CHAPTER 26

Emotion Regulation in Substance Use Disorders

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Have you ever had coffee or tea? A glass of wine? Smoked even a single cigarette? Virtually all adults report consuming psychoactive drugs[1] at some point in their lives, suggesting that casual drug use is quite common (Substance Abuse and Mental Health Services Administration [SAMHSA], 2011). On the other end of the drug use spectrum, substance use disorders (SUDs; or addictions) are complex illnesses, encompassing a host of severe negative physical, economic, and social consequences, and contributing to worldwide disability. With a lifetime prevalence of 35.3% in the general population, individuals with SUDs constitute a relatively small proportion of casual drug users, yet they also represent the most prevalent and costly of psychiatric disorders (National Institute of Mental Health [NIMH], 2007; SAMHSA, 2011).

Defined as "a problematic pattern of drug use, leading to clinically significant impairment or distress" (American Psychiatric Association, 2013, p.481), SUDs are both personally and socially devastating in that it is often chronic and can severely impair even basic life functioning. In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), SUDs are characterized by the presence of symptoms including tolerance, withdrawal, continued use despite wishes to stop, continued use despite known negative consequences, and importantly, a loss of regulatory control over drug cravings, as well as further drug use. As such, loss of regulatory control is a key feature of SUDs. The addition of *drug craving* (strong desire for drugs) as a diagnostic criterion for SUDs in DSM-5 emerged from a wealth of accumulated research over the last decade directly linking craving to drug use and *relapse* (return to drug use following abstinence; e.g., Shiffman et al., 2013; see later sections for additional discussion). This suggests that craving is also a key feature in SUDs, and that regulation of craving is a specific form of emotion regulation that can directly reduce drug use.

This chapter focuses on the crucial and complex role of emotion regulation in SUDs (see Figure 26.1 for a schematic summary). In the first section, I discuss the role of acute drug intoxication as a means of emotion regulation, arguing specifically that people use drugs in part to regulate their current emotional state. This may include increasing positive affect, ameliorating a preexisting negative state, or decreasing craving. In the next section, I explore the role of emotion dysregulation in SUDs, both as a possible cause for and a possible consequence of drug use. In this section, I make several specific arguments. First, I argue that emotion dysregulation in childhood and adolescence may be an early risk factor and/or distal causal factor in the later development of SUDs. Second, I argue that an inability to regulate negative emotion properly in specific moments may

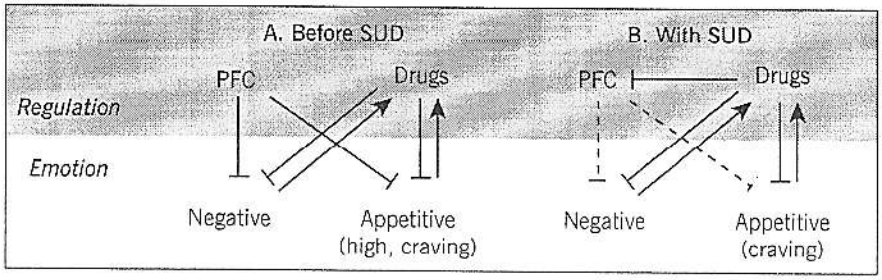

FIGURE 26.1. A simplified model of emotion regulation in SUDs. *Panel A:* Before SUDs. Prefrontal cortex (PFC) and drugs can both serve to regulate emotion. It is thought that PFC implements regulation over negative emotion and craving (indicated by downward blunted arrows). In turn, unregulated negative emotion and craving are associated with increased drug use (upward arrows). Here I propose that drugs can be seen as a form of emotion regulation as well (indicated by downward blunted arrows), increasing feelings of high, and decreasing negative emotion and craving. In this context, deficient emotion regulation or PFC control may serve as risk factors for SUDs. *Panel B:* After development of SUDs. Chronic drug use affects PFC (indicated by blunted arrow), diminishing its ability to regulate negative emotion, as well as drug craving (dashed downward blunted arrows). In turn, unregulated negative emotion and craving further lead to increased drug use (upward arrows). Drug use itself continues to regulate both negative emotion and drug craving (though perhaps less effectively). This results in a vicious cycle of reduced PFC-based emotion regulation, negative affect, craving, and increased drug use. Therefore, treatments for SUDs often focus on enhancing emotion regulation skills, especially regulation of craving, which has been linked to reduced drug use.

be a proximal causal factor for instances of drug use in individuals who are already suffering from SUDs. Third, I posit that SUDs are marked by deficits in regulation of a specific appetitive state, namely, drug craving, which is at the core of these disorders. I then review evidence that suggests differences in the structure and function of the prefrontal cortex (PFC) may be the neural mechanisms underlying emotion dysregulation in SUDs. This section further highlights that although some PFC abnormalities precede drug use, the long-term effect of chronic drug use on PFC may further impair emotion regulation in SUDs. In this way, drug use may lead to further emotion dysregulation. The chapter concludes with a section on treatments for SUDs, many of which focus on emotion regulation skills geared specifically toward regulation of craving as means of reducing substance use.

Drug Use as Emotion Regulation

Drugs can regulate emotion by pharmacologically altering one's current state. For example, although the exact pharmacological profiles of individual drugs differ, and these differences have both theoretical and neurobiological implications (e.g., Badiani, Belin, Epstein, Calu, & Shaham, 2011), many drugs are ultimately described as euphoric, increasing positive emotion (Jaffe & Jaffe, 1989). In human laboratory experiments, self-administration of drugs, including alcohol, methamphetamine, cocaine, and marijuana, significantly increase feelings of "high" and "good drug effects" (e.g., Hart, Ward, Haney, Foltin, & Fischman, 2001; see Figure 26.1A). Consistently, it is has been proposed that these positive effects of drugs lead to positive reinforcement and increase the likelihood of future drug use (Kober, Turza, & Hart, 2009). Furthermore, drug users often develop positive expectancies regarding drug use (e.g., "If I drink, I will feel good") that are associated with increased drug use and increased risk of developing SUDs (e.g., Jones, Corbin, & Fromme, 2001).

In addition to increasing positive emotion, various drugs are known to alleviate negative emotional states, including anxiety (e.g., alcohol, and anxiolytic medication such as Valium and Xanax), sadness and

depression (e.g., stimulants such as cocaine and amphetamines), and pain (e.g., heroin, morphine, and other synthetic prescription opiates such as Vicodin). Consistently, it has been proposed that these negativity-reducing effects of drugs lead to negative reinforcement, thus increasing the likelihood of future drug use (Koob & Le Moal, 2008). This idea was initially popularized by the "self-medication hypothesis" proposed by Khantzian (1985), which has two main components: (1) Unpleasant affective states predispose individuals to drug use, and (2) the choice of drug is not random; rather, it is the nature of the drug's effects in ameliorating the preexisting negative state that renders a particular drug more or less reinforcing. In other words, those with a particular predisposition to negative affect states are more likely to develop an SUD for a drug that reverses those particular affective states. To illustrate, Khantzian suggested that individuals with strong rage and aggression use opiate drugs to regulate these emotions. In contrast, individuals with preexisting depression and melancholy develop cocaine use disorders due to cocaine's ability to relieve these symptoms. The self-medication hypothesis is consistent with patients' reports that "they got hooked not because they had taken the drug, but because they were not normal before in such a way that the drugs were . . . not the problem but a solution" (Le Moal, 2009), p. 542). It is further consistent with the observation that the expectancy that drugs will alleviate negative affect (e.g., "Drinking will calm me down") is associated with increased drug use and increased risk for SUDs (Jones et al., 2001).

Although the self-medication hypothesis has been challenged, several lines of evidence support the hypothesis that drug use serves to regulate negative emotion. First, SUDs frequently co-occur with a number of other psychiatric disorders, especially mood and anxiety disorders. Moreover, preexisting psychiatric diagnoses increase the likelihood of an individual to subsequently develop an SUD (e.g., Kessler et al., 2005). This suggests that individuals who already experience difficult emotions are more likely to seek and use drugs, and to develop problematic habits of drug use that presumably ameliorate their affective symptoms. A related point is that treatment for such comorbid disorders frequently reduces drug use (Nunes & Levin, 2004). Second, and similarly, those with chronic pain are far more likely to develop SUDs relative to the general, pain-free population, especially to pain-reducing drugs such as opiates (Morasco et al., 2011).

Third, even normal-range trait levels of negative affect are related to drug use. For example, trait depression and neuroticism correlate negatively with time to relapse in cigarette smokers (Gilbert, Crauthers, Mooney, McClernon, & Jensen, 1999), while trait levels of anger and anxiety correlate with craving to drink in alcoholics (Litt, Cooney, & Morse, 2000). Fourth, negative affective states are known triggers for craving in the context of both casual and problematic substance use (e.g., Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996). This phenomenon ranges from the common epithet "I had such a hard day, I need a beer or a stiff drink" to instances of relapse to drug use after experiencing a strong life stressor (e.g., death in family). Indeed, it has been well documented that both naturally occurring and experimentally induced negative affect and stress increase drug craving, drug use, and relapse (e.g., Sinha & Li, 2007).

Finally, drug use also serves to regulate the experience of craving, which is one of the most common motivators for drug use (Childress et al., 1993; Shiffman, et al., 2013). That is, individuals with SUDs use drugs to temporarily alleviate their experience of craving, thus generating a vicious cycle of increasing craving and use. Taken together, the evidence reviewed in this section suggests that drug taking can be a form of emotion regulation. Specifically, the acute effects of drugs may regulate preexisting emotions in both casual and problem drug users, including increasing positive emotion, decreasing negative emotion, and decreasing craving for drugs themselves (see Figure 26.1A).

Emotion (dys)Regulation Is a Causal Factor in SUDs

Although many people casually use drugs and alcohol, only a small percentage develop SUDs, highlighting the need to identify risk and causal factors for the initiation, development, and maintenance of these severe dis-

orders. Of course, because SUDs are complex disorders, they are likely caused and maintained by an intricate combination of factors, including genetic, cognitive, behavioral, individual-difference, and environmental variables, that likely interact across multiple levels of analysis. At this time, emotion regulation abilities are already emerging as one important contributor in the etiology and maintenance of SUDs, although in the next decade it is likely that larger longitudinal studies will allow us to identify additional factors.

Emotion (dys)Regulation as an Early Risk Factor

As reviewed below, SUDs are frequently associated with emotion regulation deficits. The specific question here is: Do these deficits precede the development of the disorder so that they may be considered a risk factor? The answer appears to be yes. Beginning with the classic "marshmallow test" experiments in the 1960s by Mischel and colleagues, it has been proposed that the ability to delay gratification, and regulate emotions like desire, is crucial to children's developmental trajectories (for review, see Mischel, Ayduk, Berman, Casey, Gotlib, et al., 2011 and Luerssen & Ayduk, this volume). In these studies, preschool children were typically presented with a tasty treat and told that they could have it now, or alternatively, wait to receive two treats at a later time—if they could delay gratification. In his seminal work, Mischel reported that children vary in their ability to delay gratification, ranging from not being able to wait at all to waiting as long as the experimenter allowed (and using a variety of spontaneous strategies to facilitate delay). In his follow-up work, Mischel (2011) reported that those preschool children who were able to delay gratification the longest (by waiting for a larger treat rather than indulging immediately in a smaller treat) later achieved higher Standard Achievement Test (SAT) scores, had better social-cognitive and emotional coping in adolescence, and importantly, were least likely to use crack cocaine in adulthood (see Mischel et al., 2011, for review; Luerssen & Ayduk, this volume). This body of work highlights how individual differences in emotion regulation (which manifest as early as preschool) may predate the development of SUDs and could therefore be conceptualized as a risk factor predicting illness onset.

In the years since this work was published, additional data has accumulated to further suggest that poor self-control[2] in childhood is indeed a risk factor for drug use and the development of SUDs. For example, Moffitt and colleagues (2011) followed 1,000 children from birth to age 32. In childhood, participants were assessed on various self-control measures related to emotion regulation, including emotional lability, frustration tolerance, and persistence. The authors report that individual differences in self-control were significantly predictive of adult health outcomes, including substance use and dependence, as much as 30 years later. Importantly, the contribution of self-control factors was distinct from the contribution of intelligence, social class, and other family-life variables. Strikingly, the highest and lowest one-fifth of the sample on measured self-control were associated with a prevalence of 3 and 10%, respectively, of polysubstance dependence in adulthood.

In addition, in childhood, the related construct of *trait impulsivity*—the tendency to act without thought or regard for consequences—has been repeatedly associated with the development of SUDs in later adolescence and adulthood (see Ivanov, Newcorn, Morton, & Tricamo, 2011; Verdejo García, Lawrence, & Clark, 2008, for reviews). Furthermore, longitudinal studies suggest that children who suffer from childhood disorders such as attention-deficit/hyperactivity disorder and conduct disorder, which are associated with poor emotional/behavioral regulation and impulsivity, are far more likely to use drugs and to receive an SUD diagnosis by late adolescence or young adulthood (e.g., August et al., 2006). It has also been suggested that the association between childhood disruptive behavior and adolescent-onset substance use may be mediated by early deficits in emotion regulation and inhibitory control (Ivanov et al., 2011). A similar construct used by Tarter and colleagues (2003), termed *neurobehavioral disinhibition*, is indexed by measures of emotion regulation, executive cognitive functioning, and behavior control. This construct distinguishes between 10- to 12-year-old boys who are at low vs. high

risk for development of SUDs (determined by parental SUD diagnosis). In addition, this construct was found to predict substance use at age 16, as well as SUDs in early adulthood (e.g., Tarter et al., 2003).

The mechanisms by which early emotion regulation problems lead to later SUDs are a target of current investigation. One prevailing hypothesis is that emotion regulation abilities (and cognitive control more generally) depend on the function of PFC regions (see Ochsner & Gross, this volume; Johnstone & Walter, this volume) that are not yet fully developed in children and adolescents (see Riediger & Klipker, this volume). Indeed, adolescence represents a period of both reduced emotion regulation abilities (Silvers et al., 2012) as well as substantial neural development (Giedd et al., 1999). Specifically, regions of lateral PFC have been found to be relatively hypoactive during emotion-related tasks in adolescents as compared to adults (e.g., Pfeifer, Lieberman, & Dapretto, 2007), with regulation-related activation in this area increasing with age (McRae et al., 2012).

Given this developmental trajectory, emotion dysregulation in adolescence may contribute to SUD risk via two parallel routes. First, immature emotion regulation capacities in adolescence may result in higher levels of stress and negative emotion, which has been shown to lead to the initiation of drug use in animal models (e.g., Haney, Maccari, Le Moal, Simon, & Vincenzo Piazza, 1995) and in human adults (see Sinha & Li, 2007, for review). Second, self-regulation failures in adolescence may underlie increased impulsivity and risk-taking behaviors that may also lead to initiation of drug use (e.g., Ivanov et al., 2011). Ultimately, the developmental trajectory of self-regulatory function suggests that at least some adolescents may be less able to recruit the neural circuitry needed to regulate their emotions optimally and to ultimately avoid substance use.

The idea that adolescents as a group may in fact be less able to recruit the necessary neurocircuitry to regulate emotions and avoid substance use—along with the observation that individual differences in the ability to do so are predictive of future substance use—is especially important, because adolescence is a period of heightened risk taking (SAMHSA, 2011) and peer influence (Steinberg, 2005), both of which expose adolescents to drugs. Thus, increased exposure to drugs, coupled with increased emotional reactivity and decreased regulatory capacities (rooted in ongoing brain development), make adolescence a particularly vulnerable period for substance use.

Indeed, drug use is most often initiated in adolescence. For example, 82.4% of first uses of alcohol occur in individuals under the age of 21 (the legal drinking age), and 58.8% of smokers have their first cigarette under the age of 18 (SAMHSA, 2011). These early use statistics are especially important, because earlier age of onset is associated with higher rates of SUDs and worse outcomes. For example, those who initiated alcohol use prior to age 14 are more than four times more likely to receive an SUD diagnosis in adulthood (16.2 vs. 3.8%; similar rates are reported for illicit drugs). Similarly, earlier age of smoking onset predicts a higher number of cigarettes smoked in adulthood (Tai oli & Wynder, 1991). Taken together, these data support the notion that emotion (dys) regulation is an early risk factor for SUDs. Next I discuss how emotion regulation may operate as an ongoing causal factor that may contribute to and exacerbate existing SUDs.

Emotion (dys)Regulation in Current SUDs

Several models of SUDs directly implicate deficient regulation as a key and primary motive for ongoing drug use and relapse, including the *relapse prevention model* (Marlatt & Witkiewitz, 2005), the *affective processing model* (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004), and the aforementioned *self-medication hypothesis* (Khantzian, 1985), among others. Indeed, whether or not emotion regulation deficits are a preexisting risk factor for SUDs (as proposed in the previous section), those who currently suffer from SUDs frequently display such deficits, which may contribute to the clinical course of the disorder. Several lines of evidence support this association (Figure 26.1B for schematic illustration).

First, self-reported emotion regulation skills are lower in individuals with SUDs than in healthy controls (e.g., Fox, Hong, & Sinha, 2008). In addition, greater difficulties in regulating emotion is associated

with more drug use (e.g., Berking et al., 2011) possibly as a means of emotion regulation (Bonn-Miller, Vujanovic, & Zvolensky, 2008). Second, less effective styles of emotion regulation (e.g., suppression vs. reappraisal) are related to increased drug use (Fucito, Juliano, & Toll, 2010). Third, individual differences in negative affect have been repeatedly associated with drug use and relapse in clinical (e.g., Gamble et al., 2010), as well as laboratory studies (e.g., Sinha & Li, 2007). Fourth, as reviewed earlier, SUDs are highly comorbid with affective disorders, such as depression, which feature impaired regulation of negative affect as a key diagnostic feature (American Psychiatric Association, 2013). Furthermore, those with co-occurring symptoms of SUDs and affective disorders show significantly higher rates of relapse to drug use after treatment (e.g., Bradizza, Stasiewicz, & Paas, 2006) offering additional support for the link between emotion (dys)regulation deficits and SUDs.

Additional evidence links constructs related to emotion regulation and SUDs. For example, *emotional intelligence*—defined as the ability to be aware of emotions, identify emotions correctly, interpret them appropriately, and regulate them effectively—is inversely associated with alcohol and drug-related problems (Riley & Schutte, 2003). Moreover, emotional intelligence moderated the association between negative emotion and alcohol craving in alcohol-dependent individuals (Cordovil de Sousa Uva et al., 2010). Furthermore, a recent meta-analysis of this construct suggests that not only is it inversely related to smoking, alcohol, and drug use, but also that individual differences in particular components, namely, "identification of emotion" and "regulation of emotion," are particularly related to SUDs (Kun & Demetrovics, 2010). Similarly, *distress tolerance*—the ability to persist in goal-directed activity when experiencing psychological distress—is related to emotion regulation and is inversely associated with substance use frequency and SUDs (Marshall-Berenz, Vujanovic, & MacPherson, 2011), as well as SUD treatment dropout and eventual relapse (e.g., Daughters et al., 2005). In addition, impulsivity is reportedly higher in those with SUDs (see Verdejo-García, et al., 2008, for review). Finally, it has been suggested that those with SUDs exhibit relative deficits in nonaffective forms of self-regulation and executive function, including working memory and response inhibition, which may also relate to PFC function (Goldstein & Volkow, 2011).

Emotion (dys)Regulation in Current SUDs: Regulation of Craving

In the previous section, I reviewed evidence suggesting that those with SUDs have difficulties regulating emotions. Notably, the evidence overwhelmingly centers on regulation of negative emotions. However, in the context of SUDs, it is critical to consider not only regulation of negative emotion but also an additional and very specific form of emotion regulation, namely, the regulation of craving.

Craving, defined here as "intense desire for drugs," has long been considered a key contributor to drug use (e.g., O'Brien, Childress, Ehrman, & Robbins, 1998). Although this view has been challenged (Perkins, 2009) substantial evidence links drug craving to drug-taking behavior, and it has been suggested that loss of control over cue-induced craving is at the root of compulsive drug taking (e.g., Goldstein & Volkow, 2011). For example, levels of reported craving predict drug use as well as relapse to drug taking following abstinence (e.g., Crits-Christoph et al., 2007; Epstein, Marrone, Heishman, Schmittner, & Preston, 2010; Galloway, Singleton, & the Methamphetamine Treatment Project Corporate Authors, 2008). Conversely, the ability to use various strategies to regulate craving is associated with lower craving (Kober, Kross, Mischel, Hart, & Ochsner, 2010; Kober, Mende-Siedlecki, et al., 2010; Westbrook et al., 2013) and lower drug use (O'Connell, Hosein, Schwartz, & Leibowitz, 2007). Further, the acquisition of strategies during cognitive-behavioral therapy (as discussed below) is associated with better long-term outcomes (Carroll, Nich, Frankforter, & Bisighini, 1999). Furthermore, the use of cognitive strategies to regulate craving both during and after treatment is associated with reduced craving and reduced relapse over time (O'Connell et al., 2007; Shiffman et al., 1996). These findings suggest that craving is a key motivator of substance use, and that effective regulation of craving is associated with lower drug use

and better outcomes for those with SUDs. This in turn suggests that regulation of craving is a specific form of regulation that is particularly important in the maintenance of drug use behavior in SUDs.

The neural mechanism by which regulation of craving operates to reduce drug use is a topic of current research. It has been shown previously that exposure to drug cues (e.g., drug-related images, movies, or paraphernalia) increases craving, as well as drug use (e.g., Shiffman et al., 2013). Furthermore, several meta-analyses have shown that such cue-induced craving is consistently associated with neural activity in a network of regions including the ventral striatum, the subgenual anterior cingulate, and the amygdala (e.g., Chase, Eickhoff, Laird, & Hogarth, 2011). These regions, which are thought to relate to learning, salience, and value encoding, previously have been associated with the acute effects of drugs. We have recently shown that when cigarette smokers use cognitive strategies in instances of craving (e.g., when they think about the long-term negative consequences of smoking), they report lower craving (Kober, Kross, et al., 2010), and exhibit lowered activity in the neural systems that underlie craving, such as the ventral striatum (Kober, Mende-Siedlecki, et al., 2010). Importantly, the regulation of craving is associated with concurrently increased activity in PFC regions including the dorsolateral (dlPFC) and ventral PFC—regions previously associated with regulation of negative emotion (see Ochsner & Gross, this volume). These findings have since been replicated with positron emission tomography in cocaine users (Volkow et al., 2010) and electrophysiological measurements in cigarette smokers (Littel & Franken, 2011).

Interestingly, we've recently shown that use of mindfulness-based strategies to regulate cue-induced craving is also associated with reductions in reported craving, and with reduced neural activity in "craving regions," including the subgenual cingulate. However, the use of such mindfulness-based strategies was not associated with concurrent increase in PFC activity (Westbrook et al., 2013). Taken together, these findings are consistent with the hypothesis that, across strategies, regulation of craving operates by reducing neural activity in regions that are thought to instantiate the experience of craving. Preliminarily, it further appears that the use of cognitive strategies to regulate craving may depend on increased activity in PFC but that mindfulness-based strategies may not, although additional data are required to confirm this pattern of results.

To summarize, this section has reviewed evidence suggesting that emotion regulation is implicated in SUDs, both as an early risk factor and as an ongoing motivator of drug use. For example, individual differences in emotion regulation and impulsivity during development are predictive of drug use initiation and SUDs. Furthermore, individuals with ongoing SUDs exhibit deficits in emotion regulation compared to healthy controls, and negative affect in such individuals is associated with instances of drug use. Importantly, most of the available evidence centers around regulation of negative emotion. However, regulation of craving is emerging as another form of regulation that is important in the etiology and maintenance of these disorders, and may constitute one key route by which targeted treatments can ameliorate SUDs, as discussed further below (Figure 26.1B).

PFC in SUDs: Mechanism for Emotion (dys)Regulation?

In the prior sections I have reviewed evidence suggesting that PFC development may underlie the role of emotion dysregulation as a distal causal factor for development of SUDs in adolescence. But is this the neural mechanism that underlies general deficits in emotion regulation present in SUDs? Indeed, many current models of SUDs propose that the loss of control over craving and drug taking (as evident in the diagnostic criteria for the disorder) is a result of reduced or compromised PFC function (e.g., Everitt & Robbins, 2005; Goldstein & Volkow, 2011; Potenza, Sofuoglu, Carroll, & Rounsaville, 2011; Volkow, Wang, Fowler, & Tomasi, 2011). And this "PFC hypothesis" is consistent with the already-established link between cognitive control generally—and emotion regulation specifically—and the function of PFC in healthy adults (see Ochsner & Gross, this volume). However, neu

roimaging studies directly testing emotion regulation abilities in SUDs are scarce. Nevertheless, in the following sections, I review findings that individuals with SUDs exhibit structural abnormalities in various PFC regions, as well as functional differences in studies of nonaffective forms of cognitive control (for a brief review of neuroimaging methodologies used in such studies, see Kober & DeLeone, 2011). Importantly, although some of these PFC abnormalities may precede the development of SUDs, I review evidence suggesting that chronic drug use is associated with both structural and functional changes in PFC. Such drug-induced changes, in turn, suggest that SUDs may also lead to decrements in PFC that may underlie further emotion dysregulation (Figure 26.1B).

In reviewing this evidence, it is important to note that the PFC is a very large structural division in the brain, and that different subregions within the PFC perform very different computations and subserve different functions—even within the general "cognitive control" framework (Miller & Cohen, 2001). However, at this stage, there are not yet sufficient data to make finer distinctions about the functional role of PFC subdivisions in SUDs, or to begin to speculate about the role each subregion might have in the neuropathology of these disorders. I hope that data collected in the next decade will allow us to answer such questions with far greater specificity than we can today.

Structural Differences in the PFC

Differences in brain structure have been reported between those with SUDs and healthy controls, using several different methodologies, especially in various subregions of PFC. For example, using voxel-based morphometry, cigarette smokers exhibited reduced PFC gray matter density compared to healthy controls, and PFC thickness was negatively correlated to reported smoking (measured in packs-per-year; Brody et al., 2004). In cocaine-dependent individuals, relatively reduced gray matter density in orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) was reported (Franklin et al., 2002). Similarly, lower thickness and volume were reported for other stimulant users in various prefrontal regions (e.g., Daumann et al., 2011) and in right ventrolateral PFC (vlPFC) specifically, where thickness was inversely correlated with drug craving (Tabibnia et al., 2011). In alcohol-dependent subjects compared to controls, lower gray matter volume was reported across the PFC (Fein, Di Sclafani, & Meyerhoff, 2002) and more specifically in the lateral and superior PFC and OFC (Durazzo et al., 2011) and medial and lateral PFC (Rando et al., 2011). In these latter studies, lower medial PFC volume was associated with more drinking posttreatment or shorter time to relapse. In addition, in some studies (but not all) PFC volume was inversely associated with cognitive control measures. For example, PFC gray matter volume correlated inversely with executive function measures in cocaine-dependent individuals (Fein et al., 2002).

Consistent with these gray matter findings in PFC, diffusion tensor imaging (DTI) measures of PFC white matter integrity distinguish between individuals with alcohol use disorders and controls (e.g., Pfefferbaum, Rosenbloom, Rohlfing, & Sullivan, 2009) and further differ between individuals who relapsed and those who sustained abstinence following treatment (Sorg et al., 2012). In cocaine-dependent participants, lower measurements of white matter integrity are consistently found in various PFC regions (e.g., Romero, Asensio, Palau, Sanchez, & Romero, 2010). Similar findings were reported in methamphetamine (Alicata, Chang, Cloak, Abe, & Ernst, 2009) and in opiate users (Bora et al., 2012; Liu et al., 2008).

Taken together, this body of structural neuroimaging work suggests that there are consistent anatomical differences between those with SUDs and healthy controls. A cautionary note here is that it is not yet clear what these differences mean. While it is tempting to interpret these differences as indicating impairment in individuals with SUDs, this link has not yet been consistently demonstrated. For instance, although reportedly lower than that in controls, cortical thickness and cognitive function are often within normal range in SUDs (and see Hart, Marvin, Silver, & Smith, 2011, for extended discussion). Nevertheless, these differences are consistently reported across PFC and across types of SUDs. Furthermore, although indi-

vidual studies differ with respect to the localization of these differences (possibly due to sample characteristics, drug pharmacology, drug use patterns, and methodological and statistical differences), and only some studies find association with clinical outcomes, the PFC is repeatedly implicated, especially lateral portions. Reported differences are especially salient given the known role for PFC in emotion regulation and cognitive control in healthy adults. Taken together, these structural findings are consistent with the hypothesized mechanism by which PFC abnormalities may contribute to or underlie deficient emotion regulation in SUDs. However, future work could more directly link structural findings in PFC with emotion regulation in SUDs.

Functional Differences in PFC

Differences in measures of PFC function between individuals with SUDs and healthy controls have been consistently reported since the early days of functional neuroimaging (e.g., Volkow et al., 2011). For example, using various forms of positron emission tomography (PET), it has been established that those with SUDs often exhibit relative reductions in "D2" type receptors of the neurotransmitter dopamine in striatum and PFC, with some evidence that these reductions persist even after months of abstinence (see Volkow et al., 2011, for review). PET measures of glucose metabolism have repeatedly shown decreased activity in OFC, ACC, and dlPFC. In stimulant users decreased activity is further related to relatively decreased D2 receptor availability in striatum (Volkow et al., 2011). Notably, in alcohol-dependent individuals, striatal D2 availability is linked to not only to PFC activity but also to self-reported alcohol craving, suggesting that all three processes may be functionally related (i.e., OFC function, D2 receptor availability, and craving; Heinz et al., 2005).

More recently, several studies have specifically investigated brain function during performance of non-affective cognitive control tasks comparing individuals with SUDs and healthy controls, typically with functional magnetic resonance imaging (fMRI). One frequently used task is the go/no-go response inhibition task, in which participants are asked to respond to all letters except *X* with a button press, and to withhold responding to *X*. Using this task, a series of studies reported relatively worse performance in cocaine- and heroin-dependent individuals compared to healthy controls, along with reduced activity in several PFC regions, including the dorsal ACC (dACC), dlPFC, and vlPFC (e.g., Fu et al., 2008; Hester & Garavan, 2004). Such findings suggest at least some functional alterations in PFC circuits in SUDs, even in the absence of emotion regulation demand. Similarly, Li, Luo, Yan, Bergquist, and Sinha (2009) used the stop-signal response inhibition task, and reported lower activity in dlPFC in alcohol dependence, which further related to higher alcohol craving self-reports. In cocaine-dependent individuals, dACC activity was lower than that in controls and negatively correlated with self-reported difficulties in emotion regulation (Li et al., 2008).

The Stroop color–word task has also been used to probe inhibitory control in SUDs by comparing neural activity during incongruent (BLUE written in red ink) and congruent (BLUE written in blue ink) trials. Using PET, both marijuana- and cocaine-dependent participants showed reduced "Stroop effect" activity in dACC and dlPFC (Bolla et al., 2004; Eldreth, Matochik, Cadet, & Bolla, 2004). In the cocaine-dependent sample only, dlPFC activity negatively correlated with cocaine use (least "Stroop effect" activity for the heaviest users; (Bolla et al., 2004). Similarly, DeVito, Kober, Carroll, and Potenza (in preparation) recently used the Stroop task and fMRI in cocaine-dependent participants, and found reduced Stroop-related PFC activity compared to controls. Similar findings have been reported with methamphetamine users (Nestor, Ghahremani, Monterosso, & London, 2011). In marijuana-dependent individuals who were about to begin treatment, Kober, DeVito, DeLeone, Carroll, and Potenza (under review) found reduced "Stroop effect" activity in dlPFC compared to healthy controls, and positive correlations between PFC activity and treatment success. Similarly, Berkman, Falk, and Lieberman (2011) related neural activity during go/no-go task performance to treatment outcome and reported that increased PFC activity during the task was related to a weaker association between

craving and smoking during subsequent abstinence.

Taken together, these studies suggest that those with SUDs exhibit poorer performance in cognitive control tasks, as well as lower activity in PFC regions typically associated with emotion regulation and executive function more generally, including dlPFC and dACC. Some studies reported direct association between lower PFC function and less cognitive control or emotion regulation, while others link greater PFC activity to better treatment outcomes (e.g., Berkman et al., 2011; Kober et al., under review). These findings are therefore consistent with the hypothesis that PFC abnormalities in structure or function underlie emotion dysregulation in SUDs.

Effects of Drug Use on PFC

Data reviewed thus far suggests that those with SUDs exhibit deficits in emotion regulation, and both structural and functional differences in PFC compared to healthy controls. Notably, most of the reviewed data were generated in the context of case–control studies—measured at a single point in time, in individuals with active SUDs. Therefore, it is not clear whether some of these reported abnormalities precede the development of SUDs (and may serve as a risk factor, as discussed previously), whether they are the result of chronic drug use (and reflect the effects of drug exposure) or an interaction of both. Evidence for PFC abnormalities as a preexisting risk factor includes a recent study of individuals with SUDs (cocaine or amphetamine dependence) and their unaffected siblings compared to healthy adults. Both individuals with SUDs and their unaffected siblings shared a neurological phenotype of reduced structural connectivity in the right vlPFC, which was further related to performance on the stop-signal response inhibition task (Ersche et al., 2012). These findings suggest that potential abnormalities in lateral PFC may underlie regulatory deficits that in fact predate the onset of SUDs.

On the other hand, there is ample evidence, mostly from animal studies, that chronic/regular drug use alters both function and structure of PFC and other brain circuits (for an excellent recent review, see Lüscher & Malenka, 2011). Although it is outside of the scope of this chapter to discuss the unique mechanism of action or pharmacological effects of individual drugs, one now-classic finding is that all drugs that are abused by humans share one common effect. That is, all drugs of abuse—either directly or indirectly—increase concentrations of the neurotransmitter dopamine in the "mesocorticolimbic" pathway, which includes the ventral tegmental area, the ventral striatum, and the PFC (e.g., Dichiara & Imperato, 1988; Volkow et al., 2011).[3] In turn, this drug-induced increase in dopamine is associated with long-term changes or adaptations to neurons in this pathway, including in PFC (Lüscher & Malenka, 2011). These changes are thought to facilitate associations between drugs and drug-related cues (e.g., alcohol and the bar where one drinks; cigarettes and the lighter one uses for smoking), lead to future cue-induced drug craving, and reduce cognitive control (Volkow et al., 2011).

Furthermore, it is thought that some of the effects of acute as well as chronic drug use are *neurotoxic*—damaging to neural tissue (Weiss & Koob, 2001). Such claims emerge primarily from an animal literature experimentally documenting various forms of neuronal damage following heavy drug administration (e.g., Gouzoulis-Mayfrank & Daumann, 2009). Although it is not clear that such findings translate to human drug users (Hart et al., 2011), some studies in humans have linked length of drug use with measures of structural or functional integrity, which is consistent with animal findings. For example, in opiate users, PFC white matter integrity correlated negatively with length of opiate use (Bora et al., 2012; Liu et al., 2008). Similarly, some human studies have shown that various functional and structural abnormalities normalize following drug abstinence, implicating drug use itself in the originally observed differences in PFC (e.g., Gouzoulis-Mayfrank & Daumann, 2009). Taken together, the evidence suggests that even if some PFC abnormalities precede the development of SUDs, drug use itself is associated with long-term changes to many brain circuits, including PFC. Furthermore, these changes may create or exacerbate deficits in emotion regulation in SUDs. In essence, this suggests that chronic drug use may lead to a vicious cycle,

in which impaired emotion regulation leads to drug use, and drug use may further lead to impaired emotion regulation.

Treatment for SUDs: The Role of Emotion Regulation

Treatments for SUDs are varied and complex, as is appropriate given the heterogeneous and complex nature of the disorders that they treat. At this time, despite repeated scientific efforts, there are few FDA-approved pharmacological treatments for SUDs. Therefore, nonpharmacological (e.g., psychological) treatments are most common. While the goal of treatment may be conceptualized as reductions in drug use and in drug-related harm, and increases in psychosocial functioning, treatment success is most often measured in *abstinence*, or complete cessation of drug use. As such, the available treatments are only moderately effective; indeed, across all treatments for SUDs, the most common outcome is relapse (Dutra et al., 2008). This suggests that while some individuals successfully remain abstinent, the majority of patients either do not achieve abstinence or return to drug use within a year, even with the best of treatments. These grim findings underscore the need to better understand the mechanisms of action behind the treatments that do work, in order to improve them further.

From a clinical perspective, treatment for SUDs can be divided into three phases: detoxification, recovery, and relapse prevention (e.g., Potenza et al., 2011). The goal of the detoxification stage is to achieve abstinence and undergo withdrawal symptoms safely, until they abate. The onset, character, and length of this stage depend on the pharmacological properties of the individual drug, as well as treatment type (some treatments begin with recovery elements, then set a "quit date" to begin detoxification). The main stage of treatment is recovery, which can last from 1 week to many weeks. The goal of the recovery stage is to develop motivation to avoid drug use and relapse, as well as learn the skills to do so successfully. In that sense, what does recovery entail? The data reviewed in this chapter suggest that difficulties regulating emotions are a core feature of SUDs. Specifically, I have argued that difficulties regulating both negative (stress, anxiety, or depression) and appetitive (drug craving) states are associated with drug use and with relapse to drug use following abstinence. Therefore, it is no surprise that at this recovery phase, many of the leading treatments include training of emotion regulation skills in general, and regulation of craving in particular (e.g., Potenza, et al. 2011; see Figure 26.1B). Indeed, learning to tolerate or regulate cravings and not to act on them is the cornerstone of many of the available treatments, as discussed below. Finally, the last phase of treatment, relapse prevention, focuses on implementing long-term strategies for maintaining abstinence, which includes replacing old behaviors with a new and healthy, drug-free lifestyle. Overall, there are many types of treatments for SUDs, and each type has many unique features. The following sections focus on two types of treatment that are related to the role of emotion regulation in SUDs: cognitive-behavioral and mindfulness-based treatments.

Cognitive-Behavioral Therapies

Cognitive-behavioral therapies (CBTs) are considered the most effective treatment for many psychiatric disorders (e.g., depression and anxiety). A version developed specifically for SUDs (Carroll, 1998) has been empirically validated in multiple randomized controlled trials and is considered by many to be the "gold standard" (e.g., Dutra et al., 2008; Potenza et al., 2011). CBT for SUDs has two critical components: functional analysis and skills training. *Functional analysis* is used to identify and assess the individualized circumstances that are likely to lead to drug use, and provides insights into some of the reasons the individual may be using drugs. These "high-risk situations" are those in which new skills may be applied to avoid drug use during and after treatment. Therefore, in a complementary fashion, skills training (including emotion regulation) is individualized to help those with SUDs "unlearn old habits associated with [drug] . . . abuse and learn or relearn healthier skills and habits" (Carroll, 1998, p. 2). More specifically, these skills initially include regulating thoughts about drugs, learning strategies to regulate cravings for

drugs, and managing situations related to drug-use opportunities (e.g., refusing offers of drugs).

Subsequent treatment sessions (*modules*) focus on problem solving, tolerating and regulating negative affect, and improving social skills more generally. Ultimately, individuals who undergo CBT (compared to other treatments) are more likely to decrease drug use and/or achieve abstinence during and even after treatment has ended (i.e., "the sleeper effect"; Potenza et al., 2011). Although the treatment includes many modules and stages, one important mechanism of action is thought to be via enhancing cognitive control over negative affect that may lead to drug craving, and over drug craving and drug taking behavior (e.g., Kiluk, Nich, Babuscio, & Carroll, 2010; Potenza et al., 2011). This hypothesis is supported by the finding that the number and quality of strategies for regulation of craving increase from pre- to post-CBT treatment, and predicted relapse (e.g., Carroll, et al., 1999), and formally mediate the relationship between treatment and duration of abstinence (Kiluk et al., 2010). In turn, this increase in regulation skills is hypothesized to be mediated by improved PFC function from pre- to post-treatment (Potenza et al., 2011; see Figure 26.1B for a schematic illustration). Consistent with this hypothesis, Kober, Kross, et al. (2010) have shown that use of CBT-like cognitive strategies during cue-induced craving is associated with decreases in self-reported craving,as well as increased activity in dlPFC and vlPFC (Kober, Mende-Siedlecki, et al., 2010). In addition, DeVito et al. (2011) recently reported that those who underwent CBT exhibited increased efficiency in vlPFC and dlPFC during the Stroop task from pre- to post-CBT treatment, which is consistent with improvements in cognitive control and emotion regulation. However, future studies should test that hypothesis more directly.

Mindfulness-Based Treatments

Mindfulness-based treatments (MBTs) for a variety of psychiatric conditions have emerged in recent years, beginning with mindfulness-based stress reduction (MBSR). *Mindfulness* has been defined as a two-component construct: (1) self-regulation of attention to the present moment, coupled with (2) an attitude of acceptance toward the present moment (Bishop et al., 2004). As such, mindfulness is often practiced through mindfulness meditation, which consists of focusing attention on one's immediate experience (e.g., sensations, breathing, thoughts, emotion), and regarding it nonjudgmentally. This is thought to cultivate the ability to observe—rather than be caught up in—one's own experience, and to further facilitate more skillful or mindful responding (as opposed to automatic reaction; Zgierska et al., 2009). Importantly, meditation and MBTs have been associated with beneficial effects on stress, anxiety, pain, cardiac health, immune functions, psychological well-being, cognitive functioning, and several psychiatric disorders (including mood and anxiety disorders; see Hölzel et al., 2011, for review). Therefore, it is not difficult to extrapolate how MBTs could be beneficial for fostering better emotion regulation in SUDs.

Indeed, several mindfulness-based treatments have recently been adapted for SUDs. Unlike the well-established CBTs, these treatments have just shown preliminary efficacy and are now the focus of rigorous randomized controlled trials. MBTs for SUDs typically include training in mindfulness meditation, and a focus on attention to and acceptance of present-moment experience (including negative emotion and drug craving). The modal instruction is to regard internal experiences (e.g., drug craving) as transient, and to observe and accept them as-is, without reacting (e.g., without engaging in drug use). For example, both mindfulness-based relapse prevention (MBRP; Bowen, Chawla, & Marlatt, 2010) and mindfulness training for smoking (MTS; Brewer et al., 2011) make use of the concept of "urge surfing," the practice of regarding craving like a wave that rises, reaches a peak, and subsides naturally. Patients are instructed to attend to and accept the sensations as they rise, fall, and finally disappear—and this technique is likened to tolerating cravings rather than actively regulating them, as in CBT (Brewer et al., 2011). Consistently, Westbrook et al. (2013) have shown that mindful attention to smoking cues is associated with lower self-reported craving and lower neural activity in regions previously associated with craving, without concomitant increases in PFC activ-

ity. As such, mindful attention and acceptance may be regulatory, by preventing the amplification of craving rather than dampening them down.

Clinically, MBRP, typically administered as a follow-up to inpatient treatment, is reportedly efficacious in reducing drug use and relapse across several different populations with SUDs, including alcohol and polysubstance users (e.g., Witkiewitz & Bowen, 2010). In addition, Brewer et al. (2011) have recently shown in a pilot randomized controlled trial that MTS administered as a stand-alone treatment was effective in achieving smoking cessation. Finally, similar elements of mindful attention and acceptance are parts of dialectical behavior therapy and acceptance and commitment therapy, both of which have shown preliminary efficacy for SUDs (Hernández-López, Luciano, Bricker, Roales-Nieto, & Montesinos, 2009; Linehan et al., 2002). Taken together, these data show substantial promise for MBTs in the treatment of SUDs, although the research is still in its infancy. Nevertheless, one prominent hypothesis suggests that these treatments work by enhancing emotion regulation, as patients learn to practice mindfulness in the face of craving as well as negative emotion. This is supported by several findings, including consistent reductions in craving post-MBRP (e.g., Witkiewitz & Bowen, 2010), and a negative correlation after MTS between amount of meditation practice and smoking (Brewer et al., 2011).

Concluding Remarks

Casual drug use is quite prevalent, and a percentage of drug users develop SUDs, which are severe psychiatric conditions with staggering social, economic, and personal costs. This underscores the need to identify risk factors that render specific individuals more vulnerable to the development of SUDs. Furthermore, once established, SUDs are chronic, relapsing, and very difficult to treat psychiatric conditions; this underscores the need to better characterize the proximal causal factors that lead to continued drug use, and to better understand the mechanisms that underlie effective treatments for these disorders. In this chapter, I reviewed data suggesting that emotion regulation is one such crucial factor. Indeed, difficulties in emotion regulation in childhood and adolescence serve as predictive factors for future drug use and the development of SUDs. Subsequently, those with SUDs report greater difficulty regulating negative emotions than do healthy controls, which contributes to ongoing drug use. Furthermore, I reviewed evidence suggesting that craving for drugs is one of the key predictors of drug use, and that the ability to regulate craving effectively is directly related to reduced drug use in SUDs.

Consistent with these observations, psychosocial treatments for SUDs often focus on emotion regulation and on the regulation of craving as means for reducing drug use. Indeed, improvement in those skills following treatments such as CBT and MBTs is associated with improved abstinence. Finally, I reviewed data suggesting that differences in PFC structure, as well as function, may underlie impaired emotion regulation in those with SUDs, and that ongoing drug use leads to adaptations in PFC that may further impair emotion regulation. However, it will be critical to focus future research on more precisely characterizing the neural mechanisms behind observed PFC deficits in SUDs and behind treatment-related improvements. Indeed, it is my sincere hope that in the coming years, additional data will allow us to establish these links more firmly. This could lead to the development of better treatments that improve emotion regulation in individuals suffering from these devastating disorders.

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Notes

1. Psychoactive drugs are those that primarily act on the brain and change thinking, mood, and behavior. These include legal drugs (e.g., alcohol, nicotine, caffeine, and opioid pain medications), as well as illicit drugs (e.g., heroin, cocaine, amphetamines, and marijuana).
2. *Self-control* is often defined as the process of inhibition of an otherwise imminent thought, emotion, or action–and as such, it includes emotion regulation. Related to this is the construct of cognitive control, which more broadly includes goal maintenance, selective attention, conflict monitoring and resolution, response inhibition, and emotion regulation. See Gross (this volume) for discussion.
3. It is now known that many other neurotransmitter systems are involved in drug taking and in the development of SUDs, and the next decade will likely bring additional investigations into other neurotransmitter systems and their relation to SUDs.

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