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The clinical neurobiology of drug craving

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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 to 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.

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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 its 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 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 experienced or dependent animals [4,5]. Second, clinical research using reliable provocateurs of craving in the laboratory [6–9], 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 [13–16], 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 [17–22,23••]. 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 addictive 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, and 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 have 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).

EMA approaches have shown acute increases in drug craving in daily life are directly predictive of subsequent episodes of drug use [10,11,12•,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 acute 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]. On the basis of 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 (cf. [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 [9,31,36]. With the rise in use 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 [17,18,37], and with gender differences reported in amygdala activity and the frontal cortex response in CD 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