CHAPTER 16

Implicit and Explicit Drug Motivational Processes: A Model of Boundary Conditions

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Abstract: The model proposed in this paper is an attempt to suggest mechanisms and structures that are involved in both implicit and explicit processing of drug motivational information, and to propose when and how these mechanisms are recruited. To support this model, we first review research on negative and positive reinforcement mechanisms that establish the potent but often-implicit drug-use motivation in drug-dependent users. Next, we integrate basic cognitive neuroscience research on the cognitive control of behavior to understand how boundary conditions are imposed on these implicit motivational processes via the recruitment of attention (i.e., what constrains their occurrence and influence). Finally, model implications are proposed to guide theory and research on drug-use motivation and craving.

INTRODUCTION

The inveterate smoker may smoke cigarette after cigarette without being aware of deciding to smoke or without paying much attention to the act of smoking (Tiffany, 1990). Conversely, when making a quit attempt, the individual may agonize over whether or not to smoke and even go to elaborate lengths to secure a cigarette. Indeed, relapse cigarettes are often stolen (Brandon et al., 1990). Similarly, an alcohol-dependent individual may rather automatically consume a drink set in front of him or her, or go to elaborate lengths to distill or ferment alcohol to drink.

These observations are consistent with the notion that addictive behavior is supported by different types of information processing. Some of this information processing must be implicit: that is, occur fairly automatically without significant awareness. Other processing, however, must be explicit: that is, be planful and available to awareness. The model proposed in this paper is an attempt to suggest mechanisms and structures that are involved in both implicit and explicit processing of drug motivational information, and to propose when and how these mechanisms are recruited. In what follows, we first present a brief outline of our

proposed model. Following this, we review research on negative and positive reinforcement mechanisms that establish the potent but often implicit, drug-use motivation among dependent drug users. Next, we integrate basic cognitive neuroscience research on the cognitive control of behavior to understand how boundary conditions are imposed on these implicit motivational processes via the recruitment of attention (i.e., what constrains their occurrence and influence). Finally, model implications are proposed to guide theory and research on drug-use motivation and craving.

BRIEF OUTLINE OF MODEL TENETS

We propose the following 5 tenets about drug-use motivation, drug-craving, and actual drug use:

1. Drug-use motivation is established via both negative and positive reinforcement mechanisms.

2. Once established, drug-use motivational processes often operate implicitly. In other words, the activation of drug-seeking or administration behaviors can occur automatically without the need for attention or extensive conscious awareness. The drug user may not necessarily be aware of the motivation to use drugs, the cues that elicited the motivation, or even the drug-administration behavior itself.

3. Drug-use motivational processes will become explicit (i.e., the person will be aware of the urge to use drugs) in situations where cognitive control attentional resources are recruited. We will reserve the term "drug-craving" to describe this conscious awareness of an urge to use drugs.

4. Basic research elucidates setting events for the recruitment of cognitive control. These include response conflict (i.e., concurrent activation of competing behavior responses), unfavorable outcomes (e.g.,

performance errors, negative feedback, pain, or other conscious distress), unexpected reward or punishment, and novel situations in which stimulus-response associations have not been previously established.

5. Cognitive control can be recruited to either support or inhibit drug use. When pursuing either drug abstinence or restriction of drug use, however, cognitive control is critical to overcome drug-use motivation and bias behavior toward nondrug-use behaviors. Therefore, explication of the factors that affect the cognitive control of drug-use motivation is clinically important.

"IMPLICIT" DRUG MOTIVATION

Negative Reinforcement

Evidence suggests that physical dependence, as inferred from the capacity to experience withdrawal symptoms, can develop quite early in the course of addictive drug use (Heischman et al., 1989). Moreover, it is clear that withdrawal is aversive, with negative affect being a core feature common to the withdrawal syndromes of all addictive drugs (Kelsey & Arnold, 1994; Malin, 2001). An extensive body of research shows that withdrawal is a powerful instigator of urges and self-administration (see Baker et al., 2004). In particular, negative affect is the element of withdrawal that appears most highly associated with later relapse (Kenford et al., 2002; Piasecki et al., 2000).

Baker et al. (2004) proposed that, over repeated drug-use episodes, addicted organisms learn that discontinuation of drug use (or a mere drop in drug blood levels [Mello & Mendelson, 1970]) leads to escalating withdrawal with associated affective distress, and that resumption of drug intake dramatically ameliorates these aversive affective symptoms. This leads to withdrawal-elicited affective distress becoming a key setting event for drug self-administration (Baker et al., 1987; Baker

et al., 2004). Moreover, drug responding may generalize across similar internal states elicited by nondrug negative affect eliciting stimuli (e.g., stressful events; Gauvin, et al., 1993; Gauvin et al., 1989).

There is copious evidence that unconscious processing of affect has the capacity to affect not only attitudes, but also behavior (e.g., Murphy & Zajonc, 1993; Öhman & Mineka, 2001). We argue that internal states or cues associated with negative affect can be detected automatically and without awareness, are afforded processing priority, and can trigger drug-use motivation implicitly. Of particular relevance, there is suggestive evidence that withdrawal and negative affect can implicitly activate processing of drug information. For instance, there is evidence that for regular smokers, abstinence enhances the salience of smoking cues (Gross et al., 1993; Sayette & Hufford, 1994; Waters & Feyerabend, 2000). Further, using a first-associates method, McKee et al. (2003) showed that negative mood induction via music led smokers to generate negative reinforcement expectancies regarding smoking (also see Birch et al., Chapter 18). In general, research suggests that manipulations of both withdrawal status and affect result in the greatest interference by drug cues. There is also evidence that implicit or automatized processing has motivational significance (e.g., Stacy, 1995, 1997). For instance, Waters et al. (2003) found that the behavioral interference produced by smoking cues, as assessed via a Stroop task, predicted early relapse among smokers trying to quit smoking.

Research performed by Siegel and his colleagues shows that the initial manifestations of a mounting interoceptive response can effectively signal the later elements of that same reaction (Sokowloska et al., 2002). This research suggests that interoceptive cues have especially great associative strength relative to exteroceptive signals; overshadowing them as effective conditioned stimuli (CS) for

interoceptive reinforcers. As such, inchoate or fledgling interoceptive signs of withdrawal may serve as effective discriminative stimuli for the addicted organism's renewed self-administration of addictive drugs. This could account for drug use in the absence of marked or notable distress.

We propose that, over the course of addiction, the organism learns that initial elements of the withdrawal syndrome—or cues that typically signal incipient withdrawal—predict escalating distress. Such signals serve as potent stimuli that elicit drug self-administration. Over countless drug-use episodes, this information processing routine is proceduralized (Tiffany, 1990), so that the organism may perform this with little or no awareness, or manifestation, of the distress that served as a setting event for self-administration. In keeping with current theory regarding overlearned response patterns, we adopt the assumption from connectionist models that nodes representing repeatedly executed and reinforced responses develop low thresholds for future activation (Yeung et al., 2004). Thus, drug self-administration is likely to recur in the context of stimulus conditions (i.e., negative affect, distress) that previously signaled substantial drug reward and that frequently preceded previous self-administration.

Avoidance/withdrawal models of addiction motivation hold that addicted organisms show especially high levels of motivation for drug when suffering from withdrawal-induced distress. Some question, however, whether the mechanism of such an increase in motivation can be attributed to avoidance/withdrawal motivation (Hutcheson et al., 2001; Robinson & Berridge, 1993). We emphasize the role of avoidance/withdrawal motivation for several reasons (Baker et al., 2004). In classic motivational models, approach and avoidance motivation are distinguished on the basis of the instigating stimulus (Elliot & Thrash, 2002). We contend that many instances of drug

self-administration, especially after periods of deprivation, are occasioned by the detection of distress, or detection of cues signaling distress. Mesoaccumbens dopamine activity may mediate the salience of drug cues (Robinson & Berridge, 1993), but we believe the motivational instigator is distress. In addition, it is important to distinguish between conditions of origin versus conditions of well practiced execution, when evaluating the role of avoidance/withdrawal in addiction motivation. Thus, we believe that early in the development of addiction, drug acquires stronger incentive properties than it otherwise would because of negative reinforcement: that is, it alleviates withdrawal distress (Baker et al., 2004).

Positive Reinforcement

Considerable research shows that drugs have strong reinforcing value even in the absence of physical dependence. For instance, organisms can acquire conditioned place preferences for environments paired with initial doses of psychomotor stimulants. Also, addicted individuals report strong desires to take drugs even when experiencing positive affect (Zinser et al., 1992), suggesting significant drug-motivational processing in the absence of even mild or incipient withdrawal. Thus, not all drug motivation is spurred by withdrawal or distress.

There are reasons to question the importance of positive reinforcement as a motive for drug use (Robinson & Berridge, 1993). For instance, due to tolerance, heavy drug users may experience pleasure or reward infrequently. Although tolerance to appetitive drug effects does occur, however, it is possible that positive reinforcement remains a formative and influential factor. Addictive agents do yield strong appetitive effects even in heavy users, effects that are described by users as a "high," "rush," or "elation" (Seecof & Tennant, 1986). It is true that

these effects do not occur routinely. Evidence suggests, however, that addictive agents are especially likely to produce strong stimulus-response (S-R) connections that render the organism relatively immune to extinction, nonreinforcement, or deflation of the reinforcer (Miles et al., 2003). Moreover, one must recognize that reinforcers do not occur in isolation. It is important to ask what other reinforcers available to an addicted individual match or exceed addictive drugs in terms of intensity, availability/controllability, and rapid onset of appetitive effects (Vuchinich & Tucker, 1996).

We assert that approach motivation may be directly engaged (without prior activation of withdrawal/negative affect) via cues associated with rewarding drug effects. We assume (Baker et al., 1987) that the cues that are most effective in this regard are ones that have been associated with direct drug effects. For instance, positive affective states, produced either pharmacologically or nonpharmacologically, might prime further drug self-administration since these may serve as effective reminder cues of prior appetitive drug effects such as elation. This supposition is consistent with research showing effective reinstatement of drug self-administration by small "priming" doses of drug (Stewart et al., 1984; Stewart & Wise, 1992). It is also consistent with the observation that urges to use drug are often correlated with positive affect when drug users are using ad libitum (Zinser et al., 1992).

It is important to note that affect need not be engaged in order for self-administration to occur. For instance, drug self-administration may be elicited by cues previously contingent with self-administration, cues that do not by themselves evoke strong affective reaction. To the extent that the cues strongly evoke approach systems, however, it is likely that affective change will be observed. This is because cues may associatively elicit drug agonist effects (e.g., Kenny et al., 2003; Stewart

et al., 1984), and the approach system comprises "hardwired" affective response components such as heightened arousal.

Bottom-Up Motivational Processes

There is considerable evidence that processes necessary and sufficient for drug motivation are subcortical, and that such "bottom-up" processes can serve to spur drug pursuit via implicit processes. Thus, we believe that the signals of withdrawal, or the incentive value of drug cues, reflect the operations of subcortical systems and activate motivational processes that *may* remain implicit in the absence of environmental obstacles to self-administration.

There is ample evidence across a variety of agents that withdrawal is mediated by subcortical structures. For instance, the structures that appear to mediate opiate withdrawal responses include the periaqueductal grey (Wise, 1988), the amygdala and extended amygdala, (Harris & Gewirtz, 2004; Reti & Baraban, 2003), and the locus coeruleus (e.g., Nestler & Aghajanian, 1997). In addition, other researchers (Frenois, et al., 2002) used in situ hybridization to characterize c-fos mRNA expression in dependent rats in which opiate withdrawal was precipitated by different doses of naloxone. These researchers revealed a set of structures that responded to a low dose of naloxone (e.g., extended amygdala, lateral septal nucleus, basolateral amygdala, and field CA1 of the hippocampus) and another set of structures that responded to a higher dose of naloxone (motor striatal areas, dopaminergic and noradrenergic nuclei, hypothalamic nuclei, and periaqueductal grey). The authors speculate the former structures may mediate the motivational influence of the withdrawal syndrome, while the latter structures mediate the somatic elements of withdrawal. Finally, research suggests the involvement of brain stem mechanisms in opiate withdrawal: For

example, the classic signs of opiate withdrawal can be obtained in decerebrate cats (De Andres et al., 2004).

The rewarding and incentive effects of psychomotor stimulants also appear to be mediated subcortically. Brain regions such as the nucleus accumbens and ventral tegmentum, once thought to mediate reward, may be more intimately involved in marking incentive value (Berridge & Robinson, 1998). Imaging data show correlations between subjective pleasure and activity in regions such as the bilateral ventral tegmentum, the right cingulate gyrus, the insula, bilateral thalamus, bilateral striatum, and the bilateral pontine brainstem (Holstege et al., 2003). Indeed, research also implicates the cerebellum in intense pleasurable reactions to pharmacologic and nonpharmacologic stimuli (Hostege et al., 2003; Sell et al., 1999). Research with drug and nondrug reinforcers suggests that the central nucleus of the amygdala and the basolateral amygdala are necessary for either the acquisition or expression of appetitively consequated instrumental behaviors (Cardinal et al., 2002). Finally, Koob and his colleagues suggest that the nucleus accumbens may be critical to nonassociative cocaine reward, but that associative reward effects may involve the basolateral amygdala (Koob & Le Moal, 2001; See et al., 2001; Whitelaw et al., 1996).

In sum, a great deal of evidence supports the assertion that drug reinforcement and incentive processes are mediated by activity in subcortical regions. We believe that in the inveterate user, such processing may remain implicit in the absence of obstacles or countervailing influences.

Flow of Information Processing

We propose that internal and external cues may activate incentive systems either by activating approach or withdrawal systems. These systems provide cues that signal the

availability and potential magnitude of reinforcement, and activate attentional-incentive mechanisms that mediate the organism's pursuit of drug (Berridge & Robinson, 1998; Miles et al., 2003; Robinson & Berridge, 1993). Due to the extensive reinforcement history of addicted organisms, it is likely that drug cues can also directly activate incentive systems, but indicants of drug motivation will be weaker than when approach or withdrawal systems are engaged. Strong activation of drug motivation requires significant activation of either the approach or withdrawal system.

It is likely that approach and withdrawal systems cannot be simultaneously highly activated (Baker et al., 1987). This supposition is consistent with the observation that amygdala activity is suppressed during intense pleasure produced by either heroin, ejaculation, or viewing pictures of loved ones (Bartels & Zeki, 2000; Holstege et al., 2003). It is possible, however, that incentive mechanisms may first be activated via the withdrawal motivational system, and the approach system then activates approach motivational processing.

To review: Addictive drug-use results in the development of physical dependence, manifested as the tendency to display withdrawal signs contingent upon falling levels of drug in the body. In addition, addictive agents produce potent rewarding effects, even in inveterate users. Although the brain loci of these effects cannot be localized to discrete brain regions, there is substantial evidence that withdrawal and reward processes depend upon subcortical, meso- and meta-telencephalic structures. It is certainly the case that learning about strategies to acquire and use drug may involve much more widely distributed brain systems. Withdrawal, drug reward, and incentive effects, the central determinants of addictive drug motivation, however, reflect necessary and sufficient involvement of bottom-up neuropharmacologic mechanisms. Finally,

prior positive and negative reinforcement do affect the incentive value associated with drug and withdrawal cues (e.g., Berridge & Robinson, 1998; Hutcheson et al., 2001) and the activation of motivational processes and their impact on incentive systems typically unfolds implicitly in the absence of obstacles.

COGNITIVE CONTROL, DRUG USE, AND CRAVING

The preceding sections reviewed and integrated evidence about the positive and negative reinforcement mechanisms underlying the establishment of well learned drug-seeking and administration behaviors. It is difficult, however, to understand the role and contribution of these often-implicit drug-motivational processes without understanding their boundary conditions; that is, what constrains their occurrence and influence. Therefore, we now review theory and empirical evidence from cognitive neuroscience research on the factors and mechanisms responsible for the elicitation of cognitive control processes as they constrain implicit information processing, with reference to their potential influence on drug use.

Cognitive control has been defined as effortful, controlled activation and allocation of attention to select and process goal-relevant information to behave adaptively in tasks involving high difficulty, novelty, decision uncertainty, or response conflict (Botvinick et al., 2001; Miller & Cohen, 2001). Cognitive control resources are also critical to modify behavior after unfavorable outcomes such as response errors, or unexpected outcomes including unpredicted reward or punishment (Holroyd & Coles, 2002; Ridderinkhof et al., 2004). We focus first on research that clarifies the contribution of cognitive control processes to adaptive behavior during *response conflict*

because of its relevance to the conflict that dependent drug users experience when attempting to refrain from drug use. We will return to other functions of cognitive control, however, in the concluding "Model Implications" section.

Cognitive control is crucial to overcome well learned, habitual, or prepotent responses that are not adaptive, goal-relevant, or contextually appropriate. These prepotent responses often conflict with alternative weaker responses that are more adaptive but require additional support to compete successfully with this strong activation. Cognitive control provides this support by biasing processing in favor of the weaker, adaptive responses in the service of the individual's current goals. This cognitive control system is a general-purpose executive attention system that is recruited to guide adaptive behavior across diverse contexts, eliciting stimuli, and S-R complexes, often with no connection to drug use. It seems clear, however, that cognitive control may be recruited to regulate drug-seeking or -administration behaviors that have been well learned through repeated positive or negative reinforcement.

The Stroop task (see MacCleod, 1991) provides an experimental analogue to investigate cognitive control processes during response conflict. In this task, participants are presented with color words in varying ink colors. Participants are instructed to either read the word or name the ink color and trials can be *congruent* (ink color and word meaning match), *incongruent* (ink color and word meaning conflict), or *neutral* (one attribute does not contain color information). The robust "Stroop interference" effect refers to the relative increase in response time and error rate observed on incongruent trials when participants are instructed to name the ink color. Theory and experimental evidence suggest that this interference results from response conflict between the task-appropriate ink color-name response and the incorrect

but strongly activated word-reading response (Cohen et al., 1990; MacCleod, 1991).

Basic cognitive neuroscience research with Stroop and similar attentionally demanding paradigms (e.g., flanker task, n-back) indicate that cognitive control is implemented in an anterior attention system that includes structures such as 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). Furthermore, it appears that cognitive control and the brain systems that govern it can be subdivided into at least two separate components referred to as *evaluative* and *regulative* control (Carter et al., 2000; MacDonald et al., 2000).

The evaluative component provides an important action-monitoring function and serves to recruit additional attention when necessary to support adequate task performance or, more generally, adaptive goal-directed, behavior. ACC monitoring for *response conflict* is believed to provide one mechanism through which the evaluative component can detect the need to recruit additional attention (Botvinick et al., 2001). For example, in computational models of the Stroop task (e.g., Cohen et al., 1990), correct color-naming response on incongruent trials requires biasing input from the cognitive control system to successfully compete with the word-reading response. The evaluative control component detects this need for attention by observing the strong activation of conflicting responses units (i.e., saying "red" vs. "green"), which subsequently recruits the regulative control component to positively bias the goal-relevant, color-naming response. Strong activation of ACC on incongruent color-naming trials has been empirically verified (e.g., Carter et al., 2000; Pardo et al., 1990). In addition to response conflict, evidence suggests that ACC also responds to other indicants that additional

attention is necessary: viz. unfavorable outcomes, error feedback, and unexpected reward or punishment (Holroyd & Coles, 2002; Ridderinkhof et al., 2004; see "Model Implications" section).

Once recruited, the regulative control component is responsible for both the representation and integration of information regarding context and goals, and the actual implementation of top-down attentional control. Clearly, as task-inappropriate responses become more potent or reinforcement contingencies change, the importance of regulative control for guiding novel or weaker, but adaptive, responses increases. (Botvinick et al., 2001; Yeung et al., 2004). These regulative control functions have been found to be closely associated with activation in sectors of the prefrontal cortex. Nonhuman primate lesion studies and human neuroimaging research strongly implicate dorsolateral prefrontal cortex (DLPFC) 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; Jonides et al., 1997; Miller & Cohen, 2001). Orbital frontal cortex (OFC) integrates information about future consequences (e.g., stimulus-reinforcement associations) and may be particularly critical for adaptive behavior when reinforcement contingencies in the environment change (Bechara et al., 2000; Rogers et al., 1999).

Cognitive Control of Drug-Use Motivation

The foregoing description indicates that cognitive control is crucial to overcome potent S-R mappings that are not adaptive in the current context. For the dependent drug user who is pursuing a drug-abstinence goal, cognitive control becomes critical to overcome strong implicit drug-use motivation elicited by negative affect or drug cues in favor of alternative but weaker nondrug-use behaviors in these contexts. The Stroop task provides a useful conceptual analogue to understand the interaction of implicit drug-use motivation with cognitive control mechanisms in the dependent user. 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. Operation of positive and negative reinforcement mechanisms and repetition across the drug user's career established this strong mapping much as extensive practice has strongly established word reading. Cognitive control allows the weaker color-naming response to effectively compete against the otherwise more potent word-reading response when color-naming has been established as the task-goal. Similarly, when the drug user establishes a drug-abstinence goal, cognitive control becomes critical for nondrug behaviors to successful compete with drug use that is strongly activated by drug cues. Finally, when color-naming, the research participant is often explicitly aware of both the effort (i.e., use of cognitive control resources) to inhibit word-reading, as well as the inclination to read (the person notes that she or he "wants" to read—a feeling that is not noted when reading occurs automatically). Similarly, the drug user will be explicitly aware of the formerly implicit drug-use motivation as cognitive control is used to support alternative behaviors, resulting in the conscious experience of drug-craving.

Cognitive control processes allow weaker responses to compete effectively against well learned and more potently activated behaviors during response conflict. Cognitive control, however, is also recruited in other situations. 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. Moreover,

consideration of the tenets of this model also results in some novel and not entirely intuitive predictions.

MODEL IMPLICATIONS

1. *Self-report of drug-craving will covary with the recruitment of the cognitive control system and its neural substrates.* Research using neuroimaging techniques to examine the neural substrates of drug-craving in the cue-reactivity paradigm offers preliminary support for this model prediction. In this paradigm, drug-craving is elicited in drug-dependent users by exposing them to various cues that typically co-occur with drug administration (e.g., drug paraphernalia, photographs or video of drug administration). Neuroimaging research has demonstrated increased activation of key neural structures associated with the recruitment and implementation of cognitive control in this paradigm (also see Chapter 13, Franken et al.). In fact, recent reviews of this literature have concluded that ACC and sectors of prefrontal cortex (primarily DLPFC and OFC) are the most reliably activated neural structures across experiments (See, 2002; Wilson et al., 2004). Moreover, several studies have documented that the degree of activation of these neural substrata of the cognitive control system covaries directly with craving self-report (e.g., Bonson et al., 2002; Brody et al., 2002; Grant et al. 1996).

In other research, a modified version of the Stroop task was used to examine implicit, drug-cue-related information processing and the top-down attentional control of this processing (see Birch et al., Chapter 18, for further review of this literature). In this "drug-cue" Stroop task, drug-use-related words are substituted for the color words and presentation of these drug cues activates drug-use motivational processes that conflict with performance of the color-naming task. Analogous to the interference observed on incongruent trials in the traditional Stroop task, drug-cue interference (i.e., relative increased color-naming response time to drug cues) is used to index the conflict caused by implicit drug-related responses, and indirectly, the activation of the cognitive control system that is recruited to resolve this conflict and successfully color-name.

Research with the drug-cue Stroop task has generally supported primary assertions from our model. The drug-cue interference resulting from the predicted response conflict between implicitly activated drug motivation versus task-relevant color-naming has been verified for individuals who are dependent on alcohol (e.g., Johnsen et al., 1994; Stormark et al., 2000), cigarettes (Munafo et al., 2003; Zack et al., 2001), cocaine (Franken, Kroon, Wiers, et al., 2000), and heroin (Franken, Kroon, & Hendriks, 2000). Moreover, manipulation of acute nicotine deprivation increases this drug-cue interference (Gross et al., 1993; Waters & Feyerabend, 2000; Zack et al., 2001). Similarly, increased severity of subjective withdrawal distress during deprivation covaries positively with this interference (Zack et al., 2001) and treatments that alleviate withdrawal symptoms reduce this response conflict (i.e., nicotine patch in smokers [Waters et al., 2003]). Finally, if the cognitive control system is recruited to resolve this response conflict in Stroop, our model predicts that drug-cue interference should covary with self-reported craving. Recent research has confirmed this predicted correlation among users dependent on cocaine (Franken, Kroon, & Hendriks, 2000) and heroin (Franken, Kroon, Wiers, et al., 2000).

2. Response conflict *surrounding drug use will recruit cognitive control and precipitate drug-craving*. Our model predicts that

response conflict surrounding drug use will be one potential indicant that spurs recruitment of the cognitive control system, with resultant drug-craving. In the drug-dependent user, this response conflict will frequently occur when strong bottom-up drug motivational processes elicited by exposure to drug cues or drug-deprivation conflict with a drug-abstinence goal. In particular, the early stages of quitting are often characterized by both significant withdrawal-related distress, which strongly primes drug-use responses, and strong motivation to sustain drug abstinence. The arguably potent conflict between these competing motivations may strongly recruit cognitive control and explain the high levels of self-reported craving during early abstinence (McCarthy et al., in press).

Response conflict surrounding drug use may be observed in nonabstinent drug users as well. In fact, many theorists have argued that conflict or ambivalence surrounding drug use should be the basis of the definition of addictive behavior (Breiner et al., 1999; Heather, 1998). This conflict is clearly reflected in the diagnostic criteria for substance dependence (e.g., persistent desire for the substance despite efforts to cut down or control use).

Unfortunately, explicit, well controlled manipulations of response conflict in research on drug-craving have not yet been conducted. Instead, only weaker, post hoc support is available. For example, a recent review of neuroimaging research concluded that activation of DLPFC and OFC in response to drug cues was moderated by treatment status (Wilson et al., 2004). Thus, only those dependent subjects who presumably intended to use drugs following the experiment (i.e., were not in treatment) showed such activation. Similarly, recent data reveal that drug availability moderates the self-report of craving. This may occur because information that drug is not available reduces response conflict by shutting down implicit drug motivation (Wertz &

Sayette, 2001b). Preliminary evidence that drug unavailability reduces response conflict is available (Wertz & Sayette, 2001a), but stronger evidence would involve direct manipulation of response conflict with resultant effects on self-report of craving, regional brain activity, and behavioral indices of cognitive control activation.

In the presence of strong motives to abstain, increasing the strength of bottom-up activation of drug-use motivation would be expected to produce strong response conflict and greater requirement for cognitive control to support abstinence behaviors. As indicated above, drug cues appear to produce response conflict when color-naming in the Stroop task and the magnitude of this conflict covaries with drug-craving (Franken, Kroon, & Hendriks, 2000; Franken, Kroon, Wiers, et al., 2000). In addition, factors that may mark the strength of the implicitly activated drug-use S-R complex (e.g., measures of dependence, frequency of drug use that may mark opportunity for implicit learning) do covary with the magnitude of response conflict produced by drug cues in Stroop (e.g., latency to first cigarette in the morning [Waters & Feyerabend, 2000]; level of cigarette consumption [Zack et al., 2001]; frequency of alcohol use [Cox et al., 2003]).

3. Novel *or* unexpected outcomes *may recruit cognitive control and precipitate drug-craving.* If craving is caused largely by conflict, why is it that addicts sometimes report craving immediately after drug use (e.g., Jaffe, et al., 1989; Zinser et al., 1992)? In addition to responding to response conflict, cognitive control is involved in the acquisition of new behaviors in novel or difficult tasks (Botvinick et al., 2001; Holroyd & Coles, 2002). In particular, anterior cingulate cortex responds to mesencephalic dopaminegric activity involved in reinforcement learning when outcomes are better (unpredicted reward) or worse (absence of predicted

reward) than expected (Holroyd & Coles, 2002; Holroyd et al., 2004; Schultz, 1997). Thus, drug effects that are stronger or weaker than anticipated (e.g., because of tolerance), or unexpected/unusual, may recruit cognitive control and perhaps result in drug-craving.

4. Unfavorable outcomes *such as unsuccessful coping strategies and withdrawal distress will recruit cognitive control and precipitate drug-craving.* Considerable research suggests that the evaluative component of cognitive control serves a critical action monitoring function and is activated in response to indicants that current behavior is not adaptive. For example, electrophysiological and functional imaging studies indicate that both explicit task errors and evaluative feedback about task performance strongly activate anterior cingulate cortex and that this activation is associated with recruitment of prefrontal cortex and the execution of corrective behavior on the current or subsequent task trials (Gehring et al., 1993; Luu et al., 2003). Similarly, pain is often a salient indicant that corrective action is necessary and ACC is strongly recruited in response to manipulations that produce both physical pain (Sewards & Sewards, 2002) and psychological "pain" or distress (Eisenberger et al., 2003).

These observations may have relevance to the occurrence of drug-craving. For instance, if an individual executes a coping response (in lieu of drug use) according to our model one should expect to see *increased* drug-craving if the coping response did not "work." There is evidence, in fact, that nondrug-coping responses that are executed to avoid drug use may increase a person's craving and subsequent drug use (Shiffman, 1984). Our model would attribute increased craving in this instance to monitoring of the disappointing outcomes of coping (e.g., inadequate reduction in negative affect). One important implication is that a nondrug-coping response

that does not produce desired or expected effects may be worse than not executing a coping response. In addition, if distressing events such as pain and stressors have the capacity to engage cognitive control directly, this may account, in part, for the strong relations between stressors, thoughts about drug, and desire to use drug (Kassel et al., 2003). (In a sense, the need to exercise cognitive control or problem-solve elicits thoughts about drug.)

5. *Compromised or deficient cognitive control resources will result in a lack of craving and an inability of cognitive control to inhibit drug self-administration.* If the dependent drug user's goal is to inhibit drug use and engage in other behaviors, our model predicts that individual differences and other factors that mark impaired recruitment or implementation of cognitive control will be associated with increased probability of drug use when 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). In fact, several varied literatures provide preliminary support for this prediction. In the drug-cue Stroop paradigm, the drug user's task is to color-name. Thus, regardless of their current drug-use status (e.g., treatment seeking, drug-abstinent, actively using drug), to color-name successfully they must inhibit competition from implicitly activated drug motivation. Recent research has demonstrated that individuals that exhibit decreased ability to behave adaptively in this task, presumably because of inferior cognitive control, have more difficulty in subsequent abstinence attempts. Specifically, increased drug-cue interference prospectively predicted decreased abstinence rates at 1-week post-treatment among dependent smokers (Waters et al., 2003) and at 3 months post-treatment among alcoholics

(Cox et al., 2002). Of course, the indirect measurement of cognitive control activation via response time interference prevents stronger conclusions. Subsequent research must control for potential alternative accounts (e.g., stronger implicit motivation rather than weaker control among unsuccessful abstainers) and/or provide more direct measurement of cognitive control activation (e.g., functional imaging, ERPs).

Research on distress tolerance also provides data that link individual differences in cognitive control with drug-use probability. Across these studies, drug users are instructed to perform stressful behavioral or mental tasks (e.g., solving difficult anagrams or performing challenging mental arithmetic, mirror tracing). Presumably, drug users experience conflict between adhering to instructions to persist at the task versus 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, decreased ability to persist on the aversive tasks is associated with decreased duration of cigarette abstinence among smokers (Brandon et al., 2003; Brown et al., 2002). Similarly, decreased task persistence also predicts decreased previous drug- or alcohol-abstinence duration and probability of treatment completion (Daughters et al., in press).

Behavioral and electrophysiological evidence indicates that acute alcohol intoxication impairs cognitive control (Casbon et al., 2003; Curtin & Fairchild, 2003). This 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). This acute impairment in cognitive control, however, has important implications for individuals attempting to abstain from other drugs. For example, this alcohol-impaired cognitive control may

account for the increased risk for relapse to smoking when intoxicated (Krall et al., 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 due to alcohol intoxication, these smokers will not be successful in inhibiting this smoking motivation and will fail to maintain their abstinence goal. If the intoxication is severe enough, smokers may smoke without ever experiencing urges to do so because of their compromised recruitment of control resources.

6. *The interplay between implicit drug motivation, components of cognitive control, and craving is dynamic.* When measuring neurobiological response, attentional or behavioral consequences, or self-report of drug-craving, the timing of these measurements relative to presentation of the eliciting stimulus is critical. For example, subcortical structures (e.g., amygdala, nucleus accumbens) that support implicit drug-motivation processes may respond relatively quickly and automatically following exposure to negative affect or drug cues. Our model predicts that cognitive control processes that are recruited to regulate or support implicit drug-use motivation and precipitate the self-report of craving will lag behind these earlier implicit processes—and should persist as long as the conflict is unresolved.

Similarly, theory on cognitive control reviewed previously also implies a dynamic interplay between evaluative and regulative control and recent basic research on cognitive control has confirmed this temporal ordering. For example, Kerns et al. (2004) demonstrated that ACC activation on any specific incongruent trial in the traditional Stroop task predicted increased PFC activation on subsequent trials. In other research, Curtin and Fairchild (2003) used the increased temporal resolution of event-related brain potentials to confirm this temporal ordering of evaluative

and regulative control within a single incongruent Stroop trial.

In fact, intriguing preliminary evidence of the temporal ordering of these processes as drug-craving unfolds has been provided in a recent neuroimaging study (Wexler et al., 2001). In a cue-reactivity paradigm, cocaine-dependent participants reported real-time, self-report of drug-craving with concurrent functional MRI measurement of neural response. Consistent with other neuroimaging reports, drug-cue-specific responding was observed in ACC and sectors of PFC. The timing, however, of neural response activation relative to the onset of participants' self-report of craving varied across neural structures. Activation in anterior cingulate was observed immediately preceding report of craving, whereas PFC activation was not detected until a subsequent sampling epoch.

It would be possible to test some model elements via studies that track the evolution of drug-motivation processes across dependence development. In theory, one should observe a strong temporal congruence between the development of strong motivational responses (e.g., reflected in nucleus accumbens activity or cerebral asymmetry [Zinser et al., 1999]) and the development of activation of the ACC and associated prefrontal regions in response to blocked drug access. This would highlight the interdependence between the basic motivational processes and setting events for recruitment of cognitive control. Further, the capacity of non-drug stressors to elicit drug urges should develop only after individuals have developed physical dependence, which would allow them to appreciate the stimulus overlap between withdrawal and nonpharmacologic distress.

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