

# Neural Mechanisms Underlying Craving and the Regulation of Craving

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## Introduction

*Craving* has long been considered a core feature of addiction (World Health Organization, 1955; O'Brien, Childress, Ehrman, & Robbins, 1998; Volkow et al., 2006; Sinha & Li, 2007; Kavanagh & Connor, 2012). Consistently, over the last two decades, a wealth of research has directly linked drug craving with drug taking and relapse (e.g., Heinz et al., 2005; Crits-Christoph et al., 2007; Allen, Bade, Hatsukami, & Center, 2008; Shiffman et al., 2013; Kober, 2014 for review). On the basis of the accumulated evidence, the American Psychiatric Association recently added craving – defined as “a strong desire for drugs” – as a diagnostic criterion for substance-related and addictive disorders in the fifth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-5) (APA, 2013). Also defined as a “conscious, reportable urge” (Preston et al., 2009), craving can be experienced for a range of appetitive stimuli, including drugs – but also food, sex, and money. As such, craving is a very common phenomenon. In fact 94% of males and 100% of females report having experienced craving for a specific food at some point in their lives (Osman & Sobal, 2006).<sup>1</sup> Nevertheless, in the context of substance use disorders, a failure to regulate craving can lead to dire outcomes, such as harmful drug use. In the next sections we will review craving's central causal role in drug use and relapse and will consider the brain regions that underlie craving. Then we will review the role of the regulation of craving in reducing craving and in treatment for addiction, as well as the neural mechanisms that give rise to this ability.

## Craving and Drug Use

Although this view has been challenged (e.g., Tiffany, 1990; Perkins, 2009; Wray, Gass, & Tiffany, 2013), the recent inclusion of craving as a diagnostic criterion in DSM-5 (APA, 2013) cements it as a defining feature of addiction. Indeed, several

lines of evidence have linked drug craving to drug taking, across various legal and illegal drugs (e.g., alcohol, nicotine, cocaine). First, in retrospective studies, drug users often cite craving as the reason for continued use and relapse (e.g., Norregaard, Tonnesen, & Petersen, 1993). For example, as early as 1968, a study of cigarette smoker treatment outcomes reported that nearly half of those who had relapsed pointed to cravings as the main culprit (Peterson, Loneragan, Hardinge, & Teel, 1968). Similarly, craving was self-reported as a cause of relapse by alcohol drinkers (Maisto, O'Farrell, Connors, McKay, & Pelcovits, 1988; Connors, Maisto, & Zywiak, 1998), cocaine users (McKay, Rutherford, Alterman, Cacciola, & Kaplan, 1995), and heroin users (Heather, Stallard, & Tebbutt, 1991).

Second, prospective clinical studies have shown that craving is associated with subsequent drug use (e.g., Monti et al., 1990; O'Connor, Gottlieb, Kraus, Segal, & Horwitz, 1991; Weiss et al., 1997; Bordnick & Schmitz, 1998; Robbins & Ehrman, 1998; Allen et al., 2008; Robinson et al., 2011). Moreover, several studies have specifically shown that craving predicts drug taking and/or relapse following abstinence, including in cigarettes (Killen, Fortmann, Newman, & Varady, 1991; Killen, Fortmann, Kraemer, Varady, & Newman, 1992; Norregaard et al., 1993; Doherty, Kinnunen, Militello, & Garvey, 1995; Swan, Ward, & Jack, 1996; Killen & Fortmann, 1997; Etter & Hughes, 2006; Heffner, Lee, Arteaga, & Anthenelli, 2010; Berlin et al., 2013; Sweitzer, Denlinger, & Donny, 2013), cocaine (Weiss et al., 2003; Crits-Christoph et al., 2007; Rohsenow, Martin, Eaton, & Monti, 2007; Paliwal, Hyman, & Sinha, 2008), methamphetamine (Hartz, Frederick-Osborne, & Galloway, 2001; Galloway, Singleton, & Methamphetamine Treatment Project Corporate Authors, 2008), alcohol (Miller, Westerberg, Harris, & Tonigan, 1996; Bottlender & Soyka, 2004) and opioid drugs (Tsui, Anderson, Strong, & Stein, 2014). In one of the largest studies of this kind, 691 methamphetamine-dependent users were assessed every week for eight weeks while undergoing outpatient treatment (Galloway et al., 2008). At each assessment, they reported their cravings for methamphetamine (0-100 scale), reported any methamphetamine use in the past week, and provided urine samples (to biologically verify abstinence). The authors reported that, at each time point, cravings strongly predicted use by the following time point, such that every 1-point increase in craving score increased the probability of methamphetamine use during the following week by 0.38%. Another study investigated the relationship between daily craving and cigarette smoking after an attempt to quit (Allen et al., 2008). Over a period of 30 days, female participants provided daily reports of craving and smoking. First, the authors reported that those who relapsed reported significantly higher craving on the quit date than those who abstained the entire period. In a second analysis, craving scores were standardized within participants to more accurately identify temporal variations in craving. Within these standardized scores, craving reports increased on the 4-5 days prior to relapse and peaked on the day of relapse (with very large effect sizes of  $d > 1.0$ ).

Third, ecological momentary assessment (EMA) studies with cigarette, marijuana, cocaine, ecstasy, heroin, and poly-drug users have elegantly documented links between daily or hourly variations in craving and specific instances of drug use. In EMA studies (which are also referred to as "experience-sampling"), participants are provided with handheld devices that allow them to report their cravings and urges during daily activities. Participants are typically prompted by random reminders, and also give reports when they experience a temptation to use and/or when they use drugs. EMA

studies are especially powerful, as they provide real-life and real-time data that are difficult to reproduce in laboratory settings and are more reliable than retrospective reports. In one such study, Preston and colleagues used EMA over the course of 25 weeks to investigate the relationship between craving and cocaine use (Preston et al., 2009). They found that during periods of cocaine use, ratings of craving were significantly higher than during periods of (urine-verified) abstinence. Focusing on the five hours before reports of cocaine use, they found that craving linearly increased until cocaine use. Other EMA studies have also shown that craving increases prior to drug taking (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996; Catley, O'Connell, & Shiffman, 2000; Hopper et al., 2006; Epstein, Marrone, Heishman, Schmittner, & Preston, 2010; Buckner, Crosby, Silgado, Wonderlich, & Schmidt, 2012; Marhe, Waters, van de Wetering, & Franken, 2013; Moore et al., 2014), correlates with drug taking (Litt, Cooney, & Morse, 2000), and predicts drug taking (Shiffman et al., 1997; Shiffman et al., 2002; O'Connell, Schwartz, Gerkovich, Bott, & Shiffman, 2004; Cooney et al., 2007; Johnson, Barrault, Nadeau, & Swendsen, 2009; Buckner et al., 2012; Holt, Litt, & Cooney, 2012). Although these findings do not establish that craving is necessary or sufficient to explain every instance of drug use and relapse, taken together they do suggest that craving is a powerful predictor and a likely causal factor in drug use and relapse (e.g., Shiffman et al., 1997).

### **Cue-Induced Craving**

Several researchers have begun to distinguish between two kinds of cravings: tonic or "background" craving, and phasic or "provoked" craving, also known as *cue-induced craving* (Ferguson & Shiffman, 2009). The former type of craving is a slowly changing state; it is often induced by abstinence and fades over time. The latter kind is intense, acute, and episodic, and can be provoked by a wide range of internal and external/situational cues associated with drug use. In real life, these cues include the sight of people using drugs, contact with people with whom one previously used drugs, and paraphernalia, situations, or locations previously associated with drug use (e.g., one's favorite bar). In laboratory models of cue-induced craving, cues include photographs or movies depicting drugs, drug use, and paraphernalia, in-vivo presentation of such stimuli, imagery-based or recalled scenarios of drug use, and even olfactory cues (e.g., cigarette smoke). To this date, more than 100 studies have examined this phenomenon in cigarette smokers, alcohol drinkers, opiate, cocaine, and marijuana users. An early meta-analysis summarizing 41 such studies concluded that the presentation of drug-associated cues strongly and reliably induces the subjective experience of craving, along with a range of physiological responses such as increased heart rate and sweat response across all addicted groups (Carter & Tiffany, 1999). Drug cues are thought to lead to such reactions as a result of associative learning that took place during prior episodes of drug exposure (for discussion, see Niaura et al., 1988; Childress et al., 1993).

Importantly, a growing body of work directly links cue-induced craving to drug use. First, the presence of other drug users or of the drug itself has been linked to instances of drug use in retrospective reports (Shiffman, 1982; Gawin & Kleber, 1986; Bliss, Garvey, Heinold, & Hitchcock, 1989; Wallace, 1989; Bliss, Garvey, & Ward, 1999) as well as in EMA studies (Shiffman et al., 1996; Shiffman et al., 2002;

Epstein et al., 2009). For example, Shiffman and colleagues (1996) asked recently abstinent cigarette smokers to use EMA to record any smoking incident as well as any near lapses (e.g., when they felt they were “on the very precipice of smoking,” but didn’t). Smokers were also randomly prompted to assess craving and to report on their location, situation, activity, mood, and withdrawal symptoms. Results showed that, out of the three entry conditions (relapse, near lapse, and random), craving was most associated with relapse. Importantly, relapse entries were most likely to be reported when the participants were in situations in which others were smoking, by comparison to both near-lapse and random assessments. Multiple follow-ups from this group provide additional links between cue-exposure and craving in nicotine use and relapse (e.g., Shiffman, 2005; Shiffman et al., 2013). In another EMA study, methadone-maintained cocaine users reported different triggers that precipitated instances of drug use. Cocaine use was most strongly associated with increases in the trigger “I saw cocaine” (Epstein et al., 2009).

In addition, laboratory measures of cue reactivity have been linked to drug use and relapse in the real world. Retrospective studies show that stronger responses to laboratory measures of cue-induced craving are associated with past instances of relapse (Abrams, Monti, Carey, Pinto, & Jacobus, 1988; Erblich & Bovbjerg, 2004). Prospective studies have shown that drug users who respond more strongly to cues in the lab prior to quitting are more likely to use drugs after treatment for cigarette smoking (Abrams et al., 1988; Niaura, Abrams, Demuth, Pinto, & Monti, 1989; Waters et al., 2004; Payne, Smith, Adams, & Diefenbach, 2006; Powell, Dawkins, West, Powell, & Pickering, 2010), alcohol (Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Litt et al., 2000), and opioid use (Lubman et al., 2009; Fatseas et al., 2011). For example, Powell and colleagues (2010) measured craving increases after a 2-minute period during which participants handled and smelled their preferred brand of cigarettes in the lab, prior to quitting. Craving increases to the cigarette cues (compared to a neutral cue) predicted relapse at 1-week, 1-month, and 3-month follow-up, such that those who exhibited the greatest increase in craving were most likely to relapse at each time point. Finally, laboratory cue-induced craving was also found to predict smoking in cigarette smokers who were not seeking treatment (Carpenter et al., 2009).

A few studies have tested the effects of cues on cigarette smoking in the lab and generally show increases in both craving and smoking (Herman, 1974; Rickard-Figueroa & Zeichner, 1985; Payne, Schare, Levis, & Colletti, 1991; Perkins, Epstein, Grobe, & Fonte, 1994; Droungas, Ehrman, Childress, & O’Brien, 1995; Morgan, Davies, & Willner, 1999; Hogarth, Dickinson, & Duka, 2010; Shiffman et al., 2013). In one such study, cigarette smokers performed an aversive task for 20 minutes. During the task, half of them were exposed to cigarette cues (an ashtray with burned cigarette butts, packs of cigarettes, matches, and the odor of smoke) while the other half were not. In the post-task period, all participants were given an opportunity to smoke. Those exposed to cigarette cues began to smoke more quickly and puffed on their cigarettes for longer than those who had not been exposed to cues (Payne et al., 1991). In another elegant study, Shiffman and colleagues (2013) invited cigarette smokers for six laboratory sessions. In each session, participants were exposed to pictures for 3 minutes and then allowed to smoke up to two cigarettes over 15 minutes. During each session, a different set of pictures was presented, depicting cigarettes, alcohol, neutral objects, positive images, negative images, and “no smoking” signs.

Only exposure to smoking pictures significantly increased craving. Furthermore, craving intensity was significantly related to subsequent smoking, such that those with higher craving were more likely to smoke, more likely to smoke both cigarettes, smoked more quickly, took more puffs, puffed longer, and subsequently showed greater increases in exhaled carbon monoxide. Interestingly, these findings dovetail with those reported in animal models of addiction, which have also consistently linked drug-associated cues with drug-taking behavior. Indeed exposure to cues previously paired with drugs is known to reinstate drug-seeking behavior in animals even after long periods of abstinence – a phenomenon termed “incubation of craving” (Shaham, Shalev, Lu, de Wit, & Stewart, 2003; Crombag, Bossert, Koya, & Shaham, 2008; Pickens et al., 2011).

In sum, these lines of evidence support a strong contributory – and possibly causal – role for cue-induced craving in addictions in general and in drug-taking in particular. The findings linking drug cues to drug use are of particular clinical importance, because cue-induced craving episodes continue to occur weeks after quitting, even as “background” craving subsides (Shiffman et al., 1997; Bedi et al., 2011). This could explain why smokers continue to relapse even after withdrawal symptoms (including background craving) diminish, which has important implications for treatment, which will be discussed in sections below.

## **Neurobiology of Craving**

Given the central role of craving in drug use, a large number of studies have investigated its neural correlates over the last decade, using laboratory cue-induction paradigms. Such studies have used functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) to assess neural activity in drug users during the presentation of drug-related cues that are known to induce craving (e.g., pictures, movies, and paraphernalia). To isolate neural activity associated with cue-induced craving, neural activity during the presentation of drug cues is typically compared to neural activity during the presentation of neutral cues (e.g., picture of a chair) or appetitive non-drug cues (e.g., enticing foods). In other studies, the neural response of drug users to drug cues is compared to that of healthy non-drug-using participants.

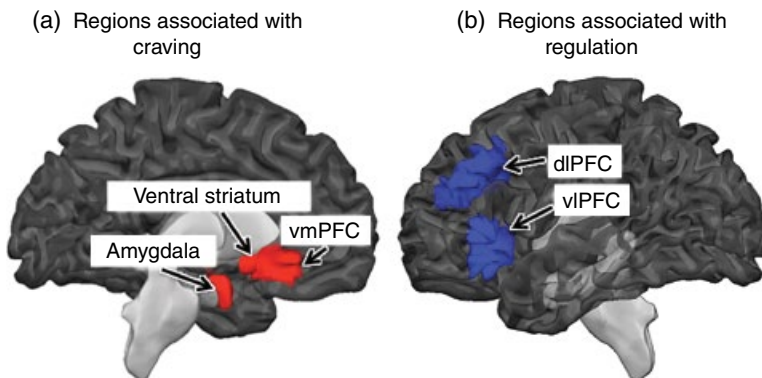
To date, over 50 imaging studies of cue-induced craving have been published, reporting results that vary somewhat across drug-using populations (e.g., cigarette vs. alcohol users), cue type (e.g., pictures vs. movies), cue presentation length (e.g., seconds vs. minutes), and imaging modality (PET vs. fMRI). In order to systematically review this literature and to identify regions that have been most consistently associated with craving, several meta-analyses have quantitatively summarized subsets of these studies (see Kober & Wager, 2010 for a discussion and comparison of meta-analytic methodologies). For example, Kühn and Gallinat (2011) used activation likelihood estimation (ALE) to summarize data from cue-reactivity studies that consisted of 13 cigarette-cue studies, 10 of alcohol, and 6 of cocaine. They included both PET and fMRI studies but restricted their analysis to contrasts comparing the presentation of drug cues and that of neutral cues for drug users. They first summarized consistent activations within each drug type, and then performed a conjunction analysis to identify regions that were cue-responsive across drug types. They reported that

the ventral striatum (VS) was the only region that showed direct overlap for all three substance types. Other regions that were activated by more than one substance type were the amygdala and the anterior cingulate cortex (ACC). In a separate analysis, the authors summarized data from a subset of 12 studies that reported positive correlations between brain activity and subjective reports of craving. For alcohol craving, they reported activity in ACC/ventromedial prefrontal cortex (vmPFC) and bilateral VS, among other regions. For cigarette craving, they reported consistent activity in regions such as the right insula and the anterior and posterior cingulate cortices (ACC, PCC).

Another ALE meta-analysis of cue-induced craving included a wider range of drug-using groups: 15 cigarette-cue studies, 13 alcohol, 7 cocaine, 5 heroin, and 1 marijuana study. It also included 2 gambling-cue studies, 1 gaming cue study, and contrasts between drug-cue presentation and either neutral-cue or baseline (Chase, Eickhoff, Laird, & Hogarth, 2011). Across all these studies, the authors reported consistent cue reactivity in the VS, amygdala, vmPFC, inferior occipital, and the right inferior frontal gyrus. A separate analysis summarized data from a subset of 18 studies that reported positive correlations with subjective craving; consistent activity was found in the amygdala, the right inferior parietal cortex, and the middle frontal cortex.

Finally, the authors separately analyzed activity from 13 contrasts from treatment-seeking drug users and 21 contrasts from non-treatment-seeking drug users. They found that, in both groups, the VS and the occipital gyrus were consistently activated in response to drug cues. In addition, in treatment-seeking participants the amygdala/hippocampus were activated, while in non-treatment-seeking the vmPFC and the right inferior frontal gyrus were consistently activated.

Taken together, these meta-analyses represent data from approximately 40 neuro-imaging studies of cue-induced craving. Although these studies contained different subsets, one consistent finding across them is that the VS, amygdala, and ACC/vmPFC are responsive to the presentation of drug-related cues and may be part of the core circuit that underlies the experience of drug craving, at least for nicotine, alcohol, and cocaine (see Figure 9.1a for illustration; and cf. Garavan, 2010 for a discussion of insula). The identification of these regions as cue-responsive is important because their activation may relate to treatment outcome in the same way that self-reported



**Figure 9.1** Brain regions underlying craving (a) and the regulation of craving (b). Source: Created by the authors.

craving does. Indeed, several studies have shown that neural responses to drug cues, including in the VS, correlate with subsequent drug use (e.g., Braus et al., 2001; Grüsser et al., 2004; Kosten et al., 2006; Wrase et al., 2008). Furthermore, these regions might serve as the target for regulation strategies and other treatments that could ameliorate craving and reduce drug use, which we discuss in the section below.

## **Regulation of Craving**

Given the role of craving in motivating drug use, it is not surprising that the ability to regulate craving is of key importance in preventing drug use. As early as the 1960s, the now classic “marshmallow test” studies demonstrated that the ability to regulate craving predicts long-term outcomes. In this landmark study, Mischel and colleagues presented preschool children with a delicious treat (such as a marshmallow or cookie). The children were then told that they could either eat the treat immediately or wait to receive two treats at a later time (i.e., if they could regulate their craving). The ability to wait – to delay gratification – varied widely across the children: some were not able to wait at all, while others waited the entire time the experimenter was gone (Mischel & Ebbesen, 1970; Mischel, Ebbesen, & Raskoff Zeiss, 1972). Importantly, the number of minutes children waited (which indicated better regulation abilities) predicted a multitude of life outcomes, reported years later in follow-up work (Mischel et al., 2011). These outcomes included higher university-admission test scores and educational achievement, superior social and emotional coping skills in adolescence, and, crucially, a lower incidence of crack cocaine use in adulthood. This work is considered by many to be the first demonstration of the importance of self-control in predicting drug use.

In the fifty years since this seminal work, several influential models of addiction have suggested that loss of control over craving is at the root of compulsive drug taking (McKay, 1999; Kalivas, 2004; Koob & Le Moal, 2001; Volkow, Fowler, & Wang, 2003; Everitt & Robbins, 2005; Goldstein & Volkow, 2011) and thus is an important target for treatment (Kosten, 1992). In fact several evidence-based treatment modalities are predicated on this exact insight. For example, cognitive-behavioral therapy (CBT; Carroll, 1998) includes key components about the regulation of craving, such as analysis of high-risk situations in which craving might occur, teaching strategies to identify drug cues/triggers, and teaching strategies to regulate craving when it arises. Cognitive regulation strategies include considering the negative consequences of drug use (e.g., “if I smoke this cigarette, my lungs will fill with tar. I will be at increased risk for emphysema and lung cancer”). As a treatment, CBT and its variants (including relapse prevention, RP) are effective in reducing drug use. Indeed, CBT’s efficacy has been shown across addictions, for example to cigarettes (Carroll, 1996; Fiore, Bailey, & Cohen, 2000; McDonald, Colwell, Backinger, Husten, & Maule, 2003), cocaine (Carroll et al., 1994; Carroll, 1996; Carroll, Nich, Ball, McCance, & Rounsaville, 1998; Carroll et al., 2004; Dutra et al., 2008), alcohol (Carroll, 1996; Project Match Research Group, 1998; Morgenstern & Longabaugh, 2000), marijuana (The Marijuana Treatment Project Research Group, 2004; Carroll et al., 2006; Budney, Roffman, Stephens, & Walker, 2007; Dutra et al., 2008), and poly-substance use (Carroll et al., 1998; Dutra et al., 2008). Furthermore, drug users who best learn strategies for coping with craving during CBT treatment are those

with the best long-term outcomes (Carroll, Nich, Frankforter, & Bisighini, 1999; McKay, 1999; Gossop, Stewart, Browne, & Marsden, 2002; Kiluk, Nich, Babuscio, & Carroll, 2010); and the quality of coping skills mediates the relationship with duration of abstinence (Kiluk et al., 2010). Lastly, craving-specific regulation-skills training is effective in reducing alcohol and drug use (Monti et al., 1993; Monti, Rohsenow, Michalec, Martin, & Abrams, 1997; Monti et al., 2001), and cognitive strategies for the regulation of craving are among those most related to abstinence (Dolan, Rohsenow, Martin, & Monti, 2013).

Similarly, mindfulness-based treatments for addiction (MBT; e.g., Bowen, Chawla, & Marlatt, 2010) also rely on identifying and regulating craving (Bowen et al., 2010; Witkiewitz & Bowen, 2010; Witkiewitz, Bowen, Douglas, & Hsu, 2013). In mindfulness-based approaches (vs. CBT), users are taught to notice cravings and to accept them as they are (e.g., “craving is impermanent, and I don’t have to act on it or avoid it; I can just be ok with it”). MBTs have shown great promise for treating addictions to alcohol (Witkiewitz, Marlatt, & Walker, 2005; Bowen, Witkiewitz, Dillworth, & Marlatt, 2007; Brewer et al., 2009), cocaine (Bowen et al., 2006; Brewer et al., 2009), poly-drug use (Bowen et al., 2006; Brewer et al., 2009), and cigarette smoking (Bowen & Marlatt, 2009; Brewer et al., 2011; Tang, Tang, & Posner, 2013). In addition, as in CBT, treatment efficacy in MBTs is linked to reduction in craving (Bowen et al., 2009; Bowen & Marlatt, 2009; Witkiewitz & Bowen, 2010; Witkiewitz et al., 2013). Furthermore, increases in mindfulness-based regulation (e.g., acceptance) reduces craving and drug use (Litvin, Kovacs, Hayes, & Brandon, 2012; Moore et al., 2014) and significantly mediates the relationship between mindfulness treatment and craving (Witkiewitz et al., 2013). Taken together, these treatment data suggest that the regulation of craving is a key mechanism of successful treatment outcome across addictions (Morgenstern & Longabaugh, 2000; Gossop et al., 2002; Kiluk et al., 2010; Dolan et al., 2013; Elwafi, Witkiewitz, Mallik, & Brewer, 2013; Witkiewitz et al., 2013).

In addition to treatment studies, several other lines of research directly address the relationship between relapse and coping strategies (usually including both cognitive and behavioral strategies). Retrospective studies have linked the use of coping strategies in moments of craving with abstinence (Bliss et al., 1999) and found that any combination of cognitive and behavioral coping strategies forestalled relapse (Shiffman, 1982, 1984), and that a greater number of coping strategies increased the likelihood of successful abstinence (Bliss et al., 1989). A few prospective studies have similarly linked the use of coping strategies to subsequent abstinence (Chaney, O’Leary, & Marlatt, 1978; Monti et al., 1993; Miller et al., 1996; Moser & Annis, 1996; Monti et al., 2001; Gossop et al., 2002; Rohsenow, Martin, & Monti, 2005; Litt, Kadden, Kabela-Cormier, & Petry, 2008). In one such study, alcohol-dependent men reported their coping skills before and after treatment (by endorsing items like “I calm myself when I get the urge to drink,” “I think about bad experiences caused by drinking”). Regardless of treatment group, change in coping skills from pre- to post-treatment predicted abstinence during the 12-month post-treatment follow-up (Litt, Kadden, Cooney, & Kabela, 2003).

EMA studies also suggest that use of regulation strategies in response to craving – measured moment by moment in real life – is related to reduced craving and lower risk of relapse, especially in cigarette smokers (Shiffman et al., 1996; O’Connell et al., 2004). For example, O’Connell and colleagues (O’Connell, Hosein, Schwartz, &



Leibowitz, 2007) asked cigarette smokers to report levels of craving, and whether they deployed regulation strategies during a quit attempt (with or without treatment). They found that deploying regulation strategies in moments of craving was associated with reduced craving and fewer instances of relapse. More specifically, the number of coping strategies predicted change in craving and the likelihood of resisting smoking. Interestingly, in another EMA study only the use of acceptance as a regulation strategy reduced the risk of relapse in a mixed group of drug users, while distraction actually increased the likelihood of relapse (Moore et al., 2014).

Recently we developed a laboratory model to experimentally investigate the effects of various regulation strategies on craving: the regulation of craving (ROC) task. The creation of the ROC task was inspired by Mischel’s seminal work on delay of gratification (Mischel & Baker, 1975) and modeled after classic emotion-regulation tasks (Gross, 1998; Gross & John, 2003). In each trial of the ROC task, drug users are exposed to drug-related cues known to increase craving (in the original version, these were photos of cigarettes, lighters, and people smoking; see Figure 9.2 for trial structure). On the baseline trials, participants are instructed to respond naturally to the cues or to focus on their immediate response to the cue (in the original version, this was indicated by the instruction word “NOW”). In contrast, during regulation trials they are instructed to use a particular strategy to regulate their craving while looking at the cues. For example, they may be instructed to use a CBT-based strategy and to think about the negative consequences associated with drug use (in the original version, this was indicated by the instruction word “LATER”).

Using the ROC task, we and others have shown that, when instructed to do so in the laboratory, drug users can employ both cognitive and mindfulness-based strategies to regulate cue-induced craving; that is, they report significantly lower craving on regulation trials. This has been shown for cigarettes (Kober, Kross, Mischel, Hart, & Ochsner, 2010; Kober, Mende-Siedlecki, et al., 2010; Hartwell et al., 2011; Littel & Franken, 2011) and for stimulant drugs like cocaine and methamphetamine (Volkow et al., 2010; Lopez, Onyemekwu, Hart, Ochsner, & Kober, under review). Similar findings have been reported with food craving as well (e.g., Wang et al., 2009; Kober, Kross, et al., 2010; Kober, Mende-Siedlecki, et al., 2010; Siep et al., 2012; Giuliani, Calcott, & Berkman, 2013; Yokum & Stice, 2013). Findings from ROC studies provide experimental evidence for the effect of regulatory strategies on craving, which has been previously shown in clinical contexts. They further suggest that drug users may not suffer from a generalized deficit in cognitive control that would prevent them from regulating their cravings in their daily lives, given adequate training.



**Figure 9.2** ROC task trial structure. Source: Created by the authors.

Taken together, the findings presented in this section suggest a clear link between regulation or coping strategies, reductions in craving, and reductions in drug use. Theoretically, this is consistent with several models of addiction, which have traditionally implicated loss of cognitive control in compulsive drug taking (e.g., McKay, 1999; Goldstein & Volkow, 2011). Clinically, the findings suggest that, when instructed to do so in the lab or when taught more thoroughly to do so in the context of treatment, drug users are able to use strategies to regulate their craving. In turn, regulation reduces craving and their own chances of relapse. Given this, it is also interesting to consider the role of motivation in deploying such strategies – but this discussion is beyond the scope of the present chapter.

### Neurobiology of ROC

As the ability to regulate craving has important clinical implications, understanding the neural systems that support it is of central importance. To further elucidate these mechanisms, we and others used the ROC task and similar paradigms in conjunction with neuroimaging methods such as fMRI and PET. For example, we first used the ROC task and fMRI to probe the neural systems that underlie the use of cognitive strategies to regulate craving in cigarette smokers (Kober, Mende-Siedlecki, et al., 2010). As described above, we exposed cigarette smokers to cigarette-picture cues and asked them either to focus on their immediate response to the cues (the “craving” baseline condition) or to think about the negative consequences of continued smoking (a CBT-based strategy; the “regulation” condition). We then compared both self-reported craving and neural activity between the two conditions and found several important results: (1) smokers reported lower craving when they used regulation strategies (replicating our prior work); (2) during regulation, neural activity in regions previously associated with craving (such as the VS, amygdala, and vmPFC) was significantly decreased; and (3) cognitive regulation of craving was associated with increased activity in regions associated with cognitive control and the regulation of emotion, such as the dorsolateral and ventrolateral prefrontal cortex (dlPFC, vlPFC; see Figure 9.1b for illustration). We also found that activity in VS was positively correlated with self-reported craving, such that activity increased when craving increased. Conversely, we found that activity in dlPFC was negatively correlated with craving, such that, as activity increased, the reported craving decreased. Lastly, we found that the VS and the dlPFC were inversely related, such that, as dlPFC activity increased, VS activity decreased. This pattern is consistent with many prior models that characterize addiction as an imbalance between the PFC, which mediates cognitive-control processes (regulation), and subcortical regions like the VS, which underlie reward and motivation processes (including craving, as described earlier in this section; see also Kober, 2014). Therefore we subjected the data to a formal mediation analysis and found that activity in the VS fully mediated the relationship between dlPFC and self-reported craving. This is consistent with an inhibitory role for the lateral PFC over the VS during the regulation of craving and implicates this prefrontal–striatal pathway in the regulation of craving more broadly.

Similar findings have been reported by several other groups (e.g., Hartwell et al., 2011; Wilson, Sayette, & Fiez, 2013). For example, in a PET study of cocaine users, Volkow and colleagues reported lower glucose metabolism in limbic regions (including the ventral striatum and subgenual cingulate) during regulation of cocaine cravings in

cocaine-dependent subjects (Volkow et al., 2010). They further reported an inverse correlation between VS activity and activity in the vLPFC during regulation, which is again consistent with an inhibitory role for lateral PFC over the VS during the regulation of craving. Similarly, Littel and Franken (2011) used event-related potentials (ERPs) and reported modulation of the late positive potential on frontal electrodes during the regulation of craving, suggesting that regulatory strategies modulate craving-related neural responses very quickly (< 2000 msec).

A growing body of work has directly tested the role of dlPFC in the regulation of craving by manipulating neural activity with repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Both procedures are noninvasive and use either magnetic fields (rTMS) or electrical current (tDCS) to stimulate (increase) or to inhibit (decrease) neuronal activity. One such tDCS study compared bilateral dlPFC stimulation to sham stimulation following an alcohol video that increased craving in alcohol-dependent users (Boggio et al., 2008). The authors reported reduction of cue-induced alcohol craving after real but not after sham stimulation to either the right or the left dlPFC. Furthermore, when participants were presented with a second alcohol movie, tDCS stimulation of the dlPFC was shown to prevent additional increases in craving.

A similar study in cigarette smokers produced comparable results: tDCS to the right or left dlPFC again resulted in decreased cue-induced craving immediately and also after a second craving-induction session that consisted of a smoking movie as well as paraphernalia (Fregni, Liguori, et al., 2008; but cf. Xu, Fregni, Brody, & Rahman, 2013). Other tDCS studies have shown similar effects on cue-induced food craving (Fregni, Orsati, et al., 2008; Goldman et al., 2011) and on marijuana craving (Boggio et al., 2010), as well as on “background” craving (Montenegro et al., 2012; Fecteau et al., 2014).

rTMS studies have also shown that stimulation of the right and/or left dlPFC decreased craving for alcohol (Mishra, Nizamie, Das, & Praharaj, 2010), cigarettes (Li, Hartwell, et al., 2013; Pripfl, Tomova, Rieckensky, & Lamm, 2014), and food (Uher et al., 2005) compared to sham stimulation. In cocaine users, rTMS stimulation of the right dlPFC reduced cocaine craving (Camprodon, Martínez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007). These and other studies were recently summarized in a meta-analysis that explored the effects of rTMS and tDCS stimulation of dlPFC on craving (Jansen et al., 2013). Across 17 studies of craving for drugs or food, stimulation of either right or left dlPFC was consistently associated with reductions in craving – including craving for nicotine, alcohol, marijuana, and food. Complementing these findings, low-frequency rTMS (which inhibits rather than stimulates), applied to the left dlPFC, served to increase cue-induced methamphetamine craving (Li, Malcolm, et al., 2013). Further extending these findings are a few studies that tested the effects of 1–13 sessions of stimulation on cigarette smoking and have shown promising results (i.e., decreases in smoking following stimulation; Eichhammer et al., 2003; Amiaz, Levy, Vainiger, Grunhaus, & Zangen, 2009; Boggio et al., 2009). In one of these studies, reductions in smoking were still seen at a 6-month follow-up (Dinur-Klein et al., 2014).

Taken together, findings from fMRI, PET, EEG, TMS, and tDCS studies support the notion that neural activity in the lateral prefrontal cortex underlies the regulation of craving, possibly by modulating activity in subcortical regions that underlie craving. These findings are consistent with existing models of emotion regulation that have

articulated an interaction between PFC (including dlPFC) and the amygdala in the regulation of negative emotion (Ochsner & Gross, 2005) and have postulated that similar mechanisms may underlie the regulation of emotions more generally, including craving (see Buhle et al., 2013 for our recent meta-analysis of emotion-regulation studies). In addition, these findings are consistent with models that have characterized addiction as an imbalance between PFC-mediated cognitive-control processes (regulation) and subcortical regions that underlie reward and motivation processes (including craving; e.g., Everitt & Robbins, 2005; Goldstein & Volkow, 2011; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). Notably, the stimulation studies specifically support a critical causal role for dlPFC activity in reducing craving. However, it is not clear from these studies which subregion within the dlPFC may be implicated. Further, as dlPFC lacks direct neuronal connections to regions such as the VS, the exact functional mechanism for this effect remains to be elucidated in future work.

Understanding the role of dlPFC in the regulation of craving is crucial, especially when we consider that it is likely that some regulatory strategies operate via distinct psychological and neural mechanisms (e.g., Goldin, McRae, Ramel, & Gross, 2008; Hartwell et al., 2011). One striking example is that of mindfulness-based regulation. As discussed above, similarly to CBTs, MBTs also focus on identifying and regulating craving. However, MBTs do so by teaching mindful attention and acceptance of craving rather than by teaching reappraisal of craving or of drug taking – and this difference is evident even at a neural level. Indeed, in a recent study, we used a modified version of the ROC task to investigate neural changes associated with mindfulness-based regulation of craving (Westbrook et al., 2013). In this study cigarette smokers were asked either to respond naturally to smoking cues or to use mindfulness-based strategy (to employ a non-judgmental attitude toward craving). When comparing the two conditions, we found that mindfulness was associated with reduced craving and reduced neural activity in regions previously associated with craving (e.g., vmPFC). However, unlike in our finding with the cognitive regulation of craving, this reduction in craving and craving-related neural activity was not associated with concomitant increases in PFC activity. Further, functional connectivity analysis revealed that mindfulness of craving decreased the coupling between vmPFC and other craving-related regions. This is consistent with the hypothesis that mindfulness reduces “bottom-up” reactivity to smoking cues rather than increasing “top-down” control. Indeed, this suggests that MBTs employ a different psychological and neural mechanism to modulate craving and craving-related neural activity – one that may not depend on dlPFC. This may be a particularly important insight when we consider that some drug users may exhibit relative deficits in PFC function and structure (e.g., Kober, DeVito, DeLeone, Carroll, & Potenza, 2014). Regardless of whether these deficits precede drug use or are a result of the neurotoxic effect of drugs, drug users may especially benefit from regulatory strategies that do not depend on the integrity of these regions but are still effective in reducing craving and drug use (for review, see Kober, 2014).

### **Concluding Remarks**

The experience of craving is extremely common. People report craving for a wide range of frequently consumed substances, including food and coffee. Casual drug use is also common. In 2012, approximately 9.2% of Americans indicated that they used an illicit

substance in the past 30 days, 26.7% declared being current cigarette smokers, and a staggering 52.1% reported being current alcohol drinkers (SAMHSA, 2013). A subset of these users suffer from (or will go on to develop) addiction disorders, *which are the most common and most costly of psychiatric disorders*, with a lifetime prevalence of 35.3% of the US population (NIMH, 2007; SAMHSA, 2011). The prevalence and cost of these disorders highlights the need to understand the causal mechanisms and contributory factors that underlie the transition from recreational to compulsive use, that maintain the disorder, and that interfere with abstinence, along with the mechanisms that may promote effective treatments. In this chapter we reviewed data implicating both background and cue-induced craving in the maintenance of addiction, suggesting that craving is one of the key predictors of drug use and relapse and an important treatment target. We reviewed a wealth of research that links cue-induced craving to neural activity in the VS, amygdala, and vmPFC/ACC, identifying these regions as targets for regulation strategies and treatments for addiction. We further reviewed research that shows that the ability to regulate craving is an important component in cognitive-behavioral and mindfulness-based treatments for addiction and that, when individuals use strategies to cope with craving, they are less likely to use drugs or to relapse after abstinence. Importantly, findings from fMRI and PET studies suggest that neural activity in the dlPFC and vlPFC underlies the use of cognitive strategies to regulate craving, potentially by modulating activity in regions such as the VS. Additionally, tDCS and rTMS studies suggest a causal role for the dlPFC in decreasing the subjective experience of craving. Finally, we suggested that, despite the role of the dlPFC in reducing craving in a “top-down” fashion, mindfulness-based strategies may serve to regulate craving via a different, “bottom-up” mechanism (that does not depend on dlPFC).

It is important to note that, although there is a wealth of research in this area, our work is far from complete. Future research efforts should identify motivational factors that may reduce drug users’ ability to learn regulatory strategies, understand potential deficits in PFC function that may interfere with cognitive regulation, and elucidate the precise mechanism by which each regulatory strategy influences craving and craving-related neural activity. Further, future work should systematically investigate the neural basis of treatment-related change for addictive disorders, as well as individual-difference variables that may influence treatment response (including variations in craving sensitivity and cognitive control). Indeed, it is our sincere hope that, in the coming years, such data will be collected that will allow us to develop better treatments for those suffering from addictions.

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## Note

- 1 Have you ever wanted a specific food, like chocolate? Perhaps salivated at the thought of your favorite meal? Responded positively to a food commercial? Felt like you really needed a cup of coffee or a glass of wine at the end of the day? If so, then you experienced craving.

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