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NEGATIVE REINFORCEMENT: POSSIBLE CLINICAL IMPLICATIONS OF AN INTEGRATIVE MODEL

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Many addicted individuals report that they crave and use drugs to escape various forms of distress (e.g., Holahan, Moos, Hyolahan, Cronkite, & Randall, 2001); however, the hypothesis that people take drugs to alleviate distress is controversial because evidence does not consistently show that distress predicts drug use (Jaffe, 1992; Lyvers, 1998; van Ree, Gerrits, & Vanderschuren, 1999).

In this chapter, we briefly review the history of models that assert that negative reinforcement learning (i.e., learning that drug self-administration is followed by a reduction in an aversive stimulus) plays a central role in addiction. We then summarize the current support for a reformulated negative reinforcement model of drug motivation (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004) that specifies the conditions in which the distress that prods drug craving and self-administration will enter awareness and thus be amenable to both self-report and cognitive control (Curtin, McCarthy, Piper, & Baker, 2006). This model may explain the inconsistency in the observed relations between distress on the one hand, and indexes of drug motivation (urge report and self-administration) on the other hand. We conclude the chapter with a discussion of clinical implications of the reformulated model.

A BRIEF HISTORY OF NEGATIVE REINFORCEMENT MODELS
OF DRUG MOTIVATION

Negative reinforcement learning has been proposed as an explanation for addictive drug use for at least the past half-century (Wikler, 1948). In *operant conditioning*, a behavior that is negatively reinforced by relief from a noxious stimulus is likely to be repeated in the future when the noxious stimulus is present. Escape from aversive drug withdrawal effects is thought to be a central motive for continued drug use due to repeated cycles of learning that drug use alleviates aversive withdrawal symptoms. Withdrawal symptoms vary across drugs of abuse, but they have in common a core of negative affect symptoms, such as irritability, anxiety, and depressed mood (Gawin & Kleber, 1986; Hughes & Hatsukami, 1986; Kosman & Unna, 1968; Mansky, 1978). Recognition of this common core of distress has helped clarify the basis of the addictive liability of substances such as nicotine that do not lead to dramatic physical signs of withdrawal. Withdrawal symptoms develop rapidly following repeated use of drugs (Schulteis, Heyser, & Koob, 1997), so negative reinforcement learning may play a role early in an individual's drug use career as well as later, when dramatic withdrawal symptoms emerge. The view that relief of negative affect constitutes the core of negative reinforcement suggests that any sort of affective distress may cue drug use for the addicted individual, even if it does not arise from drug withdrawal (see Kassel, Stroud, & Paronis, 2003).

Evidence indicates that the acute phase of withdrawal (2–7 days after discontinuation of drug use) is indeed a time of high relapse vulnerability (e.g., Kenford et al., 1994). Relapses sometimes occur long after withdrawal seems to have resolved (Brandon, Lazev, & Juliano, 1998), however, which would seem to challenge withdrawal relief as a primary motive for relapse. Wikler (1965) accounted for this by arguing that drug withdrawal responses, just like direct drug effects, can be conditioned through associative learning. Consistent with this claim, both the physical and affective symptoms of withdrawal can be reinstated by exposure to conditioned stimuli (e.g., Kenny & Markou, 2005; Mucha, 1987; O'Brien, 1976; Siegel, 1977). For example, recent research in rats demonstrated that cues (a light + tone compound) previously paired with naloxone-precipitated withdrawal elicited increased heroin consumption and decreased activity in reward pathways when presented without naloxone (Kenny, Chen, Kitamura, Markou, & Koob, 2006).

Addiction models have identified negative reinforcement as a potent influence on drug use while recognizing the positive reinforcement also provided by drugs. The *opponent process model of addiction*, for instance, posits that drugs disturb homeostasis in a positive direction initially (the hedonically positive direct drug effect is called the *a process*), but this disturbance is followed by a countervailing response (called the *b process*) that returns the

user to homeostatic balance (Solomon, 1977; Solomon & Corbit, 1973). With repeated drug use, the b process increases in amplitude and duration so that it overwhelms the initial appetitive a process, and the net effect of using drugs is a negative disturbance, which manifests as withdrawal symptoms. The opponent process model incorporates both positive and negative reinforcement learning and accounts well for the development of the tolerance and withdrawal that are hallmarks of addiction.

Recently, Koob and Le Moal (1997, 2001) have extended the opponent process model. They asserted that addiction cannot be fully accounted for by homeostatic processes because addiction is an allostatic state in which the homeostatic reward set point is itself changed by drug use. They also asserted that repeated drug use disturbs the brain's reward system set point. This change in set point places an allostatic load on the individual, and dysregulation in the reward system leads to a "spiraling distress of addiction" (Koob & LeMoal, 2001, p. 111) in which stress systems are activated and reward systems are underactivated in abstinence. In essence, addicted individuals are changed by drug use so that they experience more stress and respond less to rewards when they are abstinent, which sets the stage for negative reinforcement by drug use. The *allostatic reward model* is grounded in animal research and evidence regarding the effects of drugs on reward, stress, and cortico-thalamic brain functions (Koob & LeMoal, 2001).

Considerable evidence supports the core predictions made by these models of drug motivation. In particular, there is consistent, compelling evidence that drug use leads to aversive symptoms, primarily affective distress, when blood drug levels fall, even after a single exposure (e.g., Bickel, Stitzer, Liebson, & Bigelow, 1988; Heischman, Stitzer, Bigelow, & Liebson, 1989; Schulteis et al., 1997). According to negative reinforcement models, such distress is the setting event for negative reinforcement following readministration of drugs. Substantial evidence also supports the prediction that withdrawal distress predicts continued or renewed drug use (Baker, Piper, et al., 2004; Piasecki, Jorenby, Smith, Fiore, & Baker, 2003; Sofuoglu, Dudish-Poulsen, Poling, Mooney, & Hatsukami, 2005). Withdrawal is not always a predictor of use, however, and failures to detect such relations (e.g., Patten & Martin, 1996) have been cited as evidence that negative reinforcement is not a primary motivation for addicted drug use (e.g., van Ree et al., 1999). In addition, self-reported drug motivation, in the form of cravings or urges, is not consistently higher during withdrawal than during or immediately after use (e.g., Fischman, Foltin, Nestadt, & Pearlson, 1990).

Alternative models of drug motivation have been proposed to account for these inconsistencies. For example, Robinson and Berridge (1993, 2003) have proposed that drug motivation is characterized by sensitization of drug-wanting even as drug-liking diminishes (i.e., even when drug use is no longer reinforcing). Their *incentive sensitization model* has generated much interest

and research (e.g., Bradberry & Rubino, 2006; Heinz et al., 2007) that supports the sensitization of incentive salience over repeated drug exposures (e.g., Mogg, Bradley, Field, & De Houwer, 2003; Taylor & Horger, 1999).

The mixed evidence regarding the role of withdrawal symptoms in motivating continued or renewed drug use seems to invalidate the central tenets of negative reinforcement models of addiction. Any contemporary negative reinforcement model of drug motivation must account for the following observations: (a) Withdrawal symptoms are only sometimes predictive of drug use; (b) self-reported urges to use drugs are sometimes greater when withdrawal symptoms should be negligible or absent; (c) drug use following abstinence or stress does not consistently reduce distress; and (d) relapse sometimes occurs in the context of positive affect or euthymia, rather than distress.

THE REFORMULATED NEGATIVE REINFORCEMENT MODEL OF DRUG MOTIVATION

In 2004, Baker et al. proposed a reformulated negative reinforcement model of drug motivation that attempts to account for the inconsistencies in past research and makes novel, testable predictions about the conditions in which withdrawal distress will predict urges to use and self-administration of drugs, two principal indicators of drug motivation (Baker, Piper, et al., 2004). The reformulation adds three stipulations to traditional concepts of negative reinforcement. First, the reformulated model specifies that the primary motive for drug use is avoidance or escape from affective (rather than somatic) components of withdrawal (e.g., Khantzian, 1997; see Figure 1.1). This prediction is based on the extensive research on the nature of withdrawal that suggests that affective distress is the common core in withdrawal across substances of abuse (e.g., Kosman & Unna, 1968; Mansky, 1978; Welsch et al., 1999). In addition, research suggests that affective symptoms have greater motivational significance than do somatic symptoms and that affective symptoms are particularly predictive of drug use (e.g., Kenford et al., 2002; McAuliffe, 1982). Basic research on emotion also highlights the priority afforded to affective information in information processing and the motivational correlates and consequences of affective states (Öhman, Dimberg, & Esteves, 1989; Sutton & Davidson, 1997). The explicit focus on affective withdrawal distress as the setting event for drug use in this model can account for past failures to reveal a link between undifferentiated withdrawal composites and drug use.

Second, the reformulated model proposes that much drug motivational processing occurs outside of awareness (Baker, Brandon, & Chassin, 2004; Baker, Piper, et al., 2004); that is, although addicted individuals are usually aware that they are using drugs (but see Tiffany, 1990, and chap. 4, this volume), they are typically unaware of the motivational and decision-making
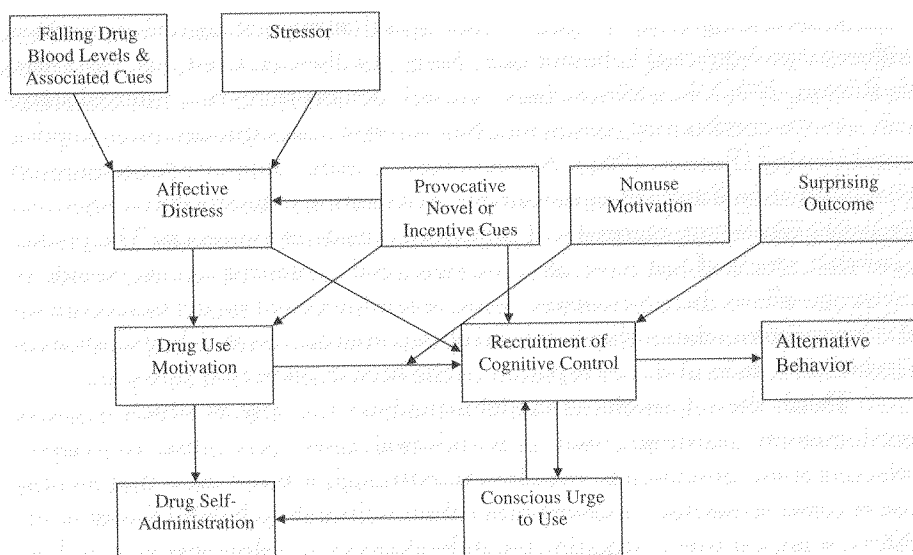
Falling Drug Blood Levels & Associated Cues

Stressor

Affective Distress

Provocative Novel or Incentive Cues

Nonuse Motivation

Surprising Outcome

Drug Use Motivation

Recruitment of Cognitive Control

Alternative Behavior

Drug Self-Administration

Conscious Urge to Use

Figure 1.1. Integrated negative reinforcement model of drug motivation and boundary conditions of urges. Because of negative reinforcement learning, both withdrawal and exogenous stressors increase drug motivation that sometimes leads to drug self-administration and recruitment of cognitive control under certain circumstances, including the presence of provocative cues, and motivation to engage in a response other than drug use, disappointing or surprising outcomes. Non–drug use motivation moderates the effect of motivation to use drugs on cognitive control recruitment, such that recruitment of cognitive control is likely when both drug use and non–drug use motivation are strong, but not when only one response option is activated. Activation of cognitive control is reciprocally linked to conscious awareness of urges to use drugs, such that conscious urges are more likely when anterior cognitive control systems are engaged and cognitive control activity is sustained by the addicted individual's desire to resolve urges.

processes that prompt use (see Figure 1.1). We posit that experiencing repeated cycles of withdrawal relieved by substance use leads to automatization of drug-seeking routines in the context of withdrawal. With greater experience, individuals learn to detect earlier and more subtle signs of withdrawal symptoms that begin to emerge as soon as blood drug levels begin to fall. With enough practice, symptom detection becomes an automatic, preconscious process of anticipation of distress to come, which then spurs avoidance behavior (i.e., drug ingestion) to prevent symptom exacerbation. Thus, a well-trained user may self-administer drugs before he or she even consciously detects the distress that implicitly motivated the behavior. In this sense, drug use has much in common with other well-practiced responses in that strong stimulus–response (S–R) mapping results in relatively automatic execution of the primed response (Cohen, Dunbar, & McClelland, 1990; Curtin et al., 2006; Palfai, 2006).

A substantial body of research indicates that implicit cognitive processes influence goal-directed behavior (e.g., Bargh, Gollwitzer, Lee-Chai, Bardollar, & Roman, 2001). In addition, basic research demonstrates that internal states can serve as conditioned stimuli for other internal states through interoceptive conditioning (Razran, 1961). As such, basic research supports the suggestion that motivational and self-monitoring (e.g., detection of interoceptive changes) processes can be automatized and performed outside of awareness. The prediction that much, if not most, drug motivational processing occurs outside of awareness allows the reformulated negative reinforcement model to account for the inconsistent relationship between self-reported distress and drug motivation (indexed by urges and use) reported in the human addiction literature.

Third, the reformulated model articulates the way in which negative reinforcement learning, based on withdrawal–relief, generalizes to aversive affective states unrelated to withdrawal. Although it is not clear that all drug use reverses stress due to causes other than falling drug levels (Kassel et al., 2003), it is clear that many addicted individuals expect drug ingestion to help them relax and reverse distress triggered by stressors (e.g., Brandon, Juliano, & Copeland, 1999; Galen & Henderson, 1999). Stress is a potent trigger for renewal of drug self-administration among humans and animals (Kassel et al., 2003; Piazza & Le Moal, 1998; Shaham, Erb, & Stewart, 2000). The reformulated negative reinforcement model asserts that this relation reflects generalization of the learning regarding withdrawal-induced distress to non-pharmacologic distress that yields similar interoceptive stimuli (see Figure 1.1); that is, we propose that addicted individuals use drugs to escape distress, whether the distress is due to drug deprivation or environmental stress, even if drugs do not effectively blunt the effects of non-withdrawal–related distress. This view is consistent with findings that suggest that, as addiction becomes more severe, the addicted individual's stress reactions become increasingly similar to his or her reactions to withdrawal and drug cues (Fox et al., 2005; Sinha, Fuse, Aubin, & O'Malley, 2000). Thus, even if addictive drugs do not reduce stress-related distress (Al'Absi, 2007; Conklin & Perkins, 2005; Kassel et al., 2003), generalization may occur across withdrawal- and stress-related distress (Gauvin, Carl, Gouldin, & Holloway, 1993). This postulate extends Wikler's (1948, 1965) concept of conditioned withdrawal to help explain relapses that occur long after pharmacological withdrawal has ended.

If interoceptive cues are critical to drug motivation, then the source of interoceptive distress cues (drug withdrawal vs. an external stressor) is less important than the interoceptive state per se. Any event that has the capacity to elicit interoceptive distress cues can trigger self-administration, for example, withdrawal, cues previously paired with drug or withdrawal, or stressors and associated stimuli. This extension of the negative reinforcement model might account for the well-documented effects of exposure to drug cues and priming doses of drug on subsequent drug self-administration (Stewart,

de Wit, & Eikelboom, 1984). Exposure to drug cues or to smaller-than-expected doses of drugs may elicit frustration or conditioned withdrawal. Such mild distress may prime drug motivation because, in the past, mild distress predicted even greater withdrawal distress (Hendricks, Ditre, Drobes, & Brandon, 2006).

These three modifications to traditional negative reinforcement models account for some of the evidence that challenged traditional negative reinforcement models. How, then, does the new model address the evidence supporting incentive-based or positive reinforcement models (see chap. 2, this volume)? Similar to other negative reinforcement models (Kenny et al., 2006; Solomon, 1977), the reformulated model does not hold that distress is the sole precipitant of urges or self-administration, although it does assert that escape or avoidance of distress is the dominant motive for use. As such, the reformulated model is congenial toward incentive-based models of addiction (Robinson & Berridge, 1993) and acknowledges the role that positive reinforcement plays in drug use, particularly during initiation of use or after a period of abstinence in which tolerance diminishes (Baker, Morse, & Sherman, 1987). Although incentive theorists have tended to assert that distress exerts little effect on drug motivation (e.g., Lyvers, 1998; Robinson & Berridge, 1993), data reveal that distress potently affects the incentive value of drug cues (e.g., Feltenstein & See, 2006). In fact, Robinson and Berridge (1993) acknowledged that background affective distress inflates the salience of incentive cues, beyond the sensitization that occurs directly because of drug effects. Negative reinforcement models make the same prediction but assert that negative reinforcement learning is at least partially responsible for this modulating effect (i.e., that incentives gain value in the presence of distress because past learning has indicated that they are particularly helpful in reducing distress in this context). Such learning could be attributed to either incentive learning, because the incentive value of cues is enhanced, or to negative reinforcement, because the enhancement of incentive value depends on drug self-administration in the context of withdrawal (Hellemans, Dickinson, & Everitt, 2006). In any case, it is clear that taking a drug in the presence of withdrawal distress increases the future likelihood and magnitude of drug self-administration in the presence of such distress.

In summary, the 2004 reformulation of negative reinforcement models strove to reconcile negative reinforcement accounts with extant data and alternative accounts of drug motivation. In so doing, the model suggested that automatic processes drive much of addictive behavior (Palfai, 2006; Tiffany, 1990). This account of drug motivation must then be reconciled with the extensive evidence that conscious processes importantly influence drug motivation. We have recently extended the model by specifying boundary conditions that influence awareness and effortful self-regulation of drug motivation. Next, we review the factors that we posit influence awareness of

drug motivation and then discuss the research and clinical implications of the integrated model.

DRUG MOTIVATION AWARENESS BOUNDARY CONDITIONS

The initial reformulated model of addiction said little about *urges*, the subjective experiences of wanting to use drugs, except to indicate that urges were more likely when negative affect was elevated and that the probability of awareness increased as negative affect increased. This simple account failed to reflect the important influence of context on urges. Evidence indicates that exposure to external cues associated with drugs elicits urges among addicted individuals (Carter & Tiffany, 1999) and the degree to which exposure does so predicts self-administration and relapse among those trying to curb drug use (e.g., Marissen et al., 2006). In addition, perceptions of drug availability also modulate the experience of urges, such that addicted individuals who know they will not have access to drugs (e.g., hospitalized smokers) experience fewer urges to smoke than do those who perceive opportunities to use drugs (e.g., Juliano & Brandon, 1998).

Any comprehensive motivational account of addiction must account for such contextual influences, and a negative reinforcement model must explain why contextual cues and distress may exert different effects on indexes of drug motivation from one occasion to another. In particular, a comprehensive model must account for why urges and drug self-administration are either poorly correlated with one another or are poorly related to withdrawal magnitude (e.g., Tiffany, 1990). Understanding this lack of coherence demands that knowledge about cognitive control and attentional processing be applied to an understanding of urges.

We propose that urges represent an awareness of underlying drug motivation that is driven, at least in part, by negative reinforcement learning. In this model of urges (Curtin et al., 2006), drug motivation is necessary but not sufficient for the experience of urges. This raises questions about the critical boundary conditions that prompt awareness of otherwise-latent motivational processes. To answer this question, we apply basic research on the cognitive control of behavior to the drug use context to generate hypotheses regarding the conditions and factors that make implicit drug motivational processing explicit (Curtin et al., 2006).

Cognitive Control of Behavior

Cognitive control has been defined as effortful, controlled activation and allocation of attention in order to select and process goal-relevant information that facilitates behavioral adaptation in tasks involving high difficulty,

novelty, decision uncertainty, or response conflict (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Miller & Cohen, 2001). Cognitive control is crucial to overcome well-learned, habitual responses that are not adaptive, goal relevant, or contextually appropriate. Such maladaptive responses often conflict with more appropriate responses that require support to compete successfully with this strong activation. Cognitive control provides this support by biasing processing in favor of weaker, adaptive responses in the service of the individual's current goals. For example, cognitive control allows individuals completing the classic color-naming Stroop (1935) task to inhibit the well-learned tendency to read words in order to succeed in the task at hand, which is naming the script color of the word.

Cognitive control processes are implemented in an anterior attention system that includes structures, such as the anterior cingulate cortex (ACC) and prefrontal cortex (PFC), that receive dopaminergic projections from the ventral tegmental area (Botvinick et al., 2001; Holroyd & Coles, 2002; Miller & Cohen, 2001). (These structures do not constitute the hardware of drug motivational processing, but the involvement of these structures in drug motivation suggests causal paths in such processing.) Cognitive control and the brain systems that govern it can be subdivided into at least two classes of processes. The first class, *action-monitoring processes*, evaluate the efficacy of current behavioral strategies in real time and titrate the level of (regulative) control to achieve optimal outcomes. The second type, *regulative control processes*, are recruited to implement top-down biasing of behavior when action-monitoring processes detect that the context demands increased control to support adaptive, goal-consistent behavior (MacDonald, Cohen, Stenger, & Carter, 2000).

Recent research on action monitoring has helped identify both its neural substrates and the factors that recruit cognitive control processes. An elegant synthesis of empirical research involving behavioral and functional imaging techniques with theory-driven computational models of response competition paradigms such as the Stroop (1935) color-naming task indicated that detection of response conflict by the ACC plays an important role in action monitoring (Botvinick et al., 2001). Other research that has used event-related brain potentials (in particular, *error-related negativity*) suggests that action-monitoring processes in the ACC are activated by task errors and negative evaluative feedback about task performance (e.g., Nieuwenhuis, Yeung, Holroyd, Schurger, & Cohen, 2004). Similarly, Holroyd and Coles (2002) documented that outcomes that are generally "worse than expected," including task errors and nondelivery of an expected reward, activate ACC, consistent with its role in action monitoring.

Once recruited, regulative control processes are responsible for both the representation and integration of information regarding context and goals in working memory and implementation of top-down attentional control. As

task-inappropriate responses become more potent, or reinforcement contingencies change, the contribution of regulative control to novel or weaker, but adaptive, responses increases (Botvinick et al., 2001; Yeung, Botvinick, & Cohen, 2004). Nonhuman primate lesion studies and human neuroimaging research strongly implicate the dorsolateral PFC in the working memory processes that are critical for the active maintenance and utilization of both goal and context representations to guide adaptive behavior (Goldman-Rakic, 1987; Miller & Cohen, 2001). The orbital frontal cortex integrates information about future consequences (e.g., S-R associations) and may be critical for adaptive behavior when reinforcement contingencies change (Bechara, Damasio, & Damasio, 2000).

The foregoing description indicates that cognitive control is crucial to overcome potent S-R mappings that are not adaptive in the current context. This cognitive control system is a general-purpose executive attention system that is recruited to guide goal-directed behavior across diverse contexts, eliciting stimuli, and S-R complexes. Cognitive control may also be recruited to regulate drug-seeking or self-administration behaviors that are strongly established through negative reinforcement. Indeed, for the dependent drug user pursuing drug abstinence, cognitive control becomes critical in overcoming routinized drug-seeking responses in favor of alternative, less practiced behaviors. Our model suggests that the conditions that recruit cognitive control are ones that also trigger urges among addicted individuals (see Figure 1.1); that is, the operational characteristics of systems affecting cognitive control serve as a basis for deducing factors that influence or produce urges to use drug. Consideration of the various situations and consequences associated with the recruitment of cognitive control provides an explanatory mechanism for many observations about drug use and craving (Curtin et al., 2006). Cue-reactivity research offers preliminary support for the prediction that self-reported urges to use drugs covary with activation of the neural substrates of cognitive control processes. In the cue-reactivity paradigm drug craving is elicited in dependent users by exposing them to various cues that typically co-occur with drug administration (e.g., drug paraphernalia). Neuroimaging research has demonstrated increased activation of key neural structures associated with the recruitment and implementation of cognitive control in this paradigm (see also Franken, Zijlstra, Booij, & van den Brink, 2006). In fact, recent reviews of this literature have concluded that the ACC and sectors of the PFC are the most reliably activated neural structures across cue-reactivity experiments (See, 2002; Wilson, Sayette, & Fiez, 2004). Moreover, several studies have documented that the degree of activation of these neural substrata of the cognitive control system covaries directly with drug craving self-report (e.g., Bonson et al., 2002; Brody et al., 2002) and mental work to resist drug craving (Brody et al., 2007). As such, research supports the relevance of cognitive control research to awareness of drug motivation in the form of cravings or urges to use.

Cognitive Control and Awareness of Drug Motivation

Our model of the boundary conditions for the recruitment of cognitive control that leads to awareness of urges to use or cravings for drugs is depicted in Figure 1.1. This model proposes that affective distress is a primary setting event for drug motivation and use and that additional factors influence the likelihood that the action monitoring and regulative cognitive control resources described earlier will be recruited and will trigger awareness of the drive to self-administer drugs. In particular, we propose that high levels of distress, provocative cues (e.g., drug cues of high incentive value), conflict between drug-use and alternative behavioral responses, and surprising outcomes following drug-use or non–drug use behaviors, are positively related to the occurrence of conscious urges to use addictive drugs. In an effort to avoid complexity, some features are not depicted in the model, such as exposure to appetitive drug cues that would also activate approach systems (Ito, Dalley, Robbins, & Everitt, 2002; see also chap. 2, this volume), and the relative weighting of drug use versus other response options, which would affect the likelihood of drug use and conflict occurrence. Our specific predictions are described next.

First, we predict that high levels of distress will lead directly to conscious urges to use drugs because both physical and emotional pain invoke cognitive control resources (Botvinick et al., 2001). Thus, we assert that distress can directly recruit cognitive control, independent of any prior association with drug use. Pain is a salient signal that corrective action is necessary, and the ACC is strongly recruited in response to manipulations that produce both physical pain (Sewards & Sewards, 2002) and psychological distress (Eisenberger, Lieberman, & Williams, 2003). Given that withdrawal is distressing, it is sensible that mounting levels of withdrawal distress will be detected by action-monitoring processes and recruit increased regulative control. Recent research has implicated the insula, which is involved in interoceptive and exteroceptive detection and processing of errors, emotional distress, and pain (e.g., Critchley, Wiens, Rothstein, Ohman, & Dolan, 2004; Seminowicz & Davis, 2007), in drug craving (Naqvi, Rudrauf, Damasio, & Bechara, 2007). The insula may provide a link between internal distress, including interoceptive signals of distress (Critchley et al., 2004), and activation of cognitive control processes.

Regulative control, once recruited, may result in drug use or abstinence, depending on the addicted individual's current goals. High levels of affective distress may simultaneously recruit and impede regulative control processes (see Tiffany, 1990) because very high levels of distress are likely to invoke stress responses and prompt execution of overlearned flight responses (e.g., avoidance of affect through drug use; Metcalfe & Mischel, 1999). Research supports these hypotheses. Among smokers, for example, mounting withdrawal distress does indeed predict urges (Hendricks et al., 2006) and relapse (Piasecki et al., 2003).

Whereas many studies have revealed reliable relations among withdrawal distress, urges, and drug self-administration, exceptions have also been found (Robinson & Berridge, 1993; Tiffany, 1990). These exceptions reflect the complex relations among these variables. Our model (see Figure 1.1) suggests that, at very low levels of distress, an individual may be guided primarily by automatic processes because the threshold of activation for unconscious drug motivational processing and automatic self-administration is lower than the threshold for cognitive control recruitment. As distress increases, an individual may become aware of the urge to alleviate distress (through drug use) and will consider either the best way to fulfill that urge or the best way to maintain abstinence. At very high levels of distress an individual is very likely to be aware of the affect and associated drug motivation, but regulative cognitive control mechanisms may be compromised so that behavior is likely to be driven by automatic, rather than effortful, processes. Also, the level of drug motivation may be sufficiently great so that regulative control processing supports drug use because the addicted individual consciously concludes that the goal of abstinence is less desirable than the goal of immediate distress relief. These complex distress effects highlight the complexity of relations with urges and self-administration that depend on consideration of other factors, such as weighting of drug use versus other goals (e.g., abstinence).

Second, cues associated with incentives of high value (e.g., cues with strong appetitive associations) also tend to engage attention and may recruit cognitive control resources, as indicated by both behavioral and brain electrophysiology measures (Peoples, 2002; Williams, Matthews, & MacLeod, 1996). Among addicted animals and humans, cues associated with their drug of choice have strong incentive values that dwarfs the value of alternative incentives (Robinson & Berridge, 1993, 2003). When very attractive incentives are available, cognitive control resources may be recruited to ensure that the opportunity for reinforcement is not missed (Peoples, 2002). It is important, however, to avoid the tendency to think of automaticity or cognitive control as dichotomous; instead, both phenomena show gradients of engagement (Cohen et al., 1990; Cohen, Servan-Schreiber, & McClelland, 1992). Cognitive neuroscience research also suggests that novel incentives are likely to recruit cognitive control resources (see Figure 1.1) and invoke evaluative and regulatory functions in a manner similar to highly valued incentives (Botvinick et al., 2001). Thus, novel stimuli may temporarily shift attentional focus from drug use.

Third, conflict between behavioral response dispositions activated by a set of cues increases the likelihood that drug motivation will enter awareness and demand ongoing processing. In Figure 1.1 we note this by indicating that motivation to engage in nonuse behavioral responses (non–drug use motivation) moderates the relationship between drug motivation and urges to use (recruitment of cognitive control). Response conflict has been shown

to increase recruitment of cognitive control. As noted earlier, the conflict between the responses of reading text (e.g., "blue") and naming script colors (e.g., "red") in the Stroop (1935) task is a classic example of response conflict. Extensive practice renders reading the dominant response to the presentation of written words. Cognitive control is required in the Stroop task because a person must resist the dominant word-reading response and substitute the less practiced response of color naming. Cognitive control facilitates this shift in response to contextual demands. Negative affect and drug cues are strongly mapped to associated drug-seeking and administration behaviors, much as Stroop color words are strongly mapped to word reading responses. Reinforcement mechanisms and repeated pairings of stimuli and drug-seeking responses across the drug user's career establish a strong mapping between interoceptive withdrawal distress and drug cue stimuli and drug use responses, such that the drug use response has become a "habit" driven by S-R associations (Everitt & Robbins, 2005).

When the drug user establishes a drug abstinence goal and reduces drug intake, cognitive control becomes critical for nondrug behaviors to compete successfully with drug use responses activated by distress. In particular, the early stages of quitting are characterized by juxtaposed significant withdrawal-related distress, which primes drug use responses, and motivation to sustain drug abstinence. The conflict between these competing motivations may recruit cognitive control and explain high levels of self-reported craving during early abstinence (e.g., Hendricks et al., 2006). Analogously, the gradual decline in urges with increased durations of abstinence may reflect both the decline of withdrawal distress as well as the increased mapping of nondrug response options.

Response conflict surrounding drug use should also occur among nonabstinent drug users and those not striving for abstinence. Some scholars argue that ambivalence about drug use is the basis of addictive behavior (Breiner, Stritzke, & Lang, 1999; Heather, 1998). Any temporary impediment to drug use should occasion conflict, and result in urges, when drug motivation is present. If drug motivation is low, such urges are likely to be transient and to occupy less mental work space than they would at high levels of motivation. In summary, response conflict is likely a daily experience among addicted individuals and is not confined to periods in which access to drugs is blocked or when an individual is trying to curb or cease drug use.

Fourth, we expect drug motivation to be experienced as cravings or urges when the outcome of response execution is disappointing or surprising (see Figure 1.1). Electrophysiological and functional imaging studies indicate that both explicit task errors and evaluative feedback about task performance strongly activate the ACC and that this activation is associated with recruitment of the PFC and the execution of corrective behavior (e.g., Gehring, Goss, Coles, Meyer, & Donchin, 1993; Luu, Tucker, Derryberry, Reed, &

Poulsen, 2003). We predict that this same action-monitoring system will recruit evaluative control when drug effects are either much better or much worse than expected (e.g., when a drink is less relaxing or provides less of a "buzz" than expected), but not when drug effects match expectations. For example, if the effects of the first drink of the night on mood are less potent than a drinker expects, this disappointment may be associated with an increase in the drinker's craving for alcohol. According to this model, the drug motivation that prompted ingestion of the first drink breaks into awareness following its disappointing impact and then spurs additional drinking. Similarly, urges may be caused by tolerance that blunts the direct effect of drug or by switching to a less satisfying form of drug delivery (Hughes, Keely, & Callas, 2005).

Evaluative control that is recruited by nondrug responses might also produce urges if such responses are made in the presence of cues with powerful drug use associations. For instance, we predict that coping responses (in lieu of drug use) that do not have the expected effects will increase drug craving. There is some evidence that non–drug use coping responses that are executed to avoid drug use may increase a person's craving and subsequent drug use (Shiffman, 1984). Our model would thus attribute increased awareness of drug motivation in this instance to monitoring of the disappointing outcomes of coping (e.g., inadequate reduction in negative affect).

As noted earlier, the factors that increase the likelihood that drug motivation will enter awareness in the form of urges to use are not necessarily the same factors that increase the likelihood of self-administration (Tiffany, 1990; see also chap. 4, this volume). For example, distress may cause an urge, but the relative mapping of drug and nondrug response options may determine whether use occurs. Multiple factors spur the recruitment of cognitive control that may resolve the response conflict in favor of either drug use or an alternative response. In the absence of motivation to engage in an incompatible response, however, drug use would proceed unimpeded without the need for cognitive control or associated awareness of the desire to use. An important point of the foregoing discussion is that conflict between use and nonuse response options does not precipitate urges; it may influence the severity or duration of an urge, but this conflict becomes significant in the context of cues that activate the drug use response (e.g., distress).

Figure 1.2 depicts the varied drug motivational outcomes that might arise from a high level of distress as a function of the modulating factors listed earlier. For instance, high levels of distress would be expected to result in strong urges, as depicted in Box A; however, such distress might not be translated into drug self-administration because strong contingencies for abstinence might result in a response weighting in favor of nondrug response options. Box B presents a situation in which weak urges are encountered because the drug use response option is so heavily weighted that little conflict occurs and drug use ensues quickly. Box C represents a situation in which
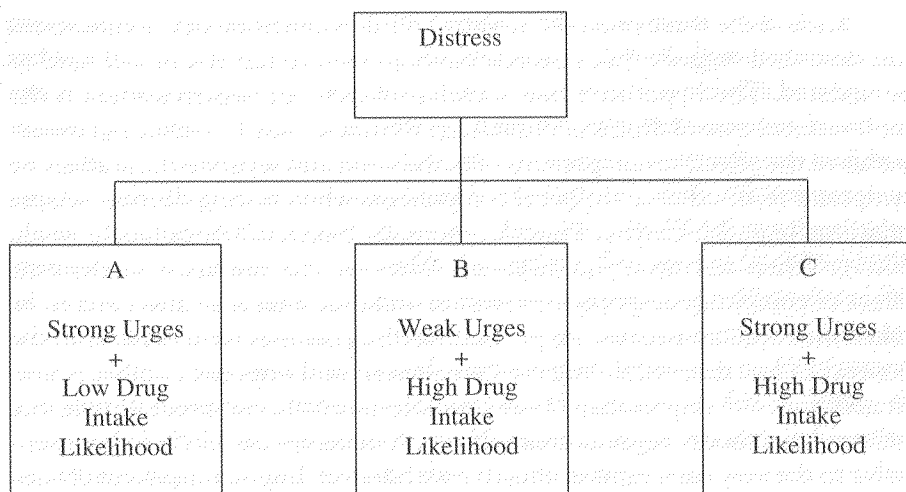
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                    ┌─────────────────┐
                    │    Distress     │
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│       A       │   │       B       │   │       C       │
│  Strong Urges │   │   Weak Urges  │   │  Strong Urges │
│       +       │   │       +       │   │       +       │
│   Low Drug    │   │   High Drug   │   │   High Drug   │
│    Intake     │   │    Intake     │   │    Intake     │
│  Likelihood   │   │  Likelihood   │   │  Likelihood   │
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Figure 1.2. Diverse theory-based outcomes of distress. One criticism of negative reinforcement models of drug motivation has been that distress is not consistently related to urge magnitude or drug use likelihood. This may occur because the relation of distress with urge and drug use is moderated by factors such as drug availability and level of response conflict. For instance, Box A reflects a pattern that occurs when high motivation to abstain causes great response conflict (along with distress) and low likelihood of drug use. The pattern depicted in Box B might occur because low reasons to abstain result in little response conflict and drug availability result in drug use. The pattern of Box C might occur because the presence of drug cues (along with distress) might recruit increased cognitive control resources and strong urges, even though drug use is imminent.

distress is present and a potent incentive cue activates anterior attentional control systems, which produces strong urges, but an absence of response conflict allows drug intake to occur unimpeded. This simple schematic reveals that a cognitive control information-processing model may be helpful in elucidating the sort of influences that can account for distinct covariation patterns among such variables as distress, urges, and drug use.

In summary, the conditions that we assert are most likely to predict awareness of drug motivation (i.e., urges) are high levels of distress, exposure to cues of great incentive value, response conflict, and detection of surprising response outcomes. We assert that the recruitment of cognitive control mediates the effects of these factors on urges. These predictions are grounded in recent findings regarding the neural substrates of cognitive control and represent a refinement of our negative reinforcement model of drug motivation. This refined model in turn allows us to make more specific predictions about the circumstances under which self-reported urges to use drugs will reliably index drug motivation and predict self-administration.

Each of the three proposed negative reinforcement model modifications just described suggests that research methods used to test the model need to be updated. The hypothesis that withdrawal-induced negative affect is the motivational core of drug addiction suggests that we need to refine our assessments of the affective components of withdrawal and separate these affective symptoms from other withdrawal components when testing distress–relapse relations (e.g., McCarthy, Piasecki, Fiore, & Baker, 2006; Sofuoglu et al., 2005). When testing withdrawal–use relations, the potential moderating effect of conflicting response motivation and drug cues may also need to be taken into account because we predict that drug use may be very likely in the context of low distress, if drug cues are present and response conflict is low. In addition, the importance of unconscious motivational processing in the reformulated model suggests that self-report measures are likely to be insensitive to the very early signs of affective withdrawal. Implicit measures of both affective processing and drug motivation are therefore essential in future tests of the model. Although such measures exist, their reliability and validity have not been established (e.g., De Houwer, 2006; Fiedler, Messner, & Bluemke, 2006; Schmukle, 2005). Furthermore, our model suggests that the validity of self-report urges may be moderated by the conditions that influence awareness of drug motivation. For example, individuals should be able to report drug motivation more accurately when distressed, in the presence of high-value incentives, when they are experiencing response conflict, or when they are disappointed with outcomes. As such, the validity of self-report assessments is likely to vary across contexts and time.

CLINICAL IMPLICATIONS OF THE REFORMULATED NEGATIVE REINFORCEMENT MODEL

The reformulated model and boundary conditions for awareness of drug motivation described earlier suggest several behavioral routes to facilitating change in addictive drug use. (We will ignore for now pharmacologic routes that reduce the negative affect or anhedonia produced by withdrawal [Piper et al., 2008] and therefore reduce the motivational press to use.) The first route to change focuses on altering directly the S-R mappings that sustain addictive drug use. The second route focuses on strengthening cognitive control. An optimal treatment strategy might involve both the first, bottom-up route, and the second, top-down route. With time and practice, drug abstinence in the presence of cues formerly associated with drug use should become the default, automatic response (Palfai, 2006).

The reformulated model suggests that mapping of drug use responses to interoceptive signals of activity in negative affect systems is the primary basis for continued drug use. Given this, Pavlovian extinction involving repeated

exposure to interoceptive cues of negative affect without drug use should weaken the distress–drug use mapping. Distress would still elicit cognitive control following extinction, but extinction would shift the balance of response mapping in favor of nondrug response options. Past interventions based on extinction have attempted to weaken the link between external cues and drug effects, with limited success (e.g., Conklin & Tiffany, 2002). Pilot research in opiate users suggests that extinction to internal cues may be more effective, at least for women (Pollack et al., 2002). In addition, operant conditioning could be used to train addicted individuals to execute drug-incompatible responses in the presence of distress cues. Contingency management programs alter the contingencies for drug use overall (so that abstaining yields positive reinforcers) and lead to significant decreases in drug use (Higgins, Roll, Wong, Tidey, & Dantona, 1999). Strong rewards for eschewing drugs would also lead to decreased drug urges to the extent that the rewards reduced response conflict by overwhelming the attractiveness of the drug use response. In either the case of extinction or operant conditioning of alternative responses, however, the key to success will be the individual's extensive practice of alternative responses across diverse internal and external contexts (Otto, Powers, & Fischman, 2005). Such repetition will be essential to compete with the overlearned, strongly mapped response of drug-seeking in various contexts.

The present model also suggests that it may be helpful to extensively rehearse nondrug responses to negative affect and urges to use before attempting to change drug use. Response conflict increases the likelihood that drug motivation will enter awareness and that prefrontal cognitive control resources will be recruited to resolve the conflict. As such, increasing response conflict by strengthening connections between drug use instigators and nondrug responses prior to a behavior change attempt may help people resolve urges without using drug. Massed pre-cessation execution of competing responses should have several effects. Whereas it might increase urges (because the alternative response options would become more balanced with drug use responses), the increased mapping of the nondrug response may make its execution more likely once cognitive control is engaged—that is, urges would be increased, but drug use would be less likely. Finally, pre-cessation execution might make the individual thoroughly familiar with the consequences of the nondrug response and thus make it less likely to yield disappointing effects that can increase urges. Seen in this light, the individual would be better off to practice extensively only a few nondrug responses versus a menu of diverse responses.

The danger that inappropriate expectations about nondrug responses might foster greater urges suggests that, instead of touting the benefits of alternative behaviors (coping responses) in treatment, perhaps clinicians should, paradoxically, promote more modest expectations of relief or reward regarding the outcomes of their coping efforts. Surpassing low expectations is associated with greater satisfaction with change than is failing to meet high expectations,

and satisfaction predicts maintenance of behavior change (Baldwin et al., 2006). These findings suggest that it may be helpful to temper rather than enhance clients' expectations regarding the outcomes of effortful coping, in particular once they have decided to try to change.

Even extensive training in alternative responses and changes in response contingencies are not likely to be sufficient to promote lasting change in addictive drug use. Effortful processing may also be helpful in preventing drug motivation and self-administration. For example, selecting environments that offer few opportunities to use drug and that have few associations with use may serve as an urge and use prevention strategy (see also chap. 11, this volume). Rather than relying on effortful cognitive control resources to help when one is already in trouble (i.e., when drug motivation has already been activated and drug opportunities are available), one can use cognitive control resources to minimize the risk that automatic drug use will occur (Palfai, 2006). In fact, evidence suggests that this strategy (i.e., avoiding drug use triggers) is effective in helping individuals achieve long-lasting abstinence (Fiore et al., 2000). However, the current conceptualization suggests particular reasons why this approach may be beneficial in addition to the usual notions that it reduces elicitation of drug-conditioned responses. One reason is that avoiding triggers does not rely on awareness of drug motivation. Another benefit is that reducing drug motivation and opportunities for use is likely to reduce demand for limited cognitive control resources. Research suggests that self-control failures are especially likely after completing earlier tasks that demand self-control (Muraven & Baumeister, 2000). This makes sense given the finite nature of cognitive control processes mediated by the ACC and PFC and their susceptibility to fatigue (Falkenstein, 2004), and therefore it makes sense to conserve resources by avoiding unnecessary demands on this system. Individuals may become worn out or fatigued from using cognitive control resources continuously as they relearn daily routines by constantly substituting effortful responses for automatic ones (Piasecki, Fiore, McCarthy, & Baker, 2002).

Any treatment strategy that relies on cognitive control must take into account variability in the recruitment and execution of controlled processing across individuals and situations. Research indicates that cognitive ability in areas such as memory and various dimensions of executive functioning moderate alcoholics' responses to treatment (Bates, Pawlak, Tonigan, & Buckman, 2006). According to our model, individual differences or states that mark impaired recruitment or implementation of cognitive control will be associated with increased probability of drug use when the individual is exposed to negative affect or drug cues (i.e., trait or state reductions in cognitive control activation are associated with increased drug use probability when pursuing drug abstinence; e.g., Naqvi et al., 2007). Recent research has demonstrated that individuals who show greater biases toward drug-related cues in modified Stroop tasks (i.e., who take longer to color-name drug-related vs. neutral words of

motivational relevance), presumably because of weaker cognitive control, have more difficulty in subsequent abstinence attempts (Cox, Hogan, Kristian, & Race, 2002; Waters et al., 2003). This interference may reflect multiple influences, including weaker cognitive control, but more research is needed to support this interpretation. In addition, it is important for research to examine the role of distress in modulating the effective exercise of cognitive control, inasmuch as there is strong evidence that it is precisely when individuals are distressed that they are most likely to relapse (e.g., Kassel et al., 2003).

Distress tolerance is another individual difference of note in addiction. Research on distress tolerance has provided data linking individual differences in cognitive control with drug use probability (Brown, Lejuez, Kahler, Strong, & Zvolensky, 2005). In distress tolerance studies, drug users are instructed to perform stressful behavioral or mental tasks (e.g., solving difficult anagrams). Drug users presumably experience conflict between adhering to instructions to persist at the task and motivation to terminate the aversive experience. Thus, duration of task persistence may be a proxy for successful application of top-down control. Consistent with this notion, decreased ability to persist on the aversive tasks is associated with decreased duration of abstinence among smokers (Brandon et al., 2003) and users of other substances (Daughters, Lejuez, Kahler, Strong, & Brown, 2005). Other interpretations are possible, but the phenomenon is also consistent with a cognitive control explanation.

In clinical settings, it may be important to identify people who are slow to recruit cognitive control or exercise control ineffectively. Treatments can be tailored for such individuals to emphasize bottom-up change strategies such as those listed earlier. Some recent research has shown promising outcomes in the training of enhanced executive function in various patient populations (e.g., computer assisted remediation; Elgamal, McKinnon, Ramakrishman, Joffe, & MacQueen, 2007; Kurtz, Seltzer, Shagan, Thime, & Wexler, 2007). In addition, it may be important to educate individuals about situations that diminish the effectiveness of cognitive control, such as intoxication (e.g., Curtin & Fairchild, 2003). Impairment in top-down attentional control process has been implicated in the general increase in behavior regulation problems observed among intoxicated individuals (e.g., aggression, impulsive risk taking; Steele & Josephs, 1990). Alcohol impairment of cognitive control may account for the increased risk for relapse to smoking when intoxicated (Krall, Garvey, & Garcia, 2002). Abstaining smokers who are in a bar or drinking context will frequently encounter smoking cues that activate strong motivation to smoke. If cognitive control processes are acutely compromised by alcohol intoxication, these smokers will not be successful in inhibiting smoking motivation and will fail to maintain abstinence. The current perspective yields the prediction that alcohol intake will increase drug use but not urges.

In summary, the reformulated model suggests that success in changing drug use may be enhanced by changing S-R mappings and associated expectancies

regarding the impact of nondrug reinforcers, particularly for interoceptive cues of distress, prior to attempts to permanently change behavior. In addition, the model highlights the relative unavailability of drug motivational processing for introspection and conscious control and the importance of developing awareness of drug motivation before it prompts strong drug urges or use. A treatment package based on this model of addiction would differ considerably from existing treatments, although some traditional treatment components, such as encouraging people to reduce exposure to drug triggers, especially those involving distress, would remain the same. In general, this model stresses the importance of preparing for a change attempt both behaviorally and cognitively and suggests that reliance on effortful coping and regulatory cognitive control mechanisms will not be helpful for people with relatively nonresponsive or ineffective cognitive control processes. Unfortunately, compromised cognitive control may be relatively common among populations of addicted individuals (Ersche, Clark, London, Robbins, & Sahakian, 2006; Verdejo-García & Pérez-García, 2007).

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