict relapse. Thus, although craving occurs in the context of high arousal states and is similar to conditions of stress, and anxiety and craving co-occur, it is craving through incentive motivation that predicts drug use, and not the concomitant increases in anxiety, as proposed in models of negative reinforcement and anxiety-related avoidance motivation [c.f. 3], and as elegantly shown in an animal study modeling incentive motivation under heroin withdrawal conditions [33]. This idea needs further empirical validation in human studies, but if supported, it would appear that with high levels of drug use, there is a progression from healthy desire to a stress-related arousal state characterized by physiological need and longing (craving), that via approach/incentive learning and habit-based processes may set in motion sensitized instrumental behaviors or habit-based responding away from goal directed responses [34]. Interestingly, such shifts from goal-directed responses to habit-based responding has also been well documented under stress, with stress inducing increases in habitual behaviors [35]. If these ideas are empirically validated, they may elude to a common pathway of high drug exposure-related adaptations in craving-related motivation that are common for conditions of stress, drug cues or drug.

## Neurobiological Adaptations underlying the Drug Craving State

The shift from normal healthy desire to drug craving with increased levels of drug use is also associated with changes in limbic, striatal and cortical brain systems. For example, changes in hypothalamic pituitary adrenal (HPA) axis responses, altered and blunted amygdala response to fear/threat potentiated startle in heavy drinkers compared to light social drinkers and autonomic imbalances in sympathetic/parasympathetic systems have been reported with increased drug use [36]; [9]; [31]. With the rise of neuroimaging techniques, a number of studies have assessed neural changes associated with the drug craving state with correlations to subjective drug craving and to drug use/relapse. Brief exposure to cocaine cues, known to increase drug craving, in cocaine dependent (CD) individuals increased activity in the amygdala and regions of the frontal cortex [37]; [17]; [18], and with gender differences reported in amygdala activity and the frontal cortex response in cocaine dependent individuals [38]; [39]. Cue induced craving for nicotine, methamphetamine and opiates also activate regions of the prefrontal cortex, amygdala, hippocampus, insula and the VTA (see [40].

As stress also increases drug craving in addicted individuals relative to controls, brain activation during stress and neutral imagery in a functional magnetic resonance imaging (fMRI) study were assessed in healthy controls and CD individuals. While both groups showed similar levels of distress and pulse changes during stress exposure, brain response to emotional stress in paralimbic regions such as the anterior cingulate cortex (ACC), hippocampus and parahippocampal regions was greater in healthy controls during stress

while CD patients showed a striking absence of such activation [21]. In contrast, patients had increased activity in the caudate and dorsal striatum region during stress, activation that was significantly associated with stress-induced cocaine craving ratings. A larger follow-up study assessed brain response to stress, drug cues and neutral-relaxing cues using individualized guided imagery in CD versus healthy social drinking men and women [41]. Findings indicated that CD versus healthy women showed greater activation in limbic-striatal regions such as the amygdala, caudate-putamen, insula and ACC during stress, while CD men relative to male controls showed significantly greater responsiveness in these regions to drug cues and in the neutral relaxing condition. These data are consistent with previously cited evidence of increased reactivity to stress and drug cues during drug craving states in patients relative to controls, and also highlight the importance of examining sex differences in drug craving-related neuroadaptations.

Evidence from PET imaging research has further pointed to the brain neurochemistry involved in drug craving states. Significant positive correlations between D2 receptor binding in the dorsal striatum and drug cue-induced cocaine craving has been reported [42]; [43]). These findings are consistent with imaging studies in alcoholic patients who show increased association between dorsal striatum, dopamine and alcohol craving in response to presentation of alcohol related stimuli [44];[45]. In both CD patients and alcoholics, a significant association between dopamine D2 receptor binding in the VS and drug craving as well as motivation for self administration has been demonstrated [22]; [19]; [20].

As previous work has clearly shown that stress-induced and drug cue-induced craving is significantly greater in addicted individuals relative to controls [9], we also assessed brain correlates of stress and cue-induced alcohol craving in abstinent, treatment engaged alcohol dependent (AD) individuals. Findings indicate a robust hyperactivity during the neutral relaxed state in the ventral striatum and the ventromedial PFC (VmPFC)/ACC which correlated with provoked stress-induced and cue-induced drug craving [23]. Stress and drug cue-induced craving was also associated with blunted responses in these regions in the stress and drug cue conditions, and both hyperactivation of the VmpFC in the neutral relaxed state and hypoactivation of the VmPFC and the insula during stress was predictive of future time to alcohol relapse and severity of alcohol relapse during the subsequent recovery period [23]. These findings identify neuroadaptations in the VmPFC, ventral striatum and insula networks that show disrupted functioning in the relaxed state, and in turn, contributes to hypoactive responses during provoked/challenge conditions in addicted individuals.

Hypofrontal activation in the ACC and VmPFC during drug cue and stress-induced craving states as reported above is consistent with a growing literature from neuropsychological and imaging studies examining prefrontal executive functions, including impulse control, decision making and set shifting, which has shown executive function deficits and hypo-frontal responses in addicted individuals compared to control volunteers [46]; [47]; [48]; [49]; [50]; [51]; [52]; [53]. Interestingly, evidence from research on stress-related shifts in goal direct motivation to habit-based responding also points to blunted responses in the medial PFC region [54]. Together, the neuroadaptations associated with addiction as well as the neural responses under conditions of stress suggest that disruption of VmPFC and ACC function with blunted responses in these regions during stress, drug cue and other challenge states may mediate increased drug craving and loss of behavioral control over drug craving. Whether it is blunted VmPFC/ACC responses due to stress/chronic drug exposure or stress-motivated habit responses or both that are required for increased risk of relapse are not fully understood. Certainly the human data from the alcohol relapse findings described above point to disrupted top-down control of cravings that increase relapse risk. A schematic representing drug craving on a dimensional continuum that is based on level of exposure and

drug history and associated neuroadaptations in circuitry and in neurochemistry (see previous reviews [55]; [31]) is presented in Figure 1.

## Conclusion and Futures Directions

This review presents evidence to support drug craving as a dimensional construct that grows with increasing levels of drug use. With increased salience of drug, there is greater motivation or 'wanting' of drug as posited by the incentive sensitization model of addiction. Evidence from human experimental and neuroimaging studies also shows increases in stress-induced wanting along with higher drug cue-induced craving in the addicted state which is accompanied by increased levels of stress-related arousal, anxiety and expanded network of corticolimbic-striatal activation under stress, drug, drug cue and relaxed exposure conditions. Interestingly, several studies show disruption of medial prefrontal activity during both craving or cognitive challenge that is associated with drug use/relapse in addicted individuals. As the medial prefrontal region has been identified as an important region in self control, it appears that compromised self control may be a key aspect of the neurobiology of drug craving state.

Despite the growing evidence on the clinical neurobiology of drug craving, a number of methodological issues remain in studying craving and its provocation, particularly to understand mechanisms driving drug use and relapse risk. If drug craving builds with high levels of drug use and with increasing incentive salience as discussed above, there is a need to identify the behavioral, neurobiological and physiological adaptations that occur with increased levels of drug use even in the absence of addictive disorders, and specifically, the key components that predict development of craving and enhanced motivation for drug. Furthermore, identification of the neuro-biological components specific to the drug craving state may result in development of valid craving-related neural markers that may be targeted for future prevention and treatment efforts. For example, as data are accruing on disrupted prefrontal control over urges as a key component of the drug craving state, targeting such compromised prefrontal function as a biomarker for normalization with agents that rescue the prefrontal cortical neurons may represent a useful strategy in treatment development. Alternatively, strategies that reduce activity in the limbic-striatal network in response to drug, cues or stress may also be useful in reducing drug craving, drug use and relapse. Studies on increasing understanding of the neurobiology of aversive states that promote sensitization and approach behaviors as well as those on the neurobiology of inhibitory control processes and compulsive habits may contribute to improving strategies for reducing drug craving and relapse prevention in addiction. Finally, it is not known if the human brain recovers from addiction-related neuroadaptations and can return to healthy levels of desire. It may well be that a realistic goal is not to decrease limbic-striatal reactivity and related alterations associated with craving, but to improve self control and regulation of drug craving, which, with long term recovery may diminish craving circuits that drive habit, automaticity and relapse risk.

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## Highlights

- Inclusion of drug craving as a symptom in DSM-V for substance use disorders.
- A craving continuum from normal healthy desire to compulsive seeking is proposed.
- The neurobiology of the shift from desire to compulsive seeking is presented.
- Habitual behaviors may depend on sensitization of brain stress pathways.

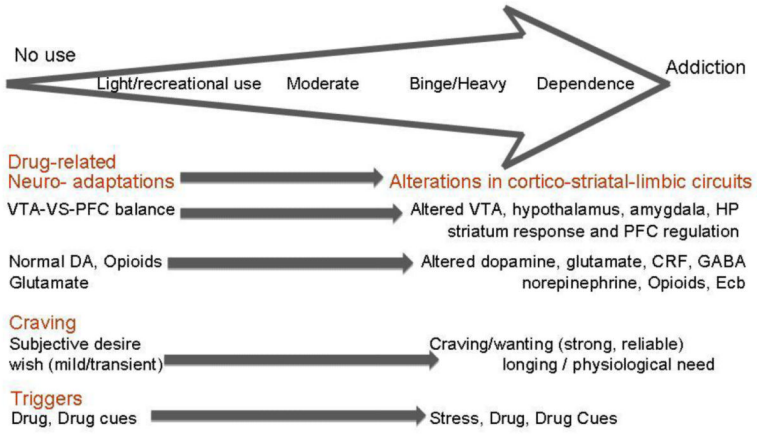


**FIGURE 1.**

A schematic diagram representing drug craving on a dimensional continuum with increasing levels of drug exposure and history is presented. Drug-related neuroadaptations in cortico-striatal limbic networks and neurochemical adaptations that may be examined for their contribution to the drug craving state are highlighted. VTA=ventral tegmental area; HP=hippocampus; CRF=corticotrophin releasing factor; VS=ventral striatum; DA=dopamine; PFC=prefrontal cortex; GABA= Gamma-aminobutyric acid ; Ecb=endocannabinoids.