Chapter 10
The Functional Significance of Craving in Nicotine Dependence

Stephen T. Tiffany, Mathew W. Warthen, and Katherine C. Goedeker

Introduction

In 1954, craving was given a death sentence. A panel of experts convened by the World Health Organization advised that the term *craving* be abandoned because "a term such as 'craving' with its everyday connotations should not be used in the scientific literature . . . if confusion is to be avoided" (Who Expert Committees on Mental Health and on Alcohol, 1955, p. 63). In the ensuing half century, craving has persisted in bedeviling scientists, but the term, and the variety of concepts it represents, simply refuses to die.

Unquestionably, craving remains an everyday word – a Google™ search of the terms *craving* or *crave* appearing in web pages updated over the past year (April 2006–March 2007) yielded approximately 10,000,000 hits. Craving has been addressed by scientists with escalating frequency. A search of the terms *craving* or *crave* in abstracts indexed by Medline or PsycINFO since 1960 (Fig. 10.1) shows that craving research was fairly limited in the 1960 s and 1970 s, began to proliferate in the 1980 s, and exploded in the 1990 s. This pace has continued to accelerate during the first half of the present decade with more than 2,100 abstracts containing the words *craving* or *crave* published over that period. Clearly, scientists have not abandoned their use of the term nor their interest in the processes it represents.

That is not to say that all disputes about craving have been resolved – craving remains a controversial topic. Nonetheless, research on craving has come a long way over the past 50 years and we now know much more about the measurement, manipulation, and functional significance of craving. However, our modern scientific understanding of craving is not universally appreciated by all drug-abuse researchers, and there remain fundamental questions about the functions of craving in addictive processes. A considerable portion of craving research has been conducted in the context of cigarette smoking and nicotine dependence and the focus of this chapter is on that research. As will be seen, craving is a robust and ubiquitous

S.T. Tiffany
Department of Psychology, University at Buffalo, the State University of New York, 368 Park Hall, Buffalo, NY 14260-4110, USA
e-mail: stiffany@buffalo.edu

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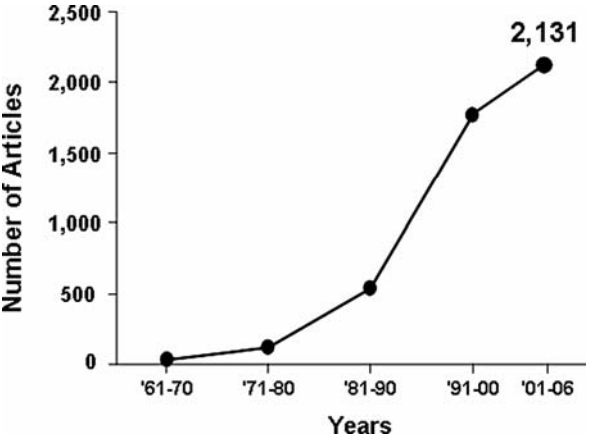

Fig. 10.1 The appearance of the terms *crave* or *craving* in abstracts since 1961 as compiled from MedLine and PsychInfo

phenomenon among cigarette smokers, so smoking represents an excellent vehicle for exposing and untangling the complexities of craving processes. Further, answers about craving generated through smoking research are likely to have considerable applicability to craving observed in other drug-abuse disorders.

Conventional Craving Assumptions

The customary conception of craving, one that has endured for at least the past 50 years, is that craving indexes the core motivation for drug addiction (Tiffany, 1990). For example, in a major review of the neurobiology of relapse, Weiss (2005) concluded, "Current conceptualizations of addiction recognize craving as a central driving force for ongoing drug use, as well as for relapse following abstinence." Over the years, other prominent researchers have made similar assertions about the role of craving in drug-abuse disorders (e.g., Anton, 1999; Baker, Morse, & Sherman, 1987; Ludwig, Wikler & Stark, 1974; Robinson & Berridge, 1993; Wise, 1988). The proposal that craving is at the motivational core of addiction has been assumed, explicitly and implicitly, by most models of craving proposed over the past 50 years.

A distinct implication of this formulation is that measures of craving and drug use should be strongly associated, and that relapse should be preceded by craving. Moreover, as drug-abuse motivation is typically presumed to represent the co-opting of naturally occurring motivational systems by drug-appetitive processes, the mechanisms subserving craving are presumed to be somewhat biologically and psychologically primal, reflecting the operation of fundamental brain reward pathways. The neural pathway most commonly implicated in addictive motivation involves the mesolimbic dopamine system, projecting from the ventral tegmental area (located in the midbrain at the top of the brainstem) and terminating in the

nucleus accumbens (located in the base of the forebrain just ventral and medial to the head of the caudate and the putamen) Finally, craving is generally regarded as the subjective manifestation of the core motivational processes mediating addictive behavior – that is, craving is conscious (cf., Berridge & Robinson, 1995).

How Do We Study Craving?

Craving research has benefited greatly by the widespread implementation of two methodological advances. First, modern approaches to the measurement of craving rely on multi-item questionnaires that display considerable reliability and sensitivity to the dynamics of changes in craving over time (e.g., Bohn, Krahn, & Staehler 1995; Heishman, Singelton, & Liguori, 2001; Singleton, Tiffany, & Henningfield, 1994; Tiffany & Drobes, 1991; Tiffany, Singleton, Haertzen, & Henningfield, 1993, Tiffany, Fields, Singleton, Haertzen, & Henningfield, 1995). Second, craving processes can be examined under controlled laboratory conditions through the use of cue-reactivity (CR) procedures (Drummond, Tiffany, Glautier, & Remington, 1995). The CR paradigm draws on the common observation that craving can be reliably triggered when addicts are confronted with cues and situations that are strongly associated with previous episodes of drug use (Drummond et al., 1995). Most smokers, for example, will say that encounters with particular cues and situations, such as a pack of cigarettes, a friend smoking, or remembering past smoking episodes, will readily induce craving. Cue-induced craving is so widespread across addictive disorders that nearly all modern theories of drug dependence invoke cue-specific processes to explain craving and drug use.

Craving Assessment

Most research prior to 1990 evaluated craving with single-item scales of unknown psychometric properties. Over the past several years we have developed several multi-item craving instruments that allow for more precise, psychometrically sophisticated measurements of craving. Our first instrument was the Questionnaire on Smoking Urges (QSU; Tiffany & Drobes, 1991). Validation studies have provided considerable support for the reliability and stability of the latent structure of the questionnaire (e.g., Davies, Willner, & Morgan, 2000; Willner, Hardman, & Eaton, 1995). The QSU served as the prototype for subsequent alcohol, cocaine, heroin, and marijuana craving scales (Bohn et al., 1995; Heishman et al., 2001; Singelton et al., 1994; Tiffany et al., 1993, 1995). We have also developed a 10-item brief form of the QSU that yields a highly reliable estimate of craving in both laboratory and clinical settings (QSU-Brief; Cox, Tiffany, & Christen, 2001). This brief version of the QSU, which has been widely adopted in the nicotine field, has been translated into multiple languages. More recently, we have created a 4-item craving rating derived from the QSU-brief that provides a general craving measure suitable for

multiple assessments of craving over a relatively short period. This craving assessment is highly reliable (α =.95) and extremely sensitive to craving manipulations (e.g., Carter & Tiffany, 2001).

Factors that Affect Cigarette Craving

Cigarette craving can vary as function of several factors, but those that have been most clearly documented include cigarette abstinence, time of day, alcohol intoxication, stress/negative emotional states, environmental cues, and availability of cigarettes.

Cigarette Abstinence

A robust finding in the smoking literature is that cigarette craving increases dramatically when smokers are instructed to remain abstinent from cigarettes (Schuh & Stitzer, 1995; Tiffany & Drobes, 1991). As shown in Fig. 10.2, abstinence-induced craving is very common among daily smokers. This figure depicts data from daily smokers surveyed in the 2005 National Survey on Drug Use and Health (NSDUH; U.S. Department of Health and Human Services, 2006). The NSDUH is an annual survey of the use of licit and illicit drugs by the civilian, noninstitutionalized population of the United States aged 12 and older. The 2005 survey identified 8,017 daily smokers with a projected estimate of over 38 million daily smokers for the entire United States. Across all age groups, the vast majority of daily smokers, an average of nearly 93%, reported experiencing at least some craving when they had not smoked for a few hours.

In early research conducted in our laboratory, daily cigarette smokers reported significant increases in craving after only one hour of abstinence (Tiffany & Drobes,

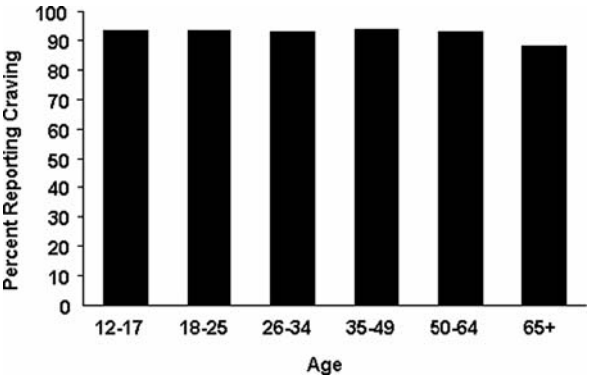

Fig. 10.2 Percentage of daily smokers reporting as experiencing at least some craving when not smoking for a few hours as a function of age group. Data Source: National Survey on Drug Use and Health (2005)

1991). Subsequent research by Schuh and Stitzer (1995) revealed that craving levels can rise within minutes of smoking a cigarette. Although the exact time course of abstinence-induced craving has not been fully mapped, abstinence-induced craving reaches peak levels within three to six hours of cigarette deprivation among daily smokers. Generalized increases in craving following cigarette abstinence appear to be controlled by nicotine deprivation, as this effect is reversed by nicotine delivered via a nicotine patch (Teneggi et al., 2002; Tiffany, Cox, & Elash, 2000).

Time of Day

The impact of time of day and abstinence on craving are clearly illustrated in research by Teneggi and his colleagues (Teneggi et al., 2002). In this study, regular cigarette smokers residing in a clinical research unit were asked to go three days without smoking or they were allowed to continue smoking at their regular rate. Over this period, they rated their craving for cigarettes at several points of each day. Fig. 10.3 shows the craving reports from these two conditions. During the ad lib smoking period, there was no systematic change in craving levels over time. In contrast, when the smokers were abstinent, there were two clear effects evident in the results. First, when abstinent, the smokers reported stronger craving than when smoking. Second, there was a strong daily patterning in craving levels, with craving lowest at the morning assessments and highest in the evening. This diurnal pattern was evident across all three assessment days. This is not the first study to show that craving levels can fluctuate over time; other researchers have reported that craving levels appear to peak in the evening hours for abstinent smokers (Fagerström, Schneider, & Lunnel, 1993; Glassman, Jackson, Walsh, Roose, & Rosenfield, 1984).

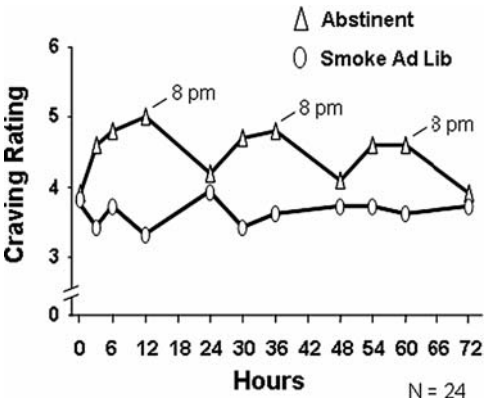

Fig. 10.3 Craving levels over a 72-hour period of cigarette abstinence or ad lib smoking. Data are from Teneggi, Tiffany, Squassante, Milleri, Luigi, & Bye (2002)

Alcohol Intoxication

Smoking and alcohol use have been reciprocally associated with future abuse and dependence (Lewinsohn, Rohde, & Brown, 1999; Werner, Walker, & Greene, 1996; Sher, Gotham, Erickson, & Wood 1996), and the probability of smoking and drinking increases based on the quantities of cigarettes or alcohol consumed (Resnicow, Smith, Harrison, & Drucker, 1999; Sutherland & Willner, 1998; Tucker, Ellickson, & Klein, 2002). Aside from these more distal associations, cigarettes and alcohol are often consumed simultaneously (Shiffman, Fischer, Paty, Gnys, Hickcox, & Kassel, 1994), suggesting possible causal links that are more proximal in nature. Burton & Tiffany (1997) found that alcohol intoxication produced a generalized increase in craving to smoke among daily cigarette smokers who were also social drinkers. The alcohol condition was compared against an alcohol-placebo condition, such that all participants believed that they were receiving alcohol, whether or not they actually did. Consequently, this result was due to the pharmacological effects of alcohol, not alcohol expectancy effects. The effect of alcohol intoxication on craving to smoke has been shown in other placebo-controlled studies with both daily and low-level smokers (Epstein, Sher, Young, & King, 2007; Glautier, Clements, White, Taylor, & Stolerman, 1996; Sayette, Martin, Wertz, Perrott, & Peters, 2005).

Stress and Negative Affect

Links between stress and smoking are abundant in clinical lore as well as experimental paradigms. Smokers report that they smoke more under stress and perceive themselves as under generally greater stress than nonsmokers (Parrott, 1999; Pomerleau & Pomerleau, 1990). Human and animal studies show strong between-subject associations between stress/negative affect (NA) and the initiation and maintenance of smoking/nicotine self-administration and good evidence for within-person effects of stress/NA cueing on relapse to smoking/nicotine self-administration (Kassel, Stroud & Paronis, 2003). Research from our laboratory revealed that induction of negative mood through imagery manipulations increases craving to smoke (Maude-Griffin & Tiffany, 1996; Tiffany & Drobes, 1990), an effect that has been replicated by other researchers (Erblich, Boyarsky, Spring, Niaura & Bovbjerg, 2003). A number of researchers have reported that exposure to acute laboratory stressors (Perkins & Grobe, 1992), or negative mood induction procedures (Conklin & Perkins, 2005; Willner & Jones, 1996) increases craving to smoke.

Smoking-Related Cues

The CR paradigm has been widely used to assess addicts' verbal and physiological responses to drug-related stimuli (Drummond et al., 1995). A meta-analysis of

over 40 CR studies with cigarette smokers, alcoholics, heroin addicts and cocaine addicts showed that craving and autonomic reactions can display a great deal of cue-specificity (Carter & Tiffany, 1999). In this study, effect sizes for craving and autonomic measures were calculated as the difference between addicts' responses to drug cues and neutral cues. On average, drug-cue presentations produced significant increases in heart rate and sweat gland activity, and significant declines in skin temperature. With the exception of studies on alcoholics, cue-specific craving across groups was extremely robust, producing average effect sizes in excess of 1.20. Overall, the craving effects were substantially larger than effects observed with the autonomic measures; these latter effects, on average, were small.

This meta-analysis showed that the CR paradigm can produce robust craving and reliable physiological effects in addicts exposed to drug-related stimuli. We have developed several different procedures for presenting smoking related cues to cigarette smokers. As one example, we pioneered the use of imagery procedures to present drug-related cues to cigarette smokers (Tiffany & Hakenewerth, 1991). The results of that experiment and multiple subsequent studies have found that vividly imagining smoking-related scenarios produces robust, cue-specific craving (Burton & Tiffany, 1997; Cepeda-Benito & Tiffany, 1996; Conklin & Tiffany, 2001; Conklin, Tiffany & Vrana, 2000; Drobes & Tiffany, 1997; Elash, Tiffany & Vrana, 1995; Maude-Griffin & Tiffany, 1996; Tiffany et al., 2000; Tiffany & Drobes, 1990). We have also directly compared the impact of imaginal with in vivo (e.g., watching an experimenter smoke a cigarette) presentation of smoking cues, and found that the magnitude of cue-specific craving effects was the same across these two modes of stimulus presentation (Burton & Tiffany, 1997; Drobes & Tiffany, 1997; Tiffany et al., 2000).

In our imagery studies, we typically employ standardized sets of imagery materials consisting of both smoking-related scenarios, designed to evoke strong craving, and smoking-neutral scenarios. Conklin and Tiffany (2001) compared these standard imagery materials with personalized imagery scenarios developed from structured interviews with smokers about situations that they strongly associated with smoking and craving or in which they would not crave cigarettes. Imagery of the personalized material generated substantially higher ratings of image vividness and relevance than imagery of the standard imagery scenes. But, interestingly, personalized craving material did not trigger stronger craving than the standard material. Rather, personalization influenced the difference in craving effects between craving and non-craving imagery material: smokers reported substantially less craving to the personalized than to the standardized non-craving material. In essence, personalization cleaned up our non-craving control stimuli such that these imagery scenarios generated relatively low levels of craving. The net result across the two types of scenarios (craving and non-craving) was a substantially stronger cue-specific craving effect. The average cue-specific craving effect size (Cohen's d) for standardized imagery material was 1.19, an effect size nearly identical to that reported in the meta-analysis by Carter & Tiffany (1999) for CR studies with smokers. The effect size for the personalized material was 1.75, an increase of almost 50% over that obtained with standardized material.

We have used CR procedures across a series of studies to examine the impact of factors that may moderate the magnitude of craving responses to smoking cues. Our research has shown that, although cigarette abstinence produces generalized increases in craving, it does not selectively increase craving reactivity to smoking cues (Drobes & Tiffany, 1997; Maude-Griffin & Tiffany, 1996; Tiffany et al., 2000). Furthermore, the nicotine patch reduces the elevation in craving brought about by abstinence; it does not selectively dampen craving responses to smoking-related cues (Tiffany et al., 2000). The observation that cigarette abstinence does not enhance craving reactions to smoking cues is not unique to our laboratory – a similar pattern has been reported by numerous other researchers (Dawkins, Powell, West, Powell, & Pickering, 2006; McClernon, Hiott, Huettel, & Rose, 2005; McDonough & Warren, 2001; Payne, Smith, Sturges, & Holleran, 1996; Powell, Dawkins & Davis, 2002). We have also found that, although alcohol consumption increases craving in smokers, it does not sensitize smokers to smoking stimuli (Burton & Tiffany, 1997; see also Field, Mogg, & Bradley, 2005, cf., Sayette et al., 2005).

Cigarette Availability and Craving

In nearly all CR research, participants are not allowed to consume their drug during the experimental session. Many researchers have speculated that drug availability should moderate the magnitude of CR (e.g., Baker et al., 1987; Childress, McLellan, & O'Brien, 1986; Ehrman, Robbins, Childress, & O'Brien, 1992; Meyer, 1998). But findings regarding the effect of availability on CR have been mixed, and, when there has been an effect, the magnitude has been extremely modest (see review by Carter & Tiffany, 2001).

Research from our laboratory indicates that the extent to which drug availability influences CR depends on the immediacy of the drug-use opportunity. Past studies on availability may be limited in their use of a CR procedure that only manipulated the expected availability of post-session drug use. That is, in most availability research, participants were informed that they would or would not be able to use their drug at the completion of the experimental session (Juliano & Brandon, 1998; Droungas, Ehrman, Childress, & O'Brien, 1995; Childress et al., 1986). With this procedure, an addict is given the expectation of remote or distal drug availability but not allowed access to the drug in the presence of drug cues during the session. In contrast, availability might be manipulated by informing the addict that he or she would have immediate access to drug use in the presence of drug cues. One may suppose that the extent to which the participant has immediate access to a drug (local availability) might have a different impact on cue reactions than the situation in which access was permitted at the end of a session (distal availability).

Carter and Tiffany (2001) examined the impact of local availability on responses to drug cues by modifying the conventional CR paradigm. This procedure, the Cue-Availability Paradigm (CAP), allowed a trial-by-trial manipulation of cue

availability. Local availability was manipulated by presenting smokers with either a glass of water or a lit cigarette behind a clear glass door and informing them of the probability (0%, 50%, or 100%) that they would be able to open the door at the end of the exposure trial and sample the cue. The door was locked or unlocked depending on the probability given to the participant at the beginning of the trial. If the door was unlocked, the smoker could take one puff of the cigarette on cigarette trials and one sip of water on the water trials. Craving ratings and physiological measures were collected in the presence of the target cues.

Carter and Tiffany (2001) found that participants reported higher craving on cigarette trials than on water trials and this difference in craving cues increased with the probability of gaining access to the cigarette (Fig. 10.4). The smokers also had higher levels of skin conductance on cigarette trials and this difference was most pronounced when they knew there was a 100% chance that the door was unlocked and they would be able to smoke the cigarette. Smokers also attempted to open the door more quickly on cigarette trials than water trials, but this effect was significant on only those trials on which they had some chance to sample the cigarette (50 and 100% trials). We have conducted a series of studies replicating these results showing that the opportunity to smoke a cigarette shortly after the presentation of a smoking cue increases the level of craving to the cue presentation (Bailey, Goedeker & Tiffany, 2007; Goedeker, Bailey & Tiffany, 2007; Tiffany, Goedeker & Bailey, 2007; see also Sayette, Wertz, Martin, Cohn, Perrott, & Hobel, 2003). Collectively, these findings show that, in a laboratory setting, the immediate availability of a cigarette has a pronounced impact on CR.

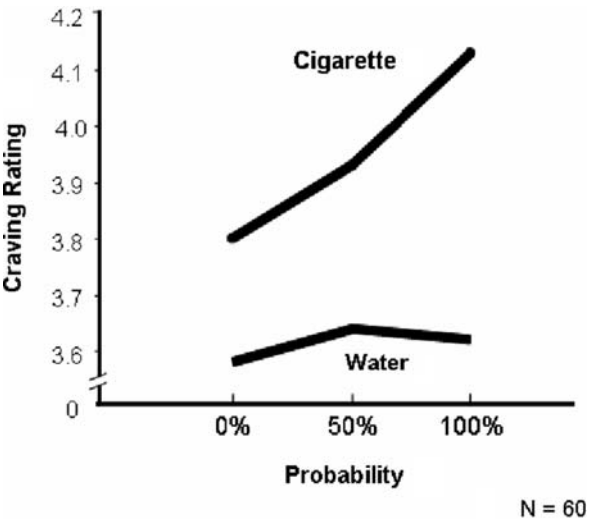

Fig. 10.4 Craving report by cue type and probability of accessing the cue on the trial. Data are from Carter & Tiffany (2001)

Tonic – Phasic Distinction in Cigarette Craving

Several researchers have suggested that craving might be decomposed into two or more components with each reflecting the operation of distinct craving processes (e.g., Drummond, 2000; Isbell, 1955; Tiffany, 2003). A continuous monitoring of craving levels within individuals would likely reveal that craving is relatively variable, displaying peaks, valleys, and brief-duration spikes over the course of a day. Such complex waveforms may comprise two fundamental components. The first component, tonic craving (Tiffany, 2003), is expressed as a slowly changing signal that may reflect abstinence or withdrawal-related craving. This pattern may also index biological processes with a relatively long time constant (e.g., withdrawal effects) and may also track diurnal variations in biological processes (Teneggi et al., 2002). The second component, superimposed on the first, captures fast onset but relatively short duration spikes in craving levels. This phasic craving (e.g., Tiffany, 2003) would presumably reflect cue-specific craving, which would only occur when addicts were confronted with environmental cues or emotionally charged stimuli that remind the addict of previous episodes of use or signal an impending occasion for drug use. Processes controlling tonic and phasic craving may operate somewhat independently. For example, as noted above, research from our laboratory suggests that abstinence-induced phasic craving and cue-specific cigarette craving appear to contribute additively to the total level of craving observed in a smoker at any given time (Bailey et al., 2007; Drobes & Tiffany, 1997; Maude-Griffin & Tiffany, 1996; Tiffany et al., 2000). Similarly, alcohol intoxication, which, like cigarette abstinence, produces a generalized increase in cigarette craving, also does not sensitize smokers to cigarette-related cues (Burton & Tiffany, 1997). We do not know the extent to which cue-reactive craving is constrained or magnified by other changes in tonic craving. In any case, the magnitude of cue-specific craving at any given point of time is best considered within the context of general levels of craving as assessed via reactions to neutral cues and/or baseline assessments of craving (Sayette, Shiffman, Tiffany, Niaura, Martin, & Shadel, 2000).

Craving and Drug Use

As noted earlier, most models of craving assume that craving represents the motivational process responsible for all drug use in the ongoing addict and all instances of relapse in the addict attempting abstinence (Tiffany, 1990). Evidence regarding the validity of this assumption is mixed, with many studies finding little or no relationship between craving and various measures of drug use including relapse (Tiffany, 1990; Tiffany & Conklin, 2000). On the other hand, there are some studies in which craving and drug use or craving and relapse are more strongly associated (e.g., Killen & Fortman, 1997; Ludwig et al., 1974; Shiffman et al., 1997). The factors that moderate the magnitude of the relationship between craving and drug use have not been identified. We hypothesize that, to the extent those relationships exist, they will be strongest when: (a) the measures of craving and drug use are highly reliable,

(b) the conditions of craving assessment and/or induction are maximally representative of the natural expression of craving, (c) neither craving nor drug-use measures are restricted in range, (d) multiple aspects of drug use are evaluated including measures of both drug seeking and drug consumption, and (e) assessments of craving and drug use are conducted in close temporal proximity. These conditions have rarely, if ever, been met in a single study. For example, few CR studies even include measures of smoking as one of the variables potentially affected by cue manipulations.

Our research with the cue-availability paradigm offers the possibility of examining craving–smoking relationships in some detail, as the procedure has multiple trials in which craving in the presence of cigarette cues is measured in conjunction with measures of latency to open the door and access the lit cigarette (drug seeking). As an example, we have looked at results from all four studies in which we used the cue-availability paradigm to calculate the correlation between craving report on trial when there is a 100% probability that the door to the cigarette is unlocked and the latency to open the door on that trial (Bailey et al., 2007; Carter & Tiffany, 2001; Goedeker, Bailey & Tiffany, 2007; Tiffany, Goedeker & Bailey, 2007). In this paradigm, craving report is at its highest level on these trials. The average correlation across studies was 0.24, which, overall, was significant with an aggregated sample size of 360 across experiments. Though significant, this association was not particularly impressive given that the coefficient of determination (r^2) represented less than 6% shared variance between craving and drug seeking. Certainly, in these data, this relationship was much weaker than suggested by the common assumption that craving drives all drug use.

Addressing the Craving– Drug Use Conundrum

Results from the past 50 years of research strongly suggest that the supposition that craving and drug use are tightly coupled presents a grossly distorted picture of the role of craving in addictive processes (Drummond, 2001). This conclusion has profound implications for research on nicotine dependence and, more broadly, all addictive disorders. First, given there is not a one-to-one relationship between craving and measures of drug seeking or drug consumption, craving cannot be used as a proxy for drug use. For example, a treatment that reduces cigarette craving will not necessarily attenuate smoking. Similarly, a treatment that does not affect cigarette craving might still reduce smoking.

Second, drug-use behaviors (seeking and consumption) cannot be used as surrogates for craving. This issue is most critical for those conducting animal research as these researchers do not have access to behaviors in their subjects that map readily on to human expressions of craving. Though many non-human animal investigators are acutely aware of the complexities of modern craving research, there continue to be studies that assert unreservedly that the results are directly indicative of the operation of craving mechanisms, with the primary dependent measure being lever pressing for drug infusions in rodents. The data generated from such studies may

be ultimately relevant to behavioral and biological mechanisms of drug-motivation and might inform us about processes that are implicated in craving. However, human research shows that craving and drug seeking (or self-administration) are not isomorphic, and the network of connections between the processes that modulate these two domains of addictive behaviors is substantially more intricate than implied by these simple interpretations. Continued misapprehension of the relevant human research on craving impedes the development of meaningful animal models that might generate crucial insights into the biological and psychological substrates of craving.

Third, data on relationships between craving and drug use require theories that can accommodate the frequent finding that these two behavioral domains are somewhat dissociated. Several years ago, one of us (Tiffany, 1990; see also Tiffany, 1992; Tiffany & Carter, 1998; Tiffany & Conklin, 2000) presented such a theory proposing that the processes that control drug seeking and drug taking can operate independently from the processes that modulate craving. According to this theory, drug use in the experienced addict takes on the characteristics of automatized behavior. That is, over the course of a history of drug use, drug seeking and drug consumption becomes rapid, highly stimulus bound, coordinated, difficult to inhibit in the presence of enabling stimuli, cognitively non-demanding, and organized outside of conscious awareness. The following anecdote from Guthrie (1935) clearly captures the automatic nature of smoking:

> I once had a caller to whom I was explaining that the apple I had just finished was a splendid device for avoiding a smoke. The caller pointed out that I was smoking at the moment. The habit of lighting a cigarette was so attached to the finish of eating that smoking had been started automatically. (p. 116)

The concept of automaticity has a long history in psychological research (e.g., James, 1890) and has been fruitfully applied to areas as broad as attention, emotion, perception, learning, memory, motivation, skill acquisition, and social cognition (see Moors & De Houwer, 2006, for review). A theme that permeates this literature is that behaviors repeated under fixed stimulus conditions become increasingly controlled by cognitive processes that differ from those that are responsible for performance when the behavior is initiated. A hallmark of addictive behavior is that addicts seek and consume their drug frequently. Consequently, if the concept of automaticity is relevant for any domain of highly practiced behavior, it certainly should apply to addictive behavior. Consider regular smokers who, during the course of any given year, smoke thousands of cigarettes and, over their lifetime, smoke hundreds of thousands of cigarettes. With the opportunity for so much practice, it is hard to imagine anything other than the automatization of much of the behavior necessary for getting and consuming cigarettes. The cognitive processing model proposes that, over a history of repeated practice, the cognitive systems controlling cigarette procurement and consumption will become automatized. Tiffany (1990) hypothesized that the procedures for carrying out these automatized skills are stored in the form of action schemata (Fig. 10.5). These are memory structures that contain adequate information for the initiation and coordination of complex sequences of

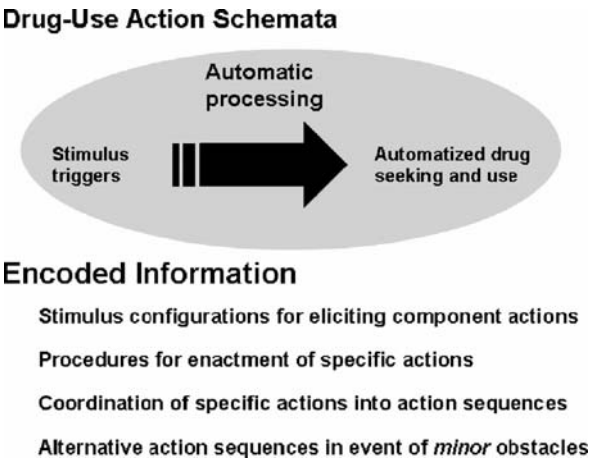

Fig. 10.5 Proposed components of drug-use action schemata

drug-use behavior. In the experienced smoker, some stimulus conditions activate drug-use action schemata that, in turn, control smoking behavior. Notice that craving is nowhere invoked in this proposed sequence of cigarette seeking and smoking.

Although automaticity has been investigated thoroughly in human studies, this concept has also been addressed in animal research. For example, Dickinson (1985, 1989) proposed that instrumental behavior in animals might be controlled by two types of processes, stimulus–response (S–R) associations (habits) in which reinforcing a response leads to the strengthening of an association between contextual cues and the response, and response–outcome (R–O) associations, which control goal-directed actions. According to this perspective, the "S–R process is analogous to the cue-elicited automatic action schemata within Tiffany's (1990) theory in that both mediate involuntary and habitual responding" (Miles, Everitt, & Dickinson, 2003; page 927). Miles et al., (2003) demonstrated that rats given extended instrumental training for a cocaine–sucrose reinforcer were relatively immune to a devaluation procedure in which the cocaine–sucrose solution was paired with an aversive outcome. These authors interpreted the results as consistent with the hypothesis that components of drug seeking and taking are automatic and habitual. Beyond these implications for the cognitive processing account of drug use, the results demonstrate that elements of a theory derived from human–information processing models can be investigated in animal preparations. (See Dickinson, Wood, & Smith, 2002, and Miles, Everitt, Dally, & Dickinson, 2004, for similar research on automaticity and drug taking.)

Typically, automatic processing is contrasted with nonautomatic cognitive processing, which is generally described as limited by fixed-capacity cognitive functioning, situationally flexible, dependent on attention and intention, relatively slow, and cognitively effortful (e.g., Logan, 1991; Moors & De Houwer, 2006). Nonautomatic processing is required in new tasks or situations in which automatic

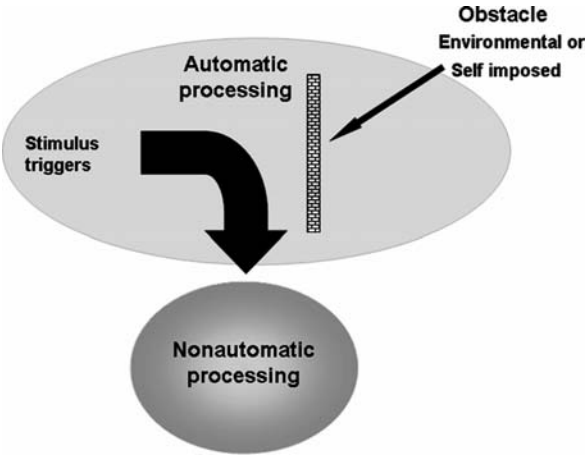

Fig. 10.6 The activation of nonautomatic processing

processing cannot adequately control responding and is also required to impede the initiation or completion of automatic processing. The cognitive processing theory associates craving with responses supported by nonautomatic cognitive processes activated in parallel with drug-use action schemata (Fig. 10.6). These are invoked when there is some obstacle that blocks the successful completion of an activated drug-use schema. This obstacle can arise from two sources: (1) Some environmental condition impedes the action schema in an addict not attempting to avoid drug use, or (2) An addict attempting to remain abstinent tries to block or impede a drug-use action schema. As an example of an environmental obstacle, what happens when a smoker, not trying to quit smoking, reaches for a pack of cigarettes only to discover that her cigarettes are gone? This situation will demand the invocation of nonautomatic processing to solve the problem.

The manifestations of this processing can be indexed across three broad classes of behavior. Motor behavior should be characterized by actions to overcome or neutralize the obstacle. Verbal responses should include reports of desire to use, a stated intention to use the drug, reports of frustration and annoyance (this is classic frustration paradigm), and, if prompted, descriptions of problem solving and planning to overcome the obstacle. Finally, there should be indices of somatovisceral activation linked both to the cognitive effort generated by the nonautomatic processing as well as responses that would support physical effort to overcome the obstacle.

Among the many implications of the cognitive processing model of drug craving and use are the following: (1) Smoking behavior, including actions to obtain and consume cigarettes, should have the hallmarks of automatic behaviors. (2) The level of automaticity represented by any single component of smoking behavior and the coordination and coherence of components across behavioral sequences will be determined by the extent to which the individual has engaged in those behaviors

under fixed stimulus conditions. (3) Craving is not necessary for either smoking or smoking relapse. (4) Craving can occur among smokers not intending to quit as well as among those who are attempting abstinence. (5) Craving will be generated under circumstances strongly associated with past episodes of smoking, including all of the conditions outlined earlier as factors that influence craving. (6) Craving is activated when habitual, automatic smoking routines are interrupted, either by environmentally imposed obstacles in those not intending to quit or by self-generated obstacles to smoking in those attempting to abstain. (7) Craving is experienced as an aversive, distracting, cognitively demanding condition that can, either acutely or cumulatively, undermine a smoker's commitment to abstinence.

If Craving and Smoking Are Not Tightly Coupled, Why Study Craving?

A question we encounter during discussions about the generally weak associations between measures of craving and drug use is "Why do research on craving if it is not strongly linked to drug use?" We believe that abandoning craving research in light of the ambiguous relationship between craving and drug use would be a counterproductive response. Indeed, there are multiple compelling reasons for programmatic research on craving. These include:

Ubiquity of Craving Among Smokers

As noted earlier in this chapter, craving is extraordinarily common among regular smokers. But craving is not restricted to chronic, heavy smokers. It is even relatively widespread among relatively inexperienced, neophyte smokers (Colby, Tiffany, Shiffman, & Niaura, 2000). Craving is also highly persistent – former smokers can experience craving years after their last cigarette (Fletcher & Doll, 1969). The intensity of craving associated with cigarette smoking may be as strong as or stronger than craving associated with other addictive disorders (Kozlowski et al., 1989). The ubiquity and persistence of craving suggests that any comprehensive model of smoking must account for this prominent feature of nicotine dependence.

Prominence of Craving Among Abstinent Smokers

Although craving is not listed as a diagnostic feature of nicotine withdrawal (or dependence) in DSM-IV (American Psychiatric Association, 2000), it is a component of the ICD-10 (World Health Organization, 1992) diagnosis of tobacco withdrawal (as well as tobacco dependence). Abstinent smokers report that craving is the most salient (Shiffman & Jarvik, 1976) and frequent (Gritz, Carr, & Marcus, 1991) symptom they experience when they quit smoking. For example, in a recent laboratory-based study, withdrawal symptoms and craving were assessed with

multiple instruments at several time points across a 72-hour period when smokers were abstinent or smoking ad lib (Teneggi et al., 2005). Abstinence produced significant increases in craving and withdrawal symptoms, but the average effect sizes for the craving differences were substantially larger (d = 1.33) than those seen in the withdrawal symptoms that did not assess craving (d = 0.43).

Aversive Nature of Craving

Tiffany (1997) described craving as the psychic pain of addiction. Abstinent smokers say that craving is the most troublesome symptom they experience when they quit smoking (Richter, McCool, Okuyemi, Mayo, & Ahluwalia, 2002; Seidman & Covey, 1999; West, Hajek, & Belcher, 1989), and concerns about craving appear to be a formidable obstacle preventing many smokers from even attempting to quit (Orleans, Rimer, Cristinzio, Keintz, & Fleisher, 1991). Craving is generally viewed as a major impediment to smokers' attempts to quit smoking, and advertisements for pharmacological smoking treatments (e.g., nicotine patches, gum, lozenges) typically emphasize the craving-relieving effects of these products. The following description of the difficulties of quitting smoking depicts the aversive, intrusive feature of craving:

> One of the more difficult aspects of quitting is an intense craving that overwhelms your ability to think about much of anything besides cigarettes, and the fear that not only are you going to suffer more, but that if you don't do something about this craving right now, it's going to get worse, and you're not going to get anything accomplished (posted by Chris on Tuesday, May 02, 2006 on Mixing Memory: http://scienceblogs.com/mixingmemory)

The aversive, cognitively demanding aspects of craving have been captured in laboratory studies. Research from our laboratory has shown that elicitation of craving through CR procedures also produces a decrement in cognitive performance on a parallel reaction-time task (Cepeda-Benito & Tiffany, 1996; see also Gross, Jarvik, & Rosenblatt, 1993; Sayette & Hufford, 1994). Similarly, in nearly all of our CR research, stimulus conditions that trigger craving also increase negative mood ratings and/or decrease positive mood ratings. The only exception to this pattern has been in our cue-availability research. Here, positive mood increases and negative mood decreases on trials in which there is a 100% probability of being able to access a lit cigarette (Bailey et al., 2007; Carter & Tiffany, 2001; Goedeker et al., 2007; Tiffany et al., 2007). At first blush, those findings might suggest that craving can be a pleasant, positive-affective experience, but a closer inspection of the data from those studies reveals a more complex story. Importantly, the level of positive mood on 100% cigarette available trials is not significantly correlated with the craving level reported on those same trials. Interestingly, the strongest affective correlate of craving on those trials is the level of negative mood on other trials in which access to the lit cigarette is completely restricted. That is, the negative mood that people experience when they are forced to look at a lit cigarette they cannot smoke is the best predictor of craving on trials when they look at a cigarette they know they will be able to access in a few seconds. Our interpretation of this pattern is that smokers

are relieved when they know they can soon smoke a cigarette and are frustrated when they are told they cannot smoke. The level of frustration, and not positive affect (or even relief), is more tightly linked to the craving generated when they are allowed to smoke.

Craving as a Predictor of Relapse

Although any single instance of craving may not be strongly associated with immediate smoking behavior, research has shown that general levels of craving expressed during or after treatment can be significantly associated with the probability of subsequent smoking relapse (al'Absi, Hatsukami, Davis, & Wittmers, 2004; Baer, Kamark, Lichtenstein, & Ransom, 1989; Brandon, Tiffany, & Baker,1987; Catley, O'Connell, & Shiffman, 2000; Doherty, Kinnunen, Militello, & Garvey, 1995; Killen & Fortmann, 1997). Thus, craving assessments might identify smokers at greatest risk for relapse and could be used to formulate relapse-prevention interventions that target high-risk smokers.

Perhaps the largest study to examine relationships between cravings expressed during treatment and subsequent relapse was by Killen and Fortmann (1997). This report summarized the results of three treatment studies involving nearly 2,700 smokers. The results across all three studies were interpreted as showing that levels of craving over the first 24–48 hours of abstinence were negatively associated with time to relapse. Interestingly, subjects across these studies were *not* asked about their level of craving – they were asked to rate "how upsetting cravings and urges had been since quitting smoking." Smokers more *upset* about craving were more likely to relapse. This finding suggests that the extent to which craving is aversive or disruptive to functioning may be a better predictor of relapse than craving levels per se (see also Brandon et al., 1987; Tiffany & Carter, 1998).

Craving as a Core Attribute of Nicotine Dependence

As noted earlier, DSM-IV does not include craving as a diagnostic feature of either nicotine dependence or nicotine withdrawal. Nonetheless, a persuasive argument could be made that, given its ubiquity, salience and intensity, craving should be recognized as a core attribute of nicotine dependence in future iterations of DSM (e.g., Colby et al., 2000). This proposal, however, begs the question of the diagnostic utility of craving in diagnosis of dependence – a question that, in turn, raises a larger matter. What are the essential diagnostic features of nicotine dependence And that question is embedded in an even more general issue – what is the fundamental latent structure of dependence?

Modern diagnostic systems (i.e., DSM and ICD) define nicotine dependence as an entity somehow qualitatively or categorically distinct from non-dependent smoking. That is, they make the assumption that there is a natural boundary between dependent and nondependent smoking, a boundary defined by the collective

presence of certain behavioral characteristics such as compulsive use, high levels of use, smoking despite knowledge of harm, tolerance, and withdrawal. In short, from this perspective, dependence represents a taxon, a conceptualization of smoking distinct from a dimensional or quantitative view of nicotine dependence (Tiffany Conklin, Shiffman & Clayton, 2004). The latter perspective, which is implicit or explicit in nearly all contemporary theoretical accounts of dependence (Tiffany et al., 2004), assumes that dependence varies along a continuum such that even very inexperienced smokers have some degree of nicotine dependence. These theories hold a dimensional perspective of dependence that does not "assume any functional discontinuity between light and heavy smokers" (Tiffany et al., 2004, p. 80). The issue – whether nicotine dependence is best conceived of as a dimension or a taxon – has not been systematically addressed by previous research.

The question of whether multiple indicators presumably indexing a single construct have a taxonic (categorical) or dimensional latent structure can be addressed by a group of statistical procedures known as taxometric analyses (Meehl, 1973; Meehl & Golden, 1982; Meehl & Yonce, 1994; Waller & Meehl, 1998). Taxometric analyses offer an empirical approach to discerning the presence (or absence) of a taxon among sets of indicators putatively representative of a construct (Ruscio, Haslam, & Ruscio, 2006; Waller & Meehl, 1998). Further, if a taxon is present in the data, these analyses will identify the indicators best suited to identifying that taxon and will estimate the base rate of the taxon in the data set.

We recently completed a taxometric analysis of smoking related data from the 2003 and 2002 National Surveys on Drug Use and Health (NSDUH; Goedeker & Tiffany, 2007). Results from MAMBAC, MAXEIG, and LMODE taxometric analyses on five indicator measures administered to adults who reported any smoking within the previous 30 days produced strong and consistent evidence of a nicotine dependence taxon across all analyses. The valid indicators included three multi-item subscales of the Nicotine Dependence Symptom Scale (NDSS; Shiffman, Waters, & Hickcox, 2004): Drive, Tolerance, and Continuity. The two additional indicators were each single items assessing the latency to smoke the first cigarette after waking and the number of cigarettes smoked per day. The dependence taxon, which had a base rate of 48% among past 30-day smokers, was highly replicable across both years of the survey (with over 11,000 smokers assessed at each year) and within male and female subgroups.

The NSDSS Drive subscale, a core component of the dependence taxon as identified by the taxometric analyses is, according to Shiffman et al. (2004), represented primarily by craving-related items. For example, the Drive item that correlates most strongly with the subscale total score is worded "When you don't smoke for a few hours, you start to crave cigarettes." Thus, members of the dependent taxon had stronger craving to smoke, higher levels of tolerance to nicotine, more rigid smoking patterns, shorter latencies to smoke their first cigarette upon waking, and smoked more cigarettes per day compared to nontaxon members. Beyond the importance of these findings for our understanding of the fundamental nature of nicotine dependence, the results also support the diagnostic utility of caving as a critical feature of the nicotine dependence taxon.

Future of Craving Research

We have no doubt that research on craving will continue to be an important focus of smoking research over the foreseeable future. There are many paths that research can follow including more penetrating investigations of the neurobiology of craving, fuller descriptions of the natural history of craving, greater exploration of genetic contributions to craving processes, further mapping of the conditions under which craving processes and smoking behaviors are linked, refined treatments (pharmacological and behavioral) for craving, and continued development of the CR paradigm. With regard to this last point, we believe that we have not pushed CR research as far as we could. Often, tobacco seeking and tobacco consumption have been neglected as central components of CR . Further, the key parameters of cues that control reactivity have not been systematically investigated, and there has been scant work on the psychometrics of the stimuli used in this research. Relationships between reactivity measures are rarely addressed, and we know virtually nothing about the natural history of CR. By and large, reactivity measures other than craving have been selected more on the basis of convenience than theory, and the generalizability of CR over time, situation, and person has not been systematically explored.

We also believe that CR research has been needlessly constrained in one additional way: We have caged CR in the laboratory and not examined it in free-ranging smokers. The CR phenomena are not restricted to the laboratory. Addicts readily describe situations and cues that trigger craving in their everyday lives (e.g., Childress et al., 1986; Ludwig, 1986; Tiffany & Baker, 1988). However, to the best of our knowledge, all of the experimental research on CR has been conducted in the laboratory; there has been no CR research in real-world settings. The absence of such research is surprising, as there are many reasons to expect that patterns of CR are affected by factors not readily captured in the laboratory:

First, the effect of a cue on craving may be moderated by the environmental setting or meta-context of the cue exposure (Dols, van den Hout, Kindt, & Willems, 2002). For example, an environmental context replete with other reminders of smoking, such as a familiar, smoke-filled bar or a frequented smoking area outside of a smoke-free building, could easily alter the magnitude of CR in that setting. Certainly, bars or smoking areas could be recreated in the laboratory, though the verisimilitude of the same simulation for all subjects in a study will be limited. Other critical situations may involve particularly idiosyncratic social features, such as smoking with close friends, which would not be readily reproducible in the laboratory.

Second, there are numerous moderating conditions, such as current emotional state, which may influence CR but are difficult to assess thoroughly in a laboratory setting. The relationships between affect and craving are complex as are the relationships between affective state and smoking (Kassel et al., 2003; Shiffman et al., 2002). Levels of negative affect are often positively correlated with both general levels of craving and cue-induced craving (e.g., Carter & Tiffany, 2001; Drobes & Tiffany, 1997), and, as described earlier, induction of negative affect and exposure to stress situations can, in their own right, trigger craving (e.g., Tiffany & Drobes, 1990; Maude-Griffin & Tiffany, 1996; Sinha, Catapano, & O'Malley 1999;

Sinha, Fuse, & Aubin, 2000; Sinha, Talih, Malison, Cooney, Anderson, & Kreek, 2003). However, all of these relationships were established in laboratory settings. The extent to which CR varies as a function of background emotional state in the natural environment has not been examined.

Third, CR studies are typically conducted without reference to recurrent cyclical patterns such as time of day or day of the week. Earlier in this chapter, we described research suggesting that time of day is correlated with cigarette craving, with craving in abstinent smokers often lowest in the morning hours and peaking in the evening hours (Teneggi et al., 2002). Moreover, Shiffman and his colleagues found that, of all the time periods assessed in abstinent smokers, craving in the morning was the best predictor of subsequent relapse (Shiffman et al., 1997). Research conducted by Tiffany and his associates have found that smoking rates in college student smokers are strongly influenced by the day of the week, with much more smoking occurring on Fridays and Saturdays than on any other days (Tiffany et al., in press). Time of day or day of week can be addressed as moderating factors in laboratory studies, though it would be logistically prohibitive to construct complete profiles of either of these factors in a single study.

Fourth, as detailed above, drug availability can influence,CR although the parameters and dimensions of availability that most affect reactivity are unknown. Availability is likely a complex concept (Carter & Tiffany, 2001; Sayette et al., 2003), but we have little guidance from naturalistic studies of craving and availability to direct our experimental manipulations. More generally, assessment of CR in the natural environment gives us the opportunity to identify new classes and configurations of variables as candidates for more intensive, controlled study in the laboratory environment.

Fifth, much of the non-supportive evidence regarding the presumed relationships between craving and measures of drug use comes from laboratory-based studies of CR. It is possible that the craving processes generated in these laboratory studies do not reflect CR in natural settings and are unsuited for a comprehensive evaluation of associations between craving and drug use. In contrast, assessment of craving and CR in the natural environment may expose forms or profiles of craving that might be more revealing of the factors that control the associations between craving and drug use.

Finally, since the first experiments in the 1970 s, there have been over 150 studies utilizing the CRparadigm. This paradigm has become well established for studying psychological and neurobiological processes that motivate addictive drug use. Nevertheless, we know nothing about the generalizability of results from these laboratory studies to the real world, because CR has not been studied in the natural environment. That is, the external validity of the findings with regard to non-laboratory settings has not been investigated, and their relevance for the real world of the addicted person is unknown. There have been efforts to bring the real world into the laboratory through more detailed simulations of real-world cues or presentations of cues via virtual reality systems (Bordnick et al., 2004; Kuntze et al., 2001; Lee et al., 2003). These studies attempt to represent real world stimuli, but they do not demonstrate the extent to which the simulated conditions are representative of the

addict's natural environment. Any study that endeavors to bring the real world into the laboratory in an effort to enhance ecological validity must establish the degree to which the supposed real-world stimuli are relevant and representative of the natural world (Scheidt, 1981).

These considerations have motivated us to begin examining CR effects under real-world conditions. To accomplish this, we have launched research to develop a procedure for assessing cigarette smokers' reactions to smoking-related cues when those cues are presented in the natural environment of the smokers. In this research, cues are presented via a Personal Digital Assistant (PDA) that smokers carry with them over multiple days. The PDA prompts smokers to complete CR trials several times throughout each day. Smokers also use the PDA to log each cigarette that they smoke. The use of the PDA to collect information about event-related behavior is an example of Ecological Momentary Assessment (EMA), which has been used successfully to monitor a variety of behaviors in real time (Stone & Shiffman, 2002). We call our new procedure, which combines CR procedures with EMA, CREMA. We anticipate that the data generated by this procedure will allow for estimation of the external validity of results produced by laboratory based CR procedures and, more importantly, create a new tool to explore cue-specific craving in the natural environment.

Final Note

Craving research has exploded over the past 20 years, increasing 50-fold compared to the preceding 20 years. The cumulative message of this burgeoning body of research is that craving continues to be an important topic in the addictions field, and for good reason. The desire to use drugs appears to be a hallmark of addictive disorders, an assertion that seems particularly characteristic of nicotine dependence. Many researchers and clinicians assume that the compulsive nicotine use in smokers is driven by a pathological level of desire. According to that popular view, craving is a direct manifestation of the motivational core of addictive behavior. Contrary to this perspective, craving is often not strongly and immediately linked to smoking. That observation suggests that any model of smoking motivation and craving that presumes that the latter is a direct index of the former, needs revision. We have summarized the potential significance of craving processes in characterizing, predicting, and diagnosing nicotine dependence. We believe that a full scientific explanation of nicotine dependence must account for cigarette craving, in all its complexity.

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