# NICOTINE DEPENDENCE AND LABORATORY CUE-INDUCED CIGARETTE CRAVING

by

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**NICOTINE DEPENDENCE AND LABORATORY CUE-INDUCED CIGARETTE CRAVING**

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Background: The relationship between laboratory cue-induced craving and nicotine dependence is unclear. Some models consider cue-induced craving part of dependence, while others imply that responsiveness to cues disappears with dependence. These relationships are further complicated by different measures of nicotine dependence and craving. Method: Participants (n=207, 57% men) were daily smokers averaging 15.92 (6.70) cigarettes per day. We examined data from 4 cue-reactivity sessions, with cue sets (smoking, negative affect, positive affect, neutral) counterbalanced across sessions. In each session, after a 30-minute deprivation period, participants viewed 30 cue-relevant photos validated for content and shown over 3 minutes (6 seconds each). Participants rated their craving before and after cues (QSU-Brief, scaled as 1-49). Participants completed measures of nicotine dependence (FTND, NDSS, WISDM-68), which were used to predict craving. Multiple regression models were used to predict cue-induced craving (pre-post cue change scores) for QSU Factors 1 and 2. Results: Dependence measures were associated with background craving across sessions, but did not predict cue change in craving (Factor 1 or 2) for any cue. Conclusion: Laboratory cue-induced craving in response to smoking-relevant cues is unrelated to nicotine dependence, as traditionally assessed. Future work should investigate the relationship between reactivity to cues and actual smoking behavior, in order to better understand how reactivity to cues and dependence may function independently or synergistically to influence smoking behavior.

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## 1.0 Introduction

Many perspectives on addiction, and especially tobacco addiction, imply that drug addicts should demonstrate regularly spaced, stereotyped use throughout their day in order to maintain a particular level of the drug in the body (e.g., Shadel, Shiffman, Niaura, Nichter, & Abrams, 2000; Benowitz, 2009). While this appears to be an important feature of drug dependence, individuals are *also* more likely to use drugs in certain situations than in others, often those associated with prior use. This notion plays an important role in many conceptualizations of addictive behavior and relapse, such as Marlatt & Gordon's (1985) description of *high-risk relapse situations* – particular settings in which relapse is thought to be especially likely. This observation is commonly explained mechanistically by reference to conditioning processes, in which particular environmental stimuli become associated with drug use over time and act as conditioned stimuli to evoke specific responses, including drug use, in addicts.

The cue-reactivity paradigm (see Carter & Tiffany, 1999) has been used extensively to examine the relationship between drug-related stimuli and addicts' physiological and subjective reactivity. Subjective reports of craving or desire to use a drug have been the dependent variables in many of these studies, given the significant motivational role accorded to craving in addiction (e.g., West & Schneider, 1987; Robinson & Berridge, 1993). Among cigarette smokers, exposure to smoking-specific cues has been shown to reliably elicit increases in cigarette craving (Carter, 2000). However, findings regarding the relationship between cue-induced craving and smoking behavior–including relapse- have been mixed (Perkins, 2009). This raises questions about the nature of the relationship between cue-induced craving and addiction, or dependence.

In this project, I propose to investigate the relationship between nicotine dependence and cue-induced craving. In particular, I consider the following questions: Should one expect cue-induced craving to be higher among *more* dependent or *less* dependent individuals? Should cue-induced craving in response to different cue *types* differ according to severity of dependence? And, might the relationship between cue-induced craving and dependence differ depending on how one conceptualizes dependence, or which aspect of dependence one examines? I discuss these, along with other questions about the relationship between craving and dependence, in the following review.

### 1.1 Craving and Cue Reactivity

Craving to use a drug seems to be inherent to the very notion of what it means to be dependent. Craving has long been viewed as a key component of drug addiction (see Drummond, 2001), and a number of contemporary models of addiction associate the increased desire to use a drug with the advent of dependence (e.g., negative reinforcement models, classical conditioning models; see Eissenberg, 2004). In addition, craving-specific items are included in some measures of nicotine dependence (e.g., Shiffman, Waters, & Hickcox, 2004; Piper et al., 2004). Although not a criterion for DSM-IV dependence (APA, 1994), craving has been suggested for inclusion in drafts of the DSM-V and is included as a criterion for dependence in the International Statistical Classification of Diseases (Janca et al., 1994). Thus, cigarette craving appears to be an important feature of nicotine dependence.

### 1.2 Kinds of Craving

To discuss craving, it is useful to distinguish between two different ways in which craving is assessed, which may represent different kinds of craving. *Background craving* refers

to the average level of craving experienced by an individual over an extended period of time (e.g., a day or week), and appears to be influenced by duration of abstinence (e.g., Ferguson & Shiffman, 2009; Jarvik, Madsen, Olmstead, Iwamoto-Schaap, Elins, & Benowitz, 2000). Of note, background craving is typically the type referenced on dependence scales or models of addiction mentioned above. During a quit attempt, the intensity of background craving that a person experiences shortly after achieving abstinence predicts ultimate quit success (Ferguson, Shiffman, & Gwaltney, 2006; Killen & Fortmann, 1997), and smokers cite craving as one of the most difficult obstacles they face during a quit attempt (West, Hajek & Belcher, 1989). Thus, background craving appears to be an important -and clinically relevant- feature of dependence.

In addition to background craving however, comparatively fleeting episodes of intense craving –overlaid upon background craving- have also been linked to lapse and relapse (Shiffman, Paty, Gnys, Kassel, & Hickox, 1996; Shiffman, Engberg, Paty, Perz, Gnys et al., 1997; Shiffman, 2000). These *episodic* cravings typically occur in response to situational stimuli, or cues, that are associated with smoking, such as a cigarette itself, other people smoking, or consumption of alcohol or coffee (Niaura, Abrams, Demuth, Pinto, & Monti, 1988; Marlatt & Gordon, 1985). Accordingly, craving of this nature is commonly referred to as "cue-reactive" or "cue-induced" craving (N.B.: For the purpose of this review, the term *cue-induced craving* will be equated with the *increase in craving above background/baseline craving* following exposure to drug-relevant stimuli). This type of craving, relative to background craving, is more closely related to what Marlatt and Gordon (1985) term *high-risk relapse situations.* That is, the experience of craving in response to a situational drug cue in an abstainer is thought to increase the risk of using the drug.

*Background craving* and *cue-induced craving* may be considered two distinct constructs. As mentioned above, cue-induced craving -by necessity- is experienced on top of background craving. Both reflect the desire or urge to use a drug. However, the disparate etiologies of the two 'types' of craving have important consequences in terms of their effect on smoking behavior and the way in which they may relate to addiction. Background craving appears to be influenced largely by factors related to nicotine levels in the body (i.e., abstinence, withdrawal; see Ferguson & Shiffman, 2009). In contrast, the intense, acute experience of cue-induced craving may be subserved by psychological associative mechanisms. This may suggest that background and cue-induced craving reflect different aspects of drug dependence to different degrees. Nicotine replacement therapy, for example, is effective at attenuating background craving in abstinent smokers, but does not reduce levels of cue-induced craving (Tiffany, Cox, & Elash, 2000). In addition, among individuals attempting to quit, Waters et al. (2004) reported that patch treatment reduced background craving (and was associated with improved outcome), but did not reduce cue-induced craving. These findings suggest that cue-induced craving can be dissociated from background craving, and that both types of craving may be important in understanding clinical outcomes. This also implies that treating one type of craving (i.e., reducing background craving by nicotine replacement) does not necessarily ameliorate the other.

Other 'types' of craving have been discussed in the literature as well. Baker, Morse, & Sherman (1987) described two distinct kinds of craving, or 'urge', systems: positive-affect cravings and negative-affect cravings. Positive-affect cravings reflect the motivation toward the positive affect or reward associated with drug use, and are thought to arise primarily during ad lib smoking. Negative-affect cravings reflect the experience of withdrawal and the motivation to relieve negative affect and withdrawal symptoms through drug use, and are thought to arise

primarily during periods of abstinence or deprivation. While Baker, Morse, and Sherman's theory appears to address these systems only with respect to background craving, this perspective highlights the potential importance of affective state in the experience of craving in general, and the role of affect itself as a cue for eliciting craving.

Yet another perspective on craving is proposed by Tiffany's (1990) model of drug use and craving. which argues that drug use is largely driven by automatic processes whereby myriad 'practice' trials of smoking under specific stimulus configurations result in automaticity of smoking behavior. In this respect, exposure to a given stimulus configuration can lead to the automatic initiation of a drug use action plan (i.e., smoking), without craving. Craving only enters conscious awareness when the automatic drug use schema is interrupted. In this sense, craving takes on two forms, which arise in different motivational settings: 1) abstinence-avoidance, in which the individual desires to use, and 2) abstinence-promoting, in which the individual desires to abstain from use. Because Tiffany's model assigns a strong role to cues as determinants of smoking, it does suggest the importance of cue reactivity –and possibly cue-induced craving- in nicotine dependence.

In summary, 'craving' is not a uniform construct, but encompasses a range of subjective states, which share a common feature: the desire or urge to use a drug. Cue-induced craving may thus be viewed as a particular 'type' of craving that occurs under particular circumstances: it is experienced as an episodic or fleeting increase in desire to use a drug that occurs in response to a specific environmental stimulus.

### 1.3 Cue Reactivity

The relationship between episodic cravings and drug stimuli has been studied extensively in laboratory settings for decades. Such studies are generally referred to as 'cue reactivity' studies. The standard cue reactivity paradigm is as follows: a participant undergoes a baseline assessment, which may include both psychological (e.g., cigarette craving before cue exposure) and physiological (e.g., heart rate) measures. Next, the participant is exposed to a drug stimulus. During or following cue exposure, the participant once again completes a battery of assessments similar to those administered at baseline. Differences in subjective measures are then calculated based on the assumption that exposure to cues will influence the individual's subjective state, such as craving to use a drug. Studies that focus on reactivity to smoking cues frequently use intense, salient smoking stimuli (e.g., *"in vivo" cue*: physically exposing the individual to a cigarette- commonly, a *lit* cigarette) to induce craving in participants. Other commonly used stimuli include images of cigarettes/others smoking, or smoking-related auditory scripts (e.g., participant is asked to imagine himself holding a cigarette), although these methods typically yield less robust increases in cigarette craving (Carter & Tiffany, 1999).

A number of cue reactivity studies have shown that cigarette craving indeed increases in response to smoking stimuli such as pictures of lit cigarettes, others smoking, etc. (see Carter & Tiffany, 1999 for a detailed review). In one study Maude-Griffin and Tiffany (1996) found that smokers who were abstinent for six or twenty-four hours reported overall increases in craving compared to ad lib smokers. However, they found no effect of abstinence duration on change in craving in response to cues. (Note: Variations in periods of abstinence before cue exposure are discussed in greater detail below). Again, this highlights the different etiologies of background

craving and cue-induced craving: background craving increases with abstinence from smoking; cue-induced craving increases with exposure to drug cues.

### 1.4 Dependence

There is not a clear consensus among researchers regarding the exact meaning of dependence. At its core, dependence may be regarded as the state in which a person has "lost control" over his use of a drug, drugs use assumes a dominant role in the individual's life, and use persists despite deterrents and negative outcomes. Among smokers, dependence is associated with more regular, stereotyped patterns of smoking behavior (Shiffman, Waters, & Hickcox, 2004; Shadel et al., 2000). Conceptualized as a syndrome (Edwards, 1976; APA, 1994), dependence reflects a constellation of the psychological and physiological changes that may occur in individuals who use drugs of abuse (Shadel et al., 2000). The Diagnostic and Statistical Manual of Mental Disorders-IV (APA, 1994) defines dependence as "a maladaptive patterns of substance use leading to clinically significant impairment or distress." Across drugs of abuse, features of drug dependence include drug tolerance, experience of withdrawal symptoms, and persistent, compulsive use despite negative consequences, among others (APA, 1994).

While it is generally accepted that numerous processes and features play a role in dependence, different conceptualizations or theories tend to emphasize certain aspects over others. For example, nicotine dependence can be viewed primarily as a function of smoking in order to regulate levels of nicotine in the body (e.g., Benowitz, 2009). In this process, smoking is driven primarily by interoceptive cues, and little to no role is accorded for environmental influences. Similarly, the process of negative reinforcement plays a significant role in many theories of addiction, which stress the function of withdrawal-avoidance in the development of

dependence (e.g., Eissenberg, 2004), in which the individual smokes to avoid aversive withdrawal symptoms, also linked to decreases in systemic nicotine levels. Some theories emphasize the role of positive reinforcement mechanisms in the development and maintenance of addiction; that is, appetitive mechanisms based upon the rewarding aspects of the drug are thought to play a substantial role in driving persistent drug-taking behavior. Of note, positive reinforcement mechanisms may be particularly important in driving smoking behavior in the earlier stages of dependence (e.g., Glautier, 2004).

Fundamentally, drug use is a learned behavior. As such, learning processes, such as conditioning and social learning, are accorded a significant role in many theories of dependence (e.g, Siegel, 1979, 1983; Marlatt & Gordon, 1985). That is, learned associations between environmental cues and drug use/effects are important determinants of drug use and the development of dependence. Individuals may, for example, begin smoking only in the context of other smokers. Over time, the presence of other smokers may come to serve as cues to smoke (Conklin et al., 2008), such that the presence of others smoking leads the individual to smoke. In particular, the purported role of learning processes in the development of addiction suggests a potential role for cue reactivity in the genesis and maintenance of dependence. Early in a smoker's 'career', prior to the onset of tolerance and the experience of withdrawal symptoms, environmental signals may serve a particularly important role in driving smoking. This may facilitate continued/escalating smoking, which may increase the likelihood of the individual developing features of dependence, tolerance and withdrawal symptoms. In addition, as dependence develops, learned associations between smoking and environmental cues may be especially important in driving smoking, as suggested by Tiffany (1990). Thus, cue reactivity may be an important process in nicotine dependence.

## 1.5 Cue reactivity and Dependence

Different approaches to the definition and measurement of dependence and different empirical studies support competing hypotheses regarding the relationship between dependence and cue-induced craving: 1) dependence is positively associated with cue-induced craving, 2) dependence is inversely related to cue-induced craving, or 3) dependence is unrelated to cue-induced craving.

### 1.5.1 Theory

Nearly all theories of addiction conceive of dependence as a loss of control over drug use. This loss of self-control over drug use (i.e., smoking) during the dependence process can be viewed as being accompanied by an increase in the influence of stimuli (e.g., smoking cues) over drug use. Conditioning models of cue-reactivity posit that, over repeated pairings of environmental stimuli with drug use, external stimuli come to elicit conditioned responses in the user. Compensatory response theory (Siegel, 1983) suggests that, over repeated pairings of drug use with a given stimulus, organisms can respond to presentation of the stimulus in a manner similar to the unconditioned effects of the drug. The nature of the conditioned response may differ depending on whether negative-reinforcement or positive-reinforcement properties of the drug are emphasized. For example, Stewart, deWit, & Eikelbloom (1984) posit that drug cues elicit reactivity that is consistent with an appetitive state, or a positive-incentive motivational state to use the drug (i.e., craving to smoke in order to obtain positive drug effects). In contrast, withdrawal-based models of cue-reactivity predict that drug cues elicit reactivity (e.g., withdrawal symptoms, such as negative affect) that is consistent with a negative-incentive motivational state (i.e., craving to smoke in order to counteract withdrawal effects). In either case, the motivation to use the drug elicited in the user is consistent with an increase in craving

(i.e., desire to use a drug). Thus, from a conditioning perspective, one could anticipate that stronger associations between smoking and environmental stimuli predict greater increases in craving upon exposure to those stimuli. If one considers 'dependence' from a perspective of the individual having formed strong associations between environmental cues and smoking, this may suggest that *more* dependent individuals demonstrate greater cue-induced craving to a wide range of stimuli.

Similarly, other theories of drug craving suggest that, over time and repeated exposure to drug cues, dependence may be associated with greater cue-induced craving. As noted above, Tiffany (1990) posits that craving only emerges when a drug use action plan is interrupted. However, this perspective accords environmental stimuli a significant role in terms of initiating automatic drug use behavioral plans. People with longer 'rehearsal' histories (i.e., more trials of smoking associated with particular stimuli) are more likely to be dependent, and to have relevant behavioral patterns consistently triggered by various smoking stimuli. When such patterns are interrupted, craving is experienced. This suggests that more dependent individuals, with stronger associations between environmental cues and smoking, may experience greater cue-induced craving in response to smoking stimuli, at least when smoking is not immediately possible (i.e., the automaticity of smoking is interrupted).

Some theories of nicotine dependence emphasize the pharmacological role of nicotine levels in driving smoking behavior. Benowitz (1992) describes consistent smoking behavior as an individual's attempt to regulate the level of nicotine in the body. Increased rate of nicotine metabolism is also positively associated with smoking rate and dependence (Benowitz, 2009; Ray, Tyndale, & Lerman, 2009), suggesting that regulation of nicotine plays a significant role in driving smoking behavior and dependence. In addition, past research suggests that as an

individual becomes more dependent, smoking behavior –and craving (Jarvik et al., 2000)- may be driven to a greater extent by interoceptive cues, like variations in blood nicotine levels (Benowitz, 2009). This also suggests that smoking in more dependent individuals is less contingent upon external cues to smoke. As such, more dependent individuals may be less sensitive to environmental smoking cues, and may demonstrate diminished cue-induced craving relative to less dependent individuals.

Other theories suggest that the relationship between dependence and cue-induced craving may differ depending on the way in which these constructs are defined. For example, Baker et al. (1987) posit that two distinct types of background craving exist (positive-affect craving and negative-affect craving), and that these reflect different, competing motivational states to use a drug: 1) an appetitive state, in which the positive-reinforcement processes are operative, and 2) a withdrawal-avoidance state, in which negative-reinforcement processes dominate. Similarly, some measures of momentary cigarette craving, commonly used in cue reactivity studies, explicitly distinguish between different types of craving. For example, the Questionnaire on Smoking Urges-Brief (QSU-Brief; Tiffany & Drobes, 2001) is a two-factor measure of cigarette craving that distinguishes between two 'types' (factors) of craving: 1) the desire and intention to smoke, emphasizing the positive, rewarding aspects of smoking; and 2) the anticipation of relief from negative affect or withdrawal with an urgent desire to smoke (Tiffany & Drobes, 2001). Depending on the 'type' of craving one seeks to measure as an outcome (e.g., positive-affect craving or negative-affect craving), dependence could be positively or negatively associated with cue-elicited craving. In addition, as noted above, different theories and measures of dependence may emphasize positive-reinforcement and negative reinforcement processes in the definition of 'dependence' to different degrees. If dependence is measured in terms of severity of the

experience of withdrawal symptoms and craving is measured in terms of one's desire to smoke in order to *relieve* withdrawal symptoms, the experience of "negative-affect" craving in response to drug cues should be associated with dependence. Alternatively, the same definition of dependence may be unrelated to an individual's desire to smoke in order to experience reward or to enhance positive affect. As such, the way in which dependence and cue-induced craving are defined and measured has significant implications for studying their potential relationship.

### 1.5.2 Different Types of Cues

Cues such as a lit cigarette function as strong cues to smoke by virtue of the fact that they are almost always associated with the act of smoking. Conklin et al. (2008) hav labeled these "proximal" cues, as they appear close to the act of smoking, are consistently associated with smoking, and are nearly universal and uniform across smokers. However, other stimuli that are commonly –although not uniformly- associated with smoking may acquire properties of smoking cues as well. For example, certain environments or situations, such as being in a bar or being around a friend who smokes, may become associated with smoking over time. Conklin has referred to these as distal cues. Although many studies have demonstrated that proximal cues like cigarettes can elicit craving to smoke, distal environmental cues (e.g., pictures of a bar) also elicit cigarette craving in daily smokers (Conklin et al., 2008).

The notion of distal cues can be expanded to encompass not only physical environments and situations, but subjective states as well. For example, smokers commonly report smoking in response to negative affect (Gilbert, Sharpe, Ramanaiah, Detwiler, & Anderson, 2000). Indeed, many negative reinforcement theories of dependence posit that dependence develops and is maintained by the desire to avoid or ameliorate negative internal states, such as withdrawal

symptoms and negative affect. (Eissenberg, 2004). Negative affect, then, may be viewed as a distal cue to smoke. Similarly, smokers may smoke in order to enhance experience of positive states. Caggiula et al. (2009) have described nicotine's role as a reinforcement enhancer. That is, nicotine acts both as a (relatively weak) primary reinforcer and also increases the reinforcing value of other stimuli. Positive reinforcement theories of dependence highlight the rewarding properties of smoking in driving smoking behavior (Glautier, 2004). If a major component of nicotine's reinforcing qualities is its role as a reinforcement enhancer, this suggests that individuals may smoke in order to enhance positive experiences. From this perspective, one could view the experience of positive affect as a cue to smoke. Thus, in addition to proximal cigarette cues, other distal cues, including affective states, may function as cues to smoke, and may therefore be capable of eliciting cigarette cravings.

### 1.5.3 Research

Some empirical studies also address the question of how dependence and cue reactivity are related. Some of these studies suggest that dependence may be inversely related to cue-induced craving. Herman (1974) argued that internal cues (e.g., withdrawal symptoms) are the primary determinant of smoking behavior in heavy smokers, while both internal *and* external cues (i.e., cigarettes in view) are significant in driving smoking behavior in light smokers. In this study, lighter smokers were more likely to smoke when cigarettes were salient in their environment (clearly illuminated) than when cigarettes were less obvious. This was not the case for heavier smokers. In both groups, duration of abstinence was associated with smoking, which may suggest that *background* craving and a desire to avoid withdrawal symptoms were important in driving smoking behavior in both groups. From this perspective, one may infer that the smoking behavior and craving of more dependent smokers are less related to external stimuli

(i.e., smoking cues) compared to those of less dependent smokers. As noted above, greater dependence appears to be associated with more regular, stereotyped patterns of smoking behavior that are independent of cues and context (Shiffman, Waters, & Hickcox, 2004; Shadel et al., 2000). Similarly, the smoking of low/non-dependent individuals (tobacco chippers) is subject to a greater degree of stimulus control than that of more dependent smokers (Shiffman & Paty, 2006). In effect, increased dependence seems to weaken the association between drug use and discriminative drug-related stimuli in the environment. A recent study (Van Gucht, Van den Bergh, Beckers, & Vansteenwegen, 2010) in which daily smokers (ranging 4-45 cigarettes per day) recorded the environmental contexts of smoking situations reported that smokers with higher FTND scores smoked in a greater number of places and situations than less dependent smokers. In other words, less dependent smokers demonstrated greater specificity with regard to their smoking behavior, as compared to high dependent smokers. In addition, Shiffman and Paty (2006) reported that elevated craving is more consistent across both smoking and non-smoking situations for heavy smokers (i.e., higher background craving) than for tobacco chippers, whose craving is generally low, but who experience occasional elevated cravings far less regularly and with greater specificity (i.e., elevated cravings only occur in certain situations). Finally, a recent study (Watson, Carpenter, Saladin, Gray, & Upadhyaya, 2010) reported that smokers with lower scores on the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) showed greater cue-induced craving in response to smoking cues than more dependent smokers. These results suggest that *less* dependent smokers may in fact demonstrate greater cue-induced craving than more dependent smokers, as the experience of cigarette craving is more tightly bound to such smoking stimuli.

Other studies, however, suggest that dependence and cue-induced craving are unrelated. Donny et al. (2008) reported that dependence predicts pre- and post-cue craving (i.e., background craving), but does not predict *cue-elicited* craving (i.e., change in craving pre-post cue exposure). In addition, a study examining fMRI blood oxygen level dependent (BOLD) responses to smoking cues suggests that cue-induced craving and severity of dependence (FTND; Heatherton et al., 1991) may be associated with independent neural networks (Smolka et al., 2006). That is, dependence and cue-induced craving predicted increased BOLD activity in separate regions of the brain in response to smoking cues. Another study examining a genetic correlate of craving (DRD4 VNTR Polymorphism) found that individuals possessing the DRD4-L polymorphism demonstrated greater cue-elicited craving than those with the DRD4-S genotype; however, the two genotypes did not predict scores on dependence measures (Hutchison, LaChance, Niaura, Bryan, & Smolen, 2002), suggetsing that cue reactivity and dependence are relatively independent constructs. In addition, previous studies (e.g., Sayette, Martin, Wertz, et al., 2005) have reported that tobacco chippers and heavy smokers do not differ with regard to *cue-induced* craving after consuming either alcohol or a placebo before exposure to a cigarette cue. As such, it may be that dependence is unrelated to the smoker's experience of *cue-elicited craving*.

In summary, different theories and extant research support different, opposing hypotheses regarding the relationship between dependence and cue-induced craving. Some research and theories support the notion that dependence is positively associated with the magnitude of cue-induced craving. Other literature suggests that dependence may be negatively associated with cue-induced craving. Still other work implies that the two constructs are unrelated. In addition,

different approaches to defining and measuring craving and dependence may have important implications regarding the nature of their relationship.

### 1.6 Clinical Utility of Cue-Reactivity

One ideal outcome of cue reactivity research would be the development of treatments that -unlike nicotine patch- ameliorate cue induced craving, and ultimately enhance quit success. However, the relationship between the magnitude of laboratory cue-induced craving and cessation outcome is unknown. In a recent review, Perkins (2009) argues that cue reactivity research may ultimately lead to a dead end unless cue-induced craving can be shown to predictive of relapse or "some other important index of smoking persistence (dependence) in the first place" (Perkins, 2009). In other words, clarifying the relationship between cue-reactivity and dependence measures would serve as an important step in determining the practical utility of laboratory cue-reactivity studies

While background or abstinence-induced craving appears to play a clear role in the addictive process, the significance of episodic or cue-induced craving in drug addiction is unknown. As noted previously, a number of studies and reviews suggest different, conflicting potential relationships between cue-induced craving and dependence. In short, understanding the relationship between cue-induced craving and dependence is important in terms of conceptualizing addiction.

### 1.7 Nicotine Dependence Measures

A variety of different measures that attempt to capture what it means to be dependent on tobacco have been established and validated in recent years. These instruments each conceive of dependence in slightly different ways, and in turn, suggest different predictions with regard to

the relationship between dependence and cue-induced craving. Some commonly used measures of dependence include: the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991), the Nicotine Dependence Syndrome Scale (NDSS; Shiffman, Waters, & Hickcox, 2004), and the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68; Piper et al., 2004). While these different measures of dependence seek to tap a common construct, they exhibit important differences.

The FTND and its predecessor, the FTQ (Fagerstrom, 1978), measure dependence along a single dimension. Specifically, the FTND relies largely upon rate of smoking, morning smoking (e.g., time until first cigarette after waking), and ability to refrain from smoking when necessary. While commonly used, the FTND omits a number of qualities, such as subjective compulsion to smoke or physical tolerance, that are typically considered to be integral to dependence.

In contrast, the NDSS explicitly considers a variety of factors in determining degree of dependence. Whereas the FTND appears to view dependence severity in light of an individual's experience of and response to withdrawal (Piper, McCarthy, & Baker, 2006), the NDSS takes a multi-dimensional approach to dependence, grounded in Edwards' (1976) theory of the alcohol dependence syndrome (Shiffman et al., 2004). Comprised of 5 subscales (*drive*, *priority*, *tolerance*, *continuity*, and *stereotypy*) and a total score, the NDSS gauges both the physiological and psychological factors associated with nicotine dependence.

Like the NDSS, the WISDM-68 takes a multidimensional approach to dependence, with a focus on various factors associated with the motivation to use drugs in a dependent way (Piper et al., 2004; Piper, McCarthy, & Baker, 2006). However, as its name suggests, the WISDM-68 was

based upon the assessment of the full range of individuals' *motives* for smoking, *not* dependence per se. In a sense, this perspective deconstructs dependence –which can be perceived as *the primary* motive for smoking- into distinct 'reasons' for smoking. In addition, the multi-scale approach to assessing a given individual's motives for smoking is typically used to generate a 'profile' of smoking motives rather than a single dependence score.

Each of these measures has been previously associated with clinical outcomes, and all demonstrate convergent validity with other measures of dependence (namely, using FTQ/FTND as basis for comparison). The FTND has been associated with cessation outcome in a number of previous studies (e.g., relapse: Westman, Behm, Simel, & Rose, 1997; Patten, Martin, Calfas, Lento, & Wolter, 2001). The NDSS has also been associated with both relapse and other dependence measures, such as the Fagerström Tolerance Questionnaire (Shiffman et al., 2004). The WISDM-68 is also associated with FTND scores, as well as with cigarette consumption and relapse (Piper et al., 2004; Piper et al., 2008). Thus, while multiple measures of dependence exist –and are convergent- they have all been shown to predict cessation outcome.

The conceptual bases and specific components and/or subscales associated with these different dependence measures support different hypotheses regarding their relationship to cigarette craving. For example, as noted above, the FTND is not grounded in any distinct conceptualization of addiction. In addition, it does not capture an individual's subjective compulsion to smoke, but emphasizes other qualities (e.g., time to first cigarette after waking, ability to tolerate periods of abstinence) that may be more strongly associated with an individual's response to *interoceptive* cues to smoke. In addition, the FTND contains no specific reference to the degree to which smoking is related to environmental stimuli. Given these features, one may expect FTND scores to be unrelated to reports of cue-induced craving.

An important feature of nicotine dependence, as conceptualized by the NDSS, is a regular, stereotyped pattern of smoking (Shiffman, Waters, & Hickox, 2004), which may reflect a decrease in the degree to which smoking is controlled by external stimuli. Given this view of dependence, the NDSS should be *inversely* related to cue-induced craving. Certain subscales of the NDSS, based upon the qualities they purport to capture, are especially relevant to this investigation. In particular, the *stereotypy* and *continuity* subscales of the NDSS reflect a reduction in the flexibility of smoking behavior, and a diminished influence of external factors on smoking (Shiffman, Waters, & Hickox, 2004). Thus, one would predict higher scores – particularly on these subscales- to be associated with decreased cue-induced craving. In addition, the *drive* subscale of the NDSS in part reflects the experience of craving and the compulsion to smoke. Consequently, one may expect that the *drive* subscale would be associated with increased cue-induced craving. However, it is possible that *drive* is more strongly linked to background craving, and thus may be unrelated to cue-induced craving.

In stark contrast to the NDSS, the WISDM-68 explicitly counts an individual's reactivity to environmental stimuli as a measure of nicotine dependence. Several subscales of the WISDM-68 are of particular interest to this study, given their direct relationship to cue-reactivity and craving. The *Cue Exposure–Associative Processes* scale specifically taps the degree to which an individual's smoking is motivated by reactivity to stimuli. One would expect an individual's scores on this scale to be associated with the degree of cue-induced craving and subsequent smoking behavior. The *Craving* scale assesses to what degree cigarette craving motivates smoking (Piper et al., 2004). However, like the *drive* subscale of the NDSS, the *Craving* subscale may be more representative of background craving, not cue-induced craving. In addition, the *Negative Reinforcement* and *Positive Reinforcement* scales purport to capture the degree to

which an individual's smoking is motivated by relief from withdrawal symptoms or anticipation of positive effects of smoking, respectively (Piper et al., 2004). Of note, one would expect scores on each of these scales to be associated with craving related to relief from withdrawal symptoms and craving related to anticipation of reward – that is, the two subscales of the QSU. Similarly, these scales should be associated with positive affect and negative affect.

Examining the relationship between different dependence measures (FTND, NDSS, and WISDM) and cue-induced craving is an important step in assessing the clinical utility of cue-induced craving and, at a more fundamental level, determining how cue-reactivity 'fits into' the experience of nicotine dependence.

## 1.8 Methodological Considerations

A number of studies have examined the relationship between dependence and cue-elicited craving in the past, but have produced inconsistent or tentative findings. Various methodological considerations, discussed below, can be extremely important in examining the relationship between dependence and cue-induced craving.

### 1.8.1 Ceiling

Ceiling effects are a particular methodological concern when examining c*ue-elicited* craving in daily smokers. For example, Donny et al. (2008) note that craving ratings for deprived, heavy smokers prior to cue exposure were "substantially above the midpoint of the scale", which may have attenuated the extent to which craving could increase. Similarly, Payne et al. (1996) noted that highly dependent, deprived smokers reported no cue-elicited craving while highly dependent, minimally deprived individuals *did* experience a craving change. Other studies have noted similar patterns, such that minimally-deprived smokers (e.g., 30 – 40 min.

abstinent) demonstrate greater *changes* in craving pre- post cue exposure than more deprived smokers (e.g., 7hrs; Sayette et al., 2001). Essentially, prolonged abstinence appears to increase *background craving* in dependent smokers, but does not increase craving in response to smoking cues. It is possible that, by virtue of increasing the level of background craving by abstinence, increases in craving in response to cues may be less salient to the individual. That is, if craving is sufficiently high already, any increase in craving elicited by cues may be comparably small and less meaningful/noticeable to the individual. Another distinct possibility is that prolonged abstinence prior to cue exposure results in ceiling effects, such that individuals are unable to report increases in craving on conventional scales beyond an already-elevated baseline. This suggests that, in order to effectively parse out the relationship between dependence and cue-elicited craving in daily smokers, a minimal deprivation period may be optimal in order to avoid washing out the saliency of cue-induced cravings with intensified background craving and in order to avoid ceiling effects in the measurement of craving. In total, these findings highlight the importance of considering degree of deprivation as it relates to potential ceiling effect when examining the relationship between cue-reactivity and dependence.

### 1.8.2 Homogeneity of Sample

Another issue with regard to exploring the relationship between dependence and cue-induced craving is the problem of range restriction of dependence levels, evident in previous studies. Past work has largely examined differences in cue-induced craving within groups of heavy smokers (Donny et al., 2008; Payne et al., 1996) or has examined differences between highly dependent daily smokers and non-dependent tobacco chippers (Sayette et al., 2001). Both of these strategies limit the extent to which the true association between dependence and cue induced craving can be investigated. In the former, range restriction leads to an artificially

homogenous group of daily smokers, decreasing the capacity to detect a relationship between cue-induced craving and dependence. In the latter, the two groups being compared represented the extremes of dependence; individuals who fell in the middle ground of dependence were omitted, which precludes application of this finding across the entire spectrum of dependence. As such, it is important to examine smokers of varying levels of dependence in order to clarify the relationship between dependence and cue-induced craving.

### 1.8.3 Multiple Cue Types

Thus far, this review has focused on reactivity to proximal smoking cues (i.e., cigarettes, or audio/visual cues comprised of explicit smoking content). However, smoking can be strongly associated with cues that are not in and of themselves specific to smoking. Craving leading up to a relapse may be triggered by a number of situations that have previously been associated with smoking (e.g., Shiffman et al., 1996). Smokers cite negative affect as a major contributor to their smoking (McKennell, 1970), and previous studies have shown that induction of negative affect increases cigarette craving in the laboratory (Tiffany & Drobes, 1990; Payne et al, 1991). Of note, inductions of negative affect in some of these studies have incorporated both smoking *and* affective stimuli, so it is not entirely clear whether affective changes themselves would trigger craving. Also, some studies have shown that negative affect from a variety of sources (e.g., abstinence induced, stress induced, pictoral cue-induced) may differ in the extent to which it is ameliorated by smoking, although source of negative affect seems to matter less in terms of cigarette craving (Perkins et al. 2010). In addition, some theory and research suggests that cigarette craving may be associated with increases in positive affect (Baker, Morse, & Sherman, 1987; Dunbar, Scharf, Kirchner, & Shiffman, 2010). As noted above, Baker et al. (1987) describe craving as being intimately related to affective states. For example, in anticipation of

lighting a cigarette, craving should be associated with positive affect. When individuals are deprived and cannot smoke, however, craving for a cigarette should be tied to negative affect. The relationship between craving and the experience of positive affect is somewhat less clear. The capacity for nicotine to enhance the reinforcing qualities of other environmental stimuli (Caggiula et al., 2009) suggests that craving may be related to the experience of positive affect as well. That is, individuals may smoke in order to enhance the experience of positive mood, or to make positive moods 'better'. Of note, this quality is specifically addressed in the *Positive Reinforcement* scale of the WISDM-68 (Piper et al., 2004).

Investigating the relationship between dependence and cue-induced craving in response to affective cues is useful in several respects. First and foremost, doing so can provide important insight into the role that 'pure' affect (i.e., disentangled from smoking content, withdrawal, or anticipation of positive effects of smoking) plays as a trigger for episodic cigarette cravings. For example, one may expect that exposure to negative affect cues may be associated with the motivation to smoke in order to improve one's mood. Alternatively, exposure to positive affect cues may be associated with the motivation to smoke in order to enhance positive affect.

One could expect the degree of the association between affective cues and craving to differ with degree of dependence on specific measures. As discussed above, different models have conceptualized dependence a function of either positive reinforcement or negative reinforcement processes (Eissenberg, 2004; Glautier, 2004). The desire to relieve negative affect plays a substantial role in 'negative reinforcement' theories of dependence, whereas the desire to enhance positive affect plays a substantial role in 'positive reinforcement' theories of dependence. If an individual demonstrates high dependence in the sense that smoking is strongly motivated by the desire to ameliorate negative affect, the association between exposure to

negative affect cues and craving to smoke should be high. The analogous argument can be made for positive affect. Specifically, scores on the *Negative Reinforcement* and *Positive Reinforcement* subscales of the WISDM, which are intended to tap –in part- the desire to relieve negative internal states and a desire to enhance an already positive experience, respectively, should be associated with craving elicited by affective cues.

However, as noted above, one important feature of dependence may be a decrease in the relationship between external cues and actual smoking behavior. That is, dependence reflects a loss of specificity with regard to smoking behavior; more dependent individuals tend to smoke whenever, wherever, in a variety of contexts. From this perspective, 'more dependent' individuals may demonstrate lower cue-induced craving in response to affective cues. For example, the *continuity* and *stereotypy* subscales of the NDSS are theoretically linked to a smoker's relative lack of discrimination regarding smoking across different situations or cues. In particular, one could anticipate that higher scores on these subscales would be associated with decreased reactivity across all cue types, including both proximal and distal cues. Examining reactivity to affective cues, which are devoid of any smoking content, may help to clarify these questions.

**1.9 Statement of the Problem**

While past research and theories suggest that dependence may be related to magnitude of cue-induced craving in either a positive or negative direction, evidence is mixed. In addition, the available data supports a number of different, conflicting hypotheses regarding the direction of the relationship between dependence and cue-induced craving. This is further complicated by the existence of a variety of different measures of nicotine dependence, which take different theoretical approaches to the conceptualization of dependence. Clarifying the relationship

between cue-reactivity and dependence is an important step in understanding the role that cue-induced craving plays in the dependence, and may help to clarify the practical utility of cue reactivity studies. In this study, I will attempt to address the relationship between dependence and cue-induced craving by examining the relationship between multiple dependence measures, their various subscales, and cue-induced craving in response to visual cues in a large sample of minimally-deprived daily smokers.

## 2.0 Method

### 2.1 Participants

207 daily smokers were recruited as part of a larger study on smoking patterns via radio, flyer, and newspaper advertisements. Individuals underwent an initial phone screen prior to enrollment to ensure that they met the following eligibility criteria: over 21 years of age, smoking for at least 3 years, and maintained a stable pattern of daily smoking for at least 1 year prior to enrollment. Individuals smoked between 5 cigarettes per day and 30 cigarettes per day. In addition, participants reported no intention to quit smoking in the next 3 months (maximum duration of the study). All individuals provided written, informed consent and were compensated for study participation. This study was approved by the University of Pittsburgh Institutional Review Board.

## 2.2 Instruments

### 2.2.1 Demographic Measures

Participants completed a number of questionnaires to assess demographic information (e.g., ethnicity, marital status, yearly income, etc.), smoking history (years smoking, cigarettes per day, preferred brand of cigarettes, etc.), history of alcohol use, and other variables of interest.

### 2.2.2 Nicotine Dependence Measures

The Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) is a well-established and widely used 6-item measure of nicotine dependence. It has adequate internal consistency (Cronbach's $\alpha = 0.67$), is associated with level of cigarette consumption, and is associated with success in quitting (Haddock, Lando, Klesges, Talcott, & Renaud, 1999; Baker et al., 2007). The FTND has been shown to consistently predict success at quitting, although its association with exposure measures (e.g., CPD) makes it less well suited for examining variations in dependence among individuals with lower cigarette consumption (Wellman et al., 2006). In addition, studies suggest that one particular item on the FTND- time to first cigarette in the morning- accounts for much of the scale's predictive utility, and may thus be a particularly important single-item index of nicotine dependence (Baker et al., 2007).

The Nicotine Dependence Syndrome Scale (NDSS; Shiffman, Waters, & Hickcox, 2004) consists of 19-items rated on a Lickert scale (1="Not at all true", 5="Extremely true"). This multi-dimensional scale of dependence is comprised of a total score and 5 subscales: drive (craving and withdrawal, and subjective compulsion to smoke), priority (preferences for smoking), tolerance (reduced sensitivity to the effects of smoking), continuity (regularity of smoking rate), and stereotypy (invariance of smoking). Internal consistency of the NDSS-T is

strong (Cronbach's α = 0.86; Shiffman, Waters, & Hickcox, 2004), although individual subscales of the NDSS have shown relatively weak internal consistencies in other studies (α = .30-.59; Piper et al., 2008). In addition, the NDSS has been shown to predict time to first lapse and relapse among smokers trying to quit (Shiffman, Waters, & Hickcox, 2004) and abstinence at 1-week, 8-weeks, and 6-months following a quit attempt (Piper et al., 2008). The measure also discriminates between heavy smokers and tobacco chippers, and is sensitive to variations in smoking behavior even in extremely light (conventionally thought of as "non-dependent") tobacco chippers (Shiffman & Sayette, 2005). The NDSS total score, and the drive, continuity and stereotypy subscales will be examined in this study. The *drive* subscale in part taps an individual's experience of craving, although this may be more associated with background craving than cue-induced craving. The continuity and stereotypy subscales are also of particular interest in this study as they reflect a perspective that higher dependence is associated with a shift toward more regular, stereotyped smoking and a decrease in stimulus-control of smoking behavior.

The Wisconsin Inventory of Smoking Dependence Motives (WISDM; Piper et al., 2004) is a multidimensional measure of dependence based upon theoretical motives for smoking that yields 13 subscale scores and a total score. The scale is comprised of 68 items rated on a Likert scale (1=''Not true of me at all'' to 7=''Extremely true of me'') (Piper et al., 2004). The scales include "Craving" (Smoking in response to craving or experiencing intense and/or frequent cigarette cravings), ''Cue exposure/Associative processes,'' (Frequent encounters with nonsocial smoking cues or perception of a strong link between cue exposure and smoking/craving to smoke) ''Negative reinforcement,'' (Tendency or desire to smoke in order to ameliorate negative internal states), and ''Positive reinforcement,'' (Tendency or desire to smoke in order to

experience a ‘‘buzz’’ or a ‘‘high,’’ or to enhance an already positive feeling or experience) among others (Piper et al., 2004; Piper et al., 2008). Psychometric properties of the test were assessed using 6 different populations (men, women, daily smokers, non-daily smokers, White, and non-White), with the overall WISDM test in each group showed strong internal consistency (i.e., Cronbach's $\alpha > 0.96$). Due to its theoretical grounding and the use of diverse populations in its construction, the WISDM may be more sensitive to different qualities of dependence that are apparent at different points over the course of the development of dependence. For example, social and environmental factors may be particularly important in motivating smoking in neophytes (Piper et al., 2004). Thus, WISDM scores may be particularly sensitive to differences in dependence in low-rate or relatively 'new' smokers. Scores on the WISDM are associated with heaviness of smoking, DSM-IV tobacco dependence (APA, 1994), and failure to quit (Piper et al., 2004). The WISDM total score and the "Craving," "Cue exposure/Associative processes," "Negative reinforcement," and "Positive reinforcement" subscales will be examined in this study. Each subscale reflects a specific perspective of nicotine dependence (e.g., "Negative reinforcement": more dependent individuals demonstrate a greater tendency to smoke in order to ameliorate negative internal states) that is theoretically relevant to cue-induced craving. In addition, recent work suggests that additional WISDM subscales (Automaticity and Tolerance) may be particularly predictors of relapse, withdrawal and various "other dependence criteria" (Piper et al., 2008). Consequently, these scales will be examined as well.

Examining each of these dependence scales will allow for a test of the way in which particular processes contributing to dependence might be related to cue-induced craving.

### 2.2.3 Cue Sets

Smoking, negative affect, and positive affect cues (active cues) will be used in this study

in order to examine smokers' cigarette craving in response to smoking and affective stimuli. Smoking cues will be used to examine the impact of proximal (smoking-specific) cues on cigarette craving. Affective *cues* will be used as a proxy to examine the impact of positive affect and negative affect *states*, which may serve as distal cues to smoke, on cigarette craving. Neutral cues will serve as the control, and will be compared to each of the active cue conditions.

Image sets (30 pictures each) for smoking, neutral, negative affect, and positive affect cues will be compiled using pictures from the International Affective Picture System (IAPS; Lang et al., 1999), International Smoking Image Series (ISIS; Gilbert et al., 1998), images used in previous laboratory studies (Tiffany et al., unpublished), and original material. Past research has shown that brief exposure to image sets can reliably elicit changes in self reported craving and affect (Carter & Tiffany, 2001). Pilot testing was conducted to ensure adequate psychometric properties of each cue set. Briefly, each cue set demonstrated adequate face validity and construct validity. The smoking cue set was associated with greater increases in cigarette craving relative to the neutral cue set. The negative affect cue set was uniquely associated with higher self-report of negative affect (and lower self-report of positive affect), while the positive affect cue set was associated with the inverse.

### 2.2.4 Measurement of Craving

The QSU-Brief is a 10-item, 2-factor scale that measures an individual's desire to smoke, intention to smoke, and anticipation of relief from negative affect upon smoking. Factor 1 reflects desire and intention to smoke, with smoking perceived as positively rewarding, while Factor 2 reflects the individual's anticipation of relief from negative affect with an urgent desire to smoke (Tiffany & Drobes, 2001). It demonstrates similar psychometric properties to its longer

predecessor, the 32-item QSU (Tiffany & Drobes, 1991), including strong internal consistency (Cronbach's $\alpha = 0.97$) and face validity of items (e.g., "I have an urge for a cigarette right now"; Cox, Tiffany, & Christen, 2001).

Cue-elicited craving will be measured as the change in score for factors 1 and 2 of the QSU-Brief after exposure to the active cue sets (post-exposure QSU – pre-exposure QSU). Each QSU factor purports to capture a different 'type' of craving, each of which is of interest in the current study. Of particular importance, QSU factor 1 should be associated with measures of dependence which emphasize positive reinforcement mechanisms (i.e., *Positive Reinforcement* subscale of the WISDM). In contrast, QSU factor 2 should be associated with negative reinforcement mechanisms involved in dependence (i.e., *Negative Reinforcement*). In addition, the use of affective cues in this study makes the distinction between factors 1 and 2 especially interesting. For example, emphasis on negative affect states captured in Factor 2 suggests that Factor 2 craving may be less applicable to the positive affect cues, and more applicable to negative affect cues. Conversely, the emphasis on the positive/rewarding effects of smoking captured in Factor 1 may have particular importance for positive affect cues *if* one considers the reinforcement enhancing properties of nicotine, which may have particular significance when individuals are already feeling good. In short, both factors of the QSU will be examined as outcome variables in this study.

### 2.2.5 Cue-induced Craving as a Change Score

As mentioned above, cue-induced craving is experienced 'on top' of background craving. In any cue-reactivity study, the issue of how to gauge an 'increase' in craving above a given level of background craving is important to consider. Most cue reactivity studies gauge cue-

induced craving via 'change scores'; that is, the difference in craving before and after exposure to a stimulus. However, some work has questioned the validity of this approach (Sayette et al., 2000). For example, on a 100 point scale, is an increase in craving from 0 to 20 comparable to an increase in craving from 60 to 80? Moreover, does a 20-point change in craving "mean" the same thing to person A as it does to person B? Another problem with the use of change scores is the potential for ceiling effects brought about by using a numerical scale. For example, if an individual rates their craving prior to cue exposure at a 95, the maximum increase in craving is 5 points. Some researchers have attempted to address the shortcoming of standard craving rating by using change in magnitude of craving (e.g., "I'm craving twice as much now after watching people smoke for 15 minutes"). There is no definitive solution to this problem at present, and it is unclear that any other approach is superior to the use of a change score. However, minimizing the deprivation period prior to cue-exposure may minimize the potential for ceiling effects. In addition, using a multi-item scale, as opposed to a single numerical scale, may help to minimize individual differences in the experience of magnitude of craving.

**2.3 Procedure**

This study was part of a larger, ongoing investigation of cue-reactivity in daily and non-daily smokers. The parent study involved 6 laboratory cue-reactivity sessions in which individuals viewed smoking, negative affect, positive affect, alcohol, non-smoking, and neutral cues in randomized order. Participants in the current study completed a total of 4 laboratory cue-reactivity sessions, each lasting approximately 1 hour, in which they viewed smoking, negative affect, positive affect, or neutral cues. Individuals were exposed to additional cue sets (i.e., alcohol, non-smoking) not examined in this study. Upon arrival at the laboratory, participants completed a breath carbon monoxide test to provide rough biochemical verification of reported

smoking prior to the session (Jarvis et al., 1987) and rated craving level on the QSU-Brief. Participants then waited approximately 30 minutes, during which they could not smoke, before beginning the cue-exposure session. Smoking pattern prior to the session, including time since last cigarette, was also measured via participant self-report in order to more precisely gauge degree of deprivation prior to the session. During deprivation, participants completed questionnaire items (i.e., demographic information, nicotine dependence measures, etc.). Previous studies have shown that perceived availability of cigarettes is important, particularly in terms of self-reported craving, and that craving in response to cues may be suppressed when cigarettes are unavailable (Carter & Tiffany, 2001). In order to avoid potential dampening of craving, all participants were aware that they would be allowed to smoke after each cue exposure (i.e., cigarettes will be available).

Immediately prior to cue exposure, participants were seated in a quiet room in front of a television screen. All participants were given roughly 3 minutes to acclimate to the cue-exposure environment. After this period, they completed a QSU-Brief questionnaire to measure pre-cue craving. Participants were instructed to pay close attention to the video monitor as images within the cue set cycled through (each picture was viewed multiple times over the course of the session). Each picture appeared on screen for 6 seconds; a similar procedure has been shown to effectively increase craving reports in previous studies (Carter et al., 2006). The cue exposure lasted for a period of approximately 3 minutes. Following exposure, individuals completed a final craving assessment. At the end of the study, participants were debriefed and compensated for their participation in the study.

## 2.4 Data Analysis

### 2.4.1 Analyses

Regression models predicting cue-elicited craving in response to smoking cues (pre-post cue change scores for QSU Factor 1, QSU Factor 2) from dependence were generated separately for each measure of dependence as follows. First, all measures of dependence were included as an aggregate in a single multiple regression model to predict cue-induced craving. The dependence aggregate consisted of the following measures: Total FTND score, time-to-first cigarette after waking, NDSS *drive*, *continuity*, and *stereotypy* subscales, and WISDM-68 *Automaticity, Tolerance, Craving, Negative Reinforcement, Positive Reinforcement*, and *Cue Exposure-Associative Processes* scales. This was done to examine whether or not the dependence measures *as a whole* explained any significant variance in craving change (i.e., change in $R^2$ upon addition of dependence measures) for each of the smoking, negative affect, and positive affect cues. If the dependence measures as an aggregate did not predict any substantial variance in reactivity, relationships between individual dependence measures were not examined separately. If the dependence variable set significantly predicted variance in craving change, models predicting cue-elicited craving in response to cues were generated separately for each measure of dependence in the aggregate. This two-step process was conducted in order to first address whether *any* aspect of dependence correlated with cue-induced craving, and to explore (if necessary) what *specific* aspects of dependence were associated with craving change. In addition, we explored potential non-linear associations as well, by plotting the data and examining quadratic relationships when appropriate.

### 2.4.2 Data Transformation

Craving change scores demonstrated a slightly skewed distribution, such that the distribution was inflated around 0 and at the extremes. In order to address this issue and to achieve a more normalized distribution of the change score data, data were square root transformed. All regression models were based upon square root transformed values, unless otherwise noted.

### 2.4.3 Covariates

Individuals may differ in the degree that they react as a function of the procedure, rather than the 'active' cue set (i.e., smoking, negative affect, positive affect). In an attempt to isolate the effect of active cues on craving, reactivity to neutral cues were included as a control variable in all models. In addition, to control for potential order effects of stimulus presentation, the session number corresponding to each cue was included as a covariate.

### 2.4.4 Sample Size

Accounting for covariates, a sample of 207 individuals will provide adequate power (0.80) to detect increases in $R^2$ at $f^2=0.085$ ($\alpha_2=0.05$) - a small-medium effect size. Thus, the sample size will provide the capacity to detect relatively small effects of dependence measures on change in craving (Cohen, 1992).

# 3.0 Results

## 3.1 Sample Characteristics

Descriptive statistics for demographics and dependence measures across participants are given in Table 1. Briefly, the final sample (n=207) consisted of moderate smokers (Mean cigarettes per day=15.92, SD=6.70), who were middle-aged (Mean age=40.81, SD=11.23), 57.43% male, and 37.62% African American. On average, participants demonstrated moderate levels of dependence (See Table 1). Prior to starting the mandatory 30-minute deprivation period, participants reported having last smoked on average 78 minutes (SD=218 minutes) before the session.

**Table 1. Descriptive statistics for demographic and dependence measures across participants (n=207)**

| Variable | Mean/% | SD |
|---|---|---|
| **Age** | 40.93 | 11.25 |
| **Gender (Male)** | 57.43% | |
| **Race (African American)** | 37.62% | |
| **Cigarettes Per Day** | 15.95 | 6.72 |
| **FTND** | 5.08 | 1.86 |
| **TTFC (minutes)** | 20.72 | 30.89 |
| **NDSS (Total)** | -0.20 | 1.10 |
| **Drive** | -0.28 | 1.15 |
| **Stereotypy** | 0.07 | 0.90 |
| **Continuity** | -0.48 | 1.05 |
| **Tolerance** | -0.25 | 0.99 |

| | | |
|---|---|---|
| **Priority** | -0.00 | 0.94 |
| **WISDM (Total)** | 54.10 | 13.64 |
| **Automaticity** | 4.38 | 1.55 |
| **Tolerance** | 4.74 | 1.38 |
| **Positive Reinforcement** | 4.21 | 1.38 |
| **Negative Reinforcement** | 4.38 | 1.43 |
| **Craving** | 4.93 | 1.43 |
| **Cue Exposure** | 4.73 | 1.25 |

### 3.2 Background Craving

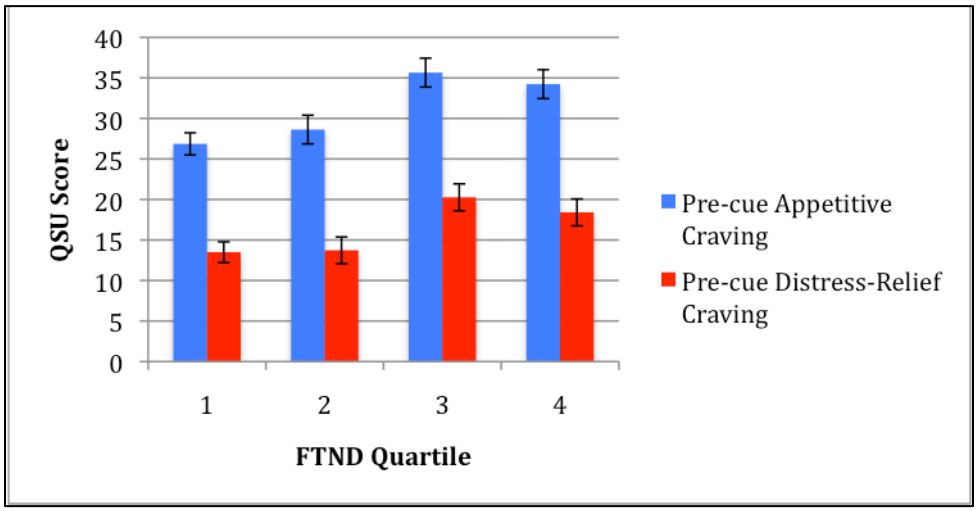
Mean pre- and post-cue appetitive and distress-relief craving scores across all cues are presented in Table 2. Across all cues, participants reported moderate pre-cue craving, but craving reports spanned the entire range of the craving scale. Appetitive craving (QSU F1) scores averaged 30.62 (SD=14.51), and distress-relief craving (QSU F2) averaged 15.95 (SD=12.39). For all cues, the dependence variable set was a significant predictor of pre-cue appetitive (Partial $R^2$=0.13, p<0.0001) and distress-relief craving (Partial $R^2$=0.17, p<0.0001). As expected, individuals in the highest quartile of FTND, NSDD, and WISDM scores demonstrated higher background (i.e., post-deprivation, pre-cue) craving relative to those with lower dependence scores (p< 0.0001) across all cues (See Figure 1).

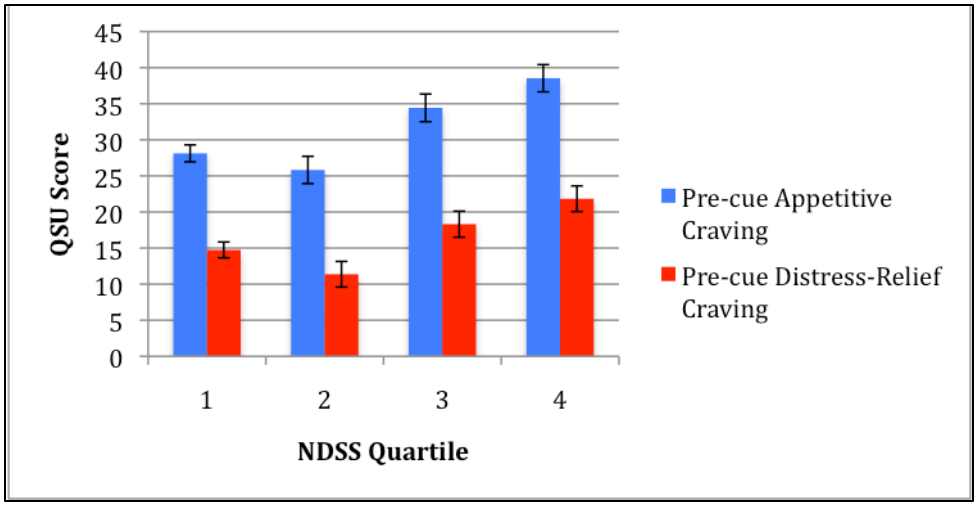
Both appetitive and distress-relief craving increased over the 30 minute deprivation period across all cues, and there were no differences in the magnitude of this change by cue type (See Figure 2).

**Table 2. Craving reports by cue.**

| Craving | Neutral (M(SD)) | Smoking | Positive | Negative |
|---|---|---|---|---|
| *Appetitive craving (QSU Factor 1)* | | | | |
| Pre-cue | 29.23 (14.87) | 30.18 (14.72) | 30.57 (14.64) | 30.75 (15.66) |
| Post-cue | 31.17 (15.00) | 34.02 (14.68) | 31.55 (14.65) | 32.91 (15.22) |
| *Distress craving (QSU Factor 2)* | | | | |
| Pre-cue | 14.85 (11.88) | 16.30 (13.00) | 15.64 (12.35) | 16.07 (12.70) |
| Post-cue | 16.26 (12.95) | 19.08 (14.09) | 16.11 (12.67) | 18.66 (13.94) |

**Figure 1.**




45
40
35
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25
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0
QSU Score
1
2
3
4
NDSS Quartile
Pre-cue Appetitive Craving
Pre-cue Distress-Relief Craving

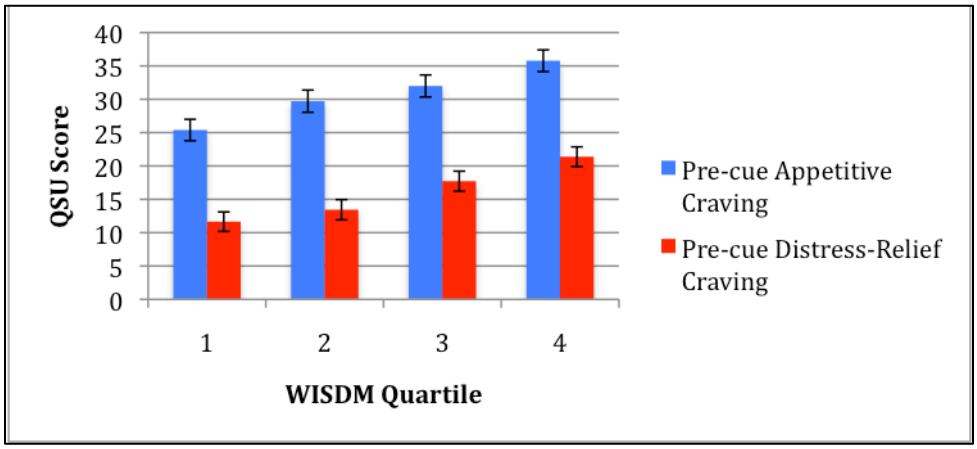
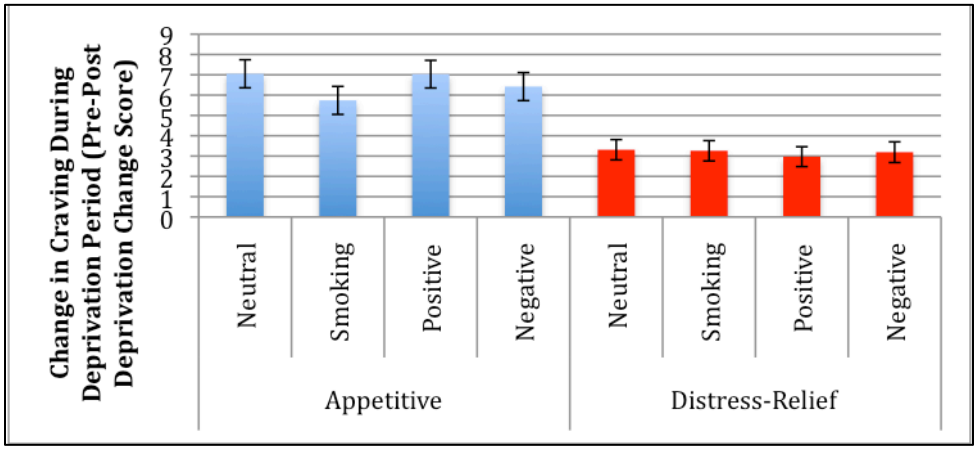

40
35
30
25
20
15
10
5
0
QSU Score
1
2
3
4
WISDM Quartile
Pre-cue Appetitive Craving
Pre-cue Distress-Relief Craving

**Figure 2.**


Change in Craving During Deprivation Period (Pre-Post Deprivation Change Score)
9
8
7
6
5
4
3
2
1
0
Neutral
Smoking
Positive
Negative
Neutral
Smoking
Positive
Negative
Appetitive
Distress-Relief

### 3.3 Change in Craving in Response to Cues

Appetitive and distress-relief craving increased over the course of nearly all cue exposures (including neutral), although the positive affect cue did not increase distress-relief craving (see Table 2). Across all cues, participants tended to report moderate post-cue craving, and values reports spanned the entire range of the craving scale (see Figure 3).

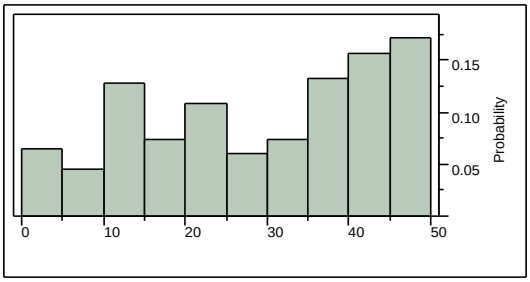
There was a main effect of cue type on change in pre-post cue craving (See Figure 4). Controlling for session number, smoking cues significantly increased both appetitive ($B=0.51$, $SE=0.17$, $p<0.01$) and distress-relief craving ($B=0.36$, $SE=0.16$, $p<0.05$), relative to neutral cues. Conversely, positive affect cues significantly decreased appetitive ($B=-0.37$, $SE=0.17$, $p<0.05$) and distress-relief ($B=-0.41$, $SE=0.16$, $p=0.01$) craving relative to neutral cues. There was a trend for negative affect cues to increase distress-relief craving ($B=0.27$, $SE=0.16$, $p=0.096$). Examining each cue separately, session number was not associated with change in appetitive or distress-relief craving, nor was the cue seen in the previous session associated with craving change (i.e., there were no carry-over effects). As cigarette consumption before each session was not standardized across participants, there was also concern that degree of abstinence prior to cue exposure may have influenced results. Results did not differ when controlling for reported time since last cigarette.

**Figure 3.**

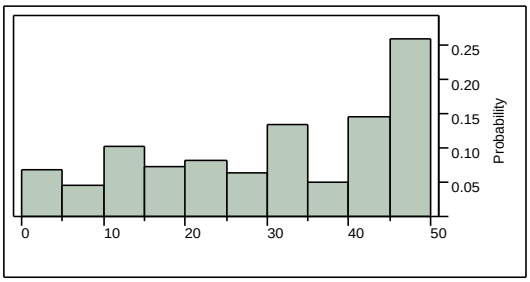
***Pre- and Post-Cue Craving Scores***

*Neutral Cue*

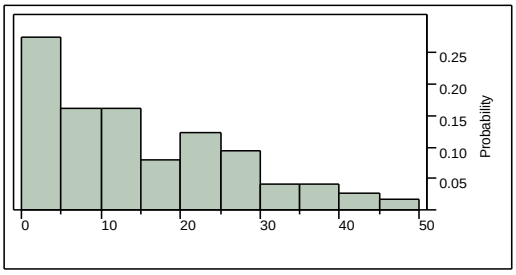
**Pre-Cue Appetitive Craving**



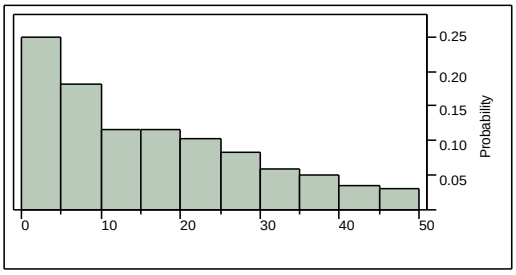

**Post-Cue Appetitive Craving**




**Pre-Cue Distress-Relief Craving**

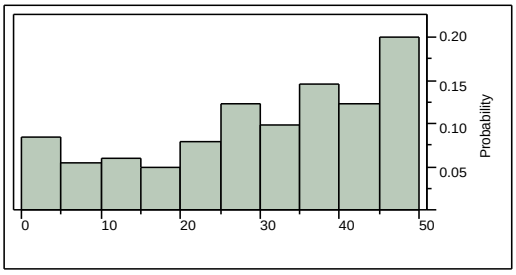



**Post-Cue Distress-Relief Craving**

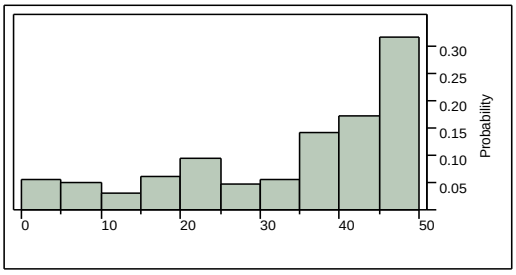



*Smoking Cue*

**Pre-Cue Appetitive Craving**

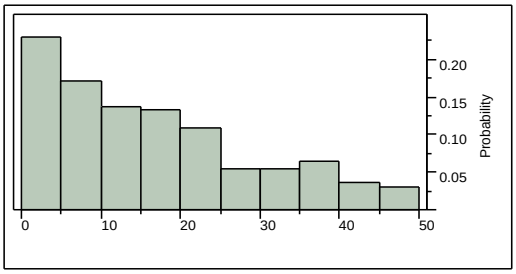


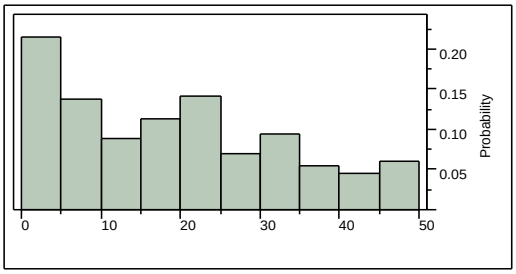

**Post-Cue Appetitive Craving**




**Pre-Cue Distress-Relief Craving**

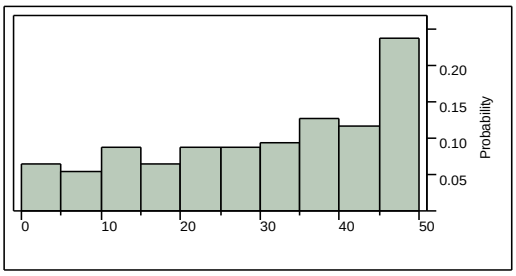
**Post-Cue Distress-Relief Craving**

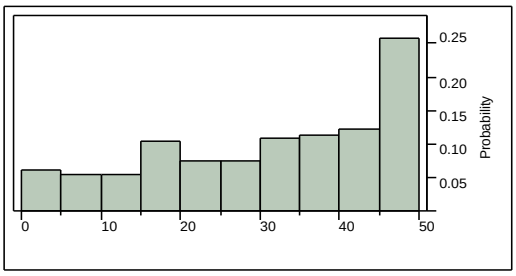


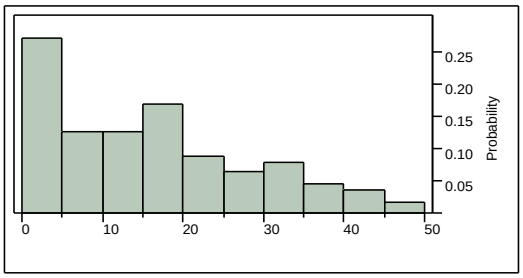

*Positive Affect Cue*

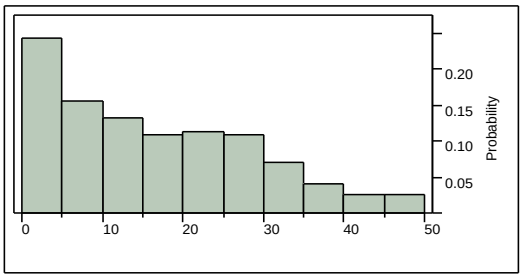
**Pre-Cue Appetitive Craving** **Post-Cue Appetitive Craving**



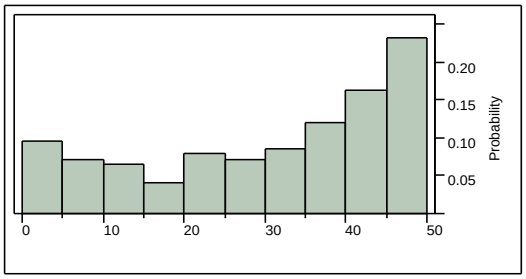

**Pre-Cue Distress-Relief Craving** **Post-Cue Distress-Relief Craving**

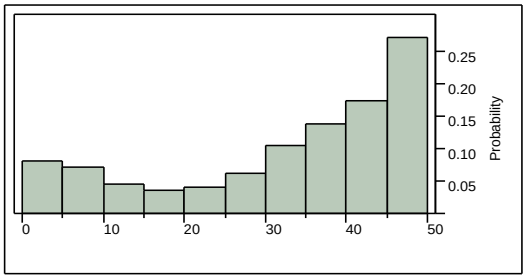


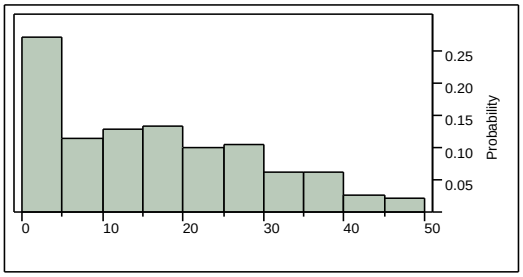

*Negative Affect Cue*

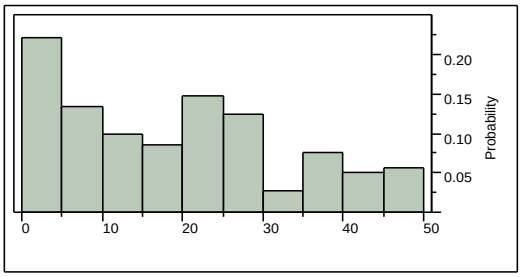
**Pre-Cue Appetitive Craving** **Post-Cue Appetitive Craving**



**Pre-Cue Distress-Relief Craving** **Post-Cue Distress-Relief Craving**

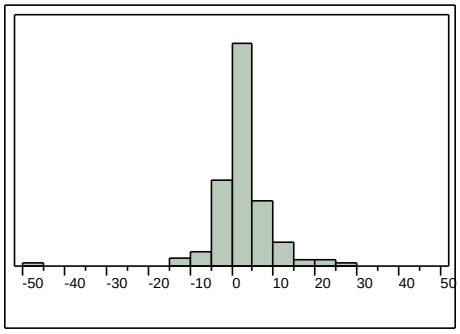


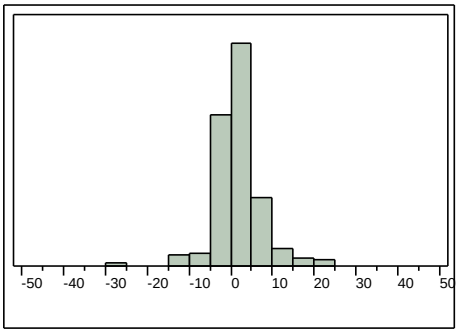




***Craving Change***

*Neutral Cue*

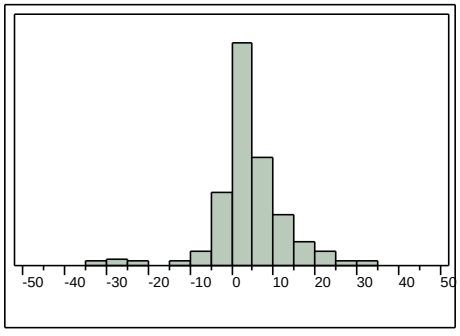
**Appetitive Craving** **Distress-Relief Craving**

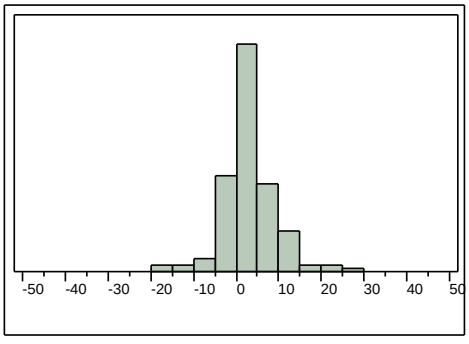



*Smoking Cue*

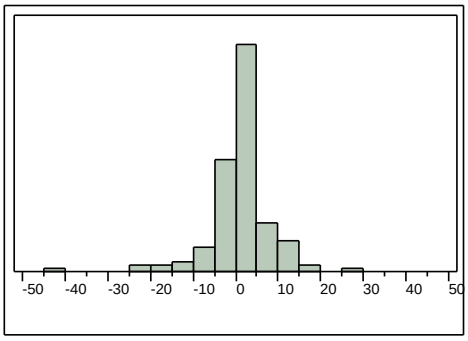
**Appetitive Craving** **Distress-Relief Craving**



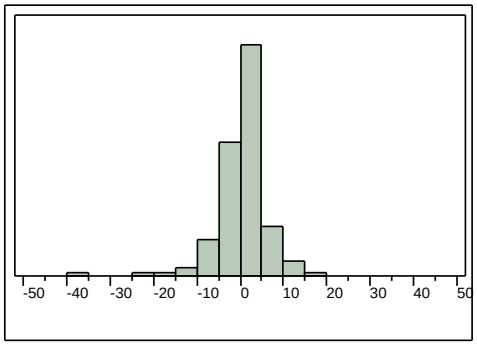



*Positive Affect Cue*

**Appetitive Craving**

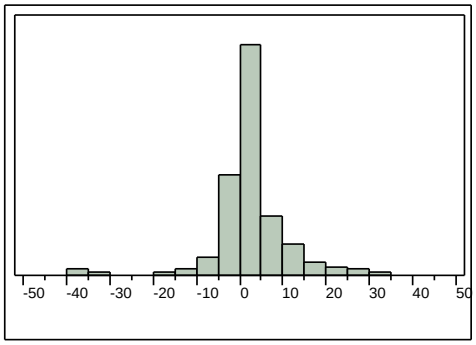



**Distress-Relief Craving**




*Negative Affect Cue*

**Appetitive Craving**




**Distress-Relief Craving**

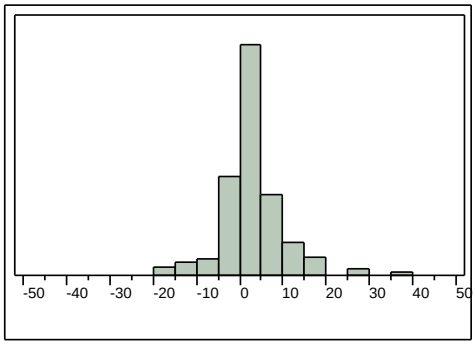
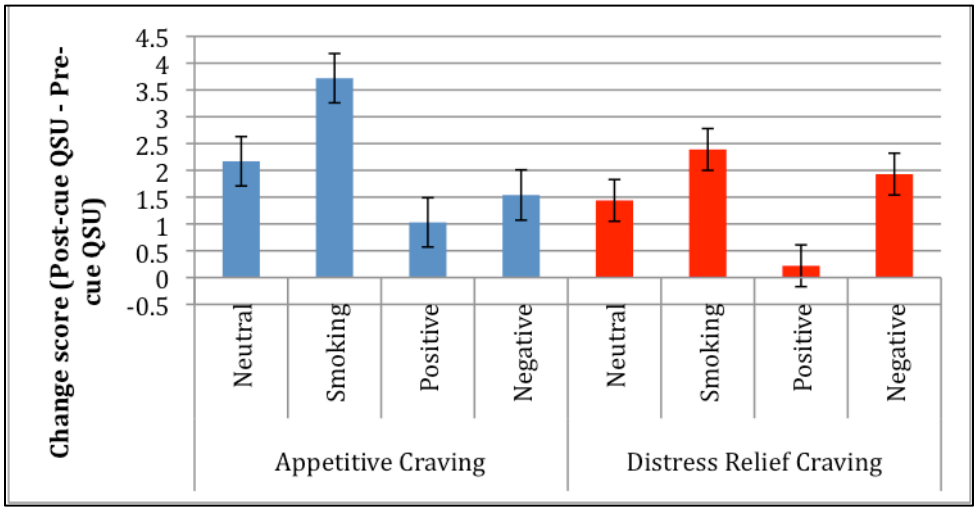


**Figure 4.**




### 3.4 Dependence and Craving Change

All analyses for active cues controlled for session number and reactivity in response to the neutral cue set. Controlling for change in craving in response to neutral cues, dependence generally did not correlate with cue-induced craving for any of the active cues.

#### 3.4.1 Smoking Cue

When controlling for reactivity to the neutral cue and session number, dependence scores did not significantly explain any variance in the change in appetitive (Partial $R^{2=}$0.035, p=0.82) or distress-relief (Partial $R^{2=}$0.012, p=0.99) craving in response to the smoking cues. Change in craving across quartiles of the FTND, NDSS, and WISDM is displayed graphically in Figure 5. When neutral reactivity was omitted from the models, results did not change.

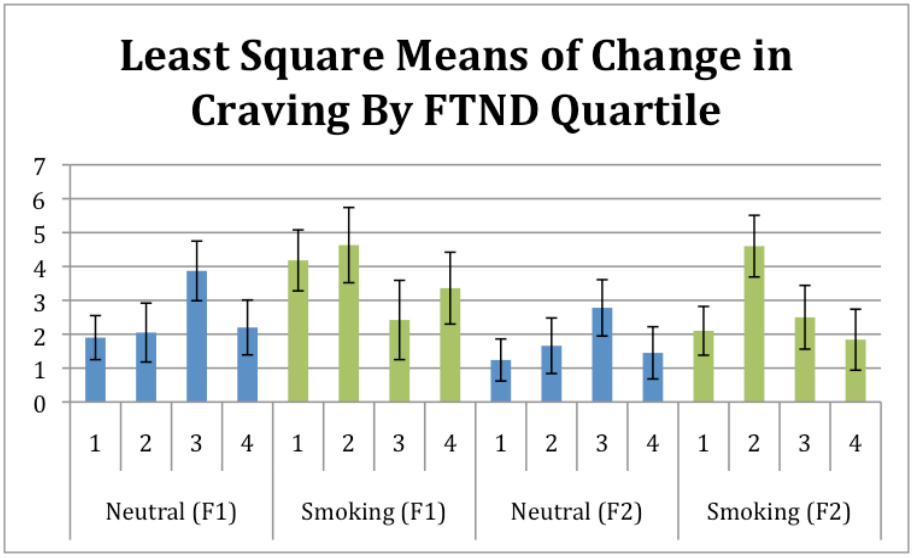
### 3.4.2 Negative Affect Cue

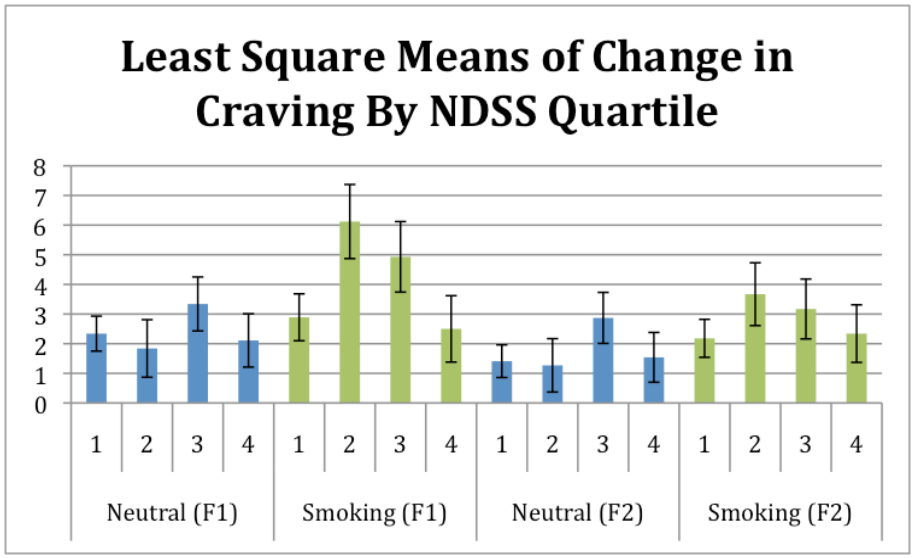
Controlling for neutral reactivity and session number, dependence scores did not significantly correlate with change in appetitive craving (Partial $R^{2=}$0.042, p=0.60) in response to negative affect cues. However, as a variable set, the dependence measures correlated with change in distress-relief craving at a trend level (Partial $R^{2=}$0.10, p=0.075). When neutral reactivity was omitted from the models, results did not change. In an exploratory analysis examining only FTND scores (controlling for session number and neutral reactivity), individuals with *greater* FTND scores demonstrated greater increases in distress-relief craving in response to the negative affect cues (B=0.17, S.E. = 0.077; p=0.03). No other measures of dependence were associated with change in craving in response to negative affect cues.

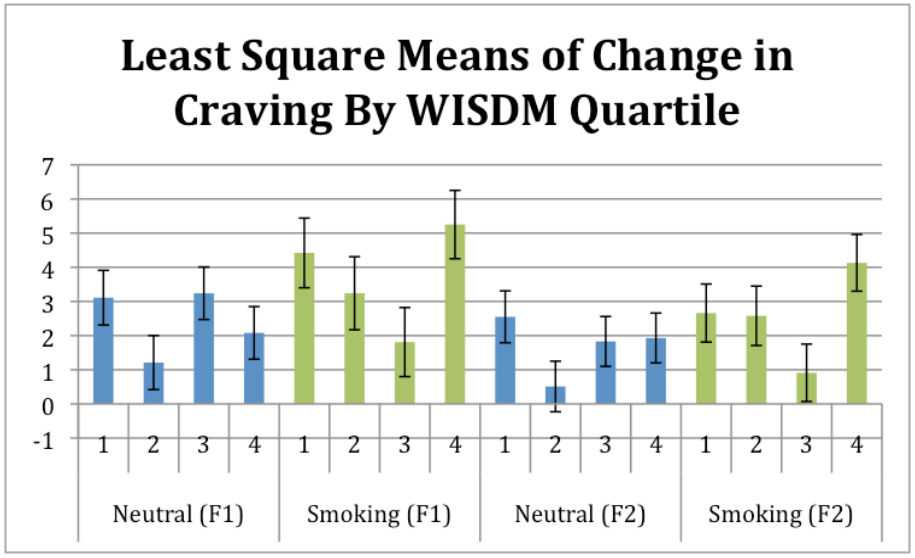
### 3.4.3 Positive Affect Cue

After controlling for neutral reactivity and session number, dependence did not significantly explain any variance in change in appetitive (Partial $R^{2=}$0.021, p=0.91) or distress-relief (Partial $R^{2=}$0.062, p=0.19) craving in response to positive affect cues. Omitting neutral reactivity from the models did not change the results.

**Figure 5.**


Least Square Means of Change in Craving By FTND Quartile
7
6
5
4
3
2
1
0
1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4
Neutral (F1)
Smoking (F1)
Neutral (F2)
Smoking (F2)


Least Square Means of Change in Craving By NDSS Quartile
8
7
6
5
4
3
2
1
0
1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4
Neutral (F1)
Smoking (F1)
Neutral (F2)
Smoking (F2)




### 3.5 Post-hoc Analyses

In an attempt to better understand this pattern of results, we conducted a number of additional post-hoc analyses.

#### 3.5.1 Non-linear Effects

Since graphs of craving change across quartiles of dependence scores suggested potential curvilinear effects across smoking cues, we examined quadratic effects of dependence scores on appetitive and distress-relief craving change. No significant quadratic effects were observed.

#### 3.5.2 Variance in Craving Change

We also examined whether or not *variance* in craving change differed across the range of dependence scores. This is a potentially important relationship that would not have been immediately apparent from the regression analyses described above. Scatter plots examining change in craving in response to smoking cues did not suggest any consistent relationship between dependence and variance in craving scores about the regression lines. Further tests for heteroscedasticity (i.e., Modified Levene's Test) on regression models predicting craving change

from dependence scores revealed no significant relationship between variance in craving change residuals and dependence scores.

### 3.5.3 Neutral Cue

Within the neutral cue set, there was no association between change in appetitive or distress-relief craving and dependence.

### 3.5.4 Gender

We examined whether or not the relationship between dependence and reactivity was moderated by gender. There was no evidence of a gender by dependence interaction.

### 3.5.5 Degree of Deprivation

Across all active cues, results did not differ when controlling for time since last cigarette (i.e., degree of abstinence prior to the session).

### 3.5.6 Multicollinearity

For all multivariate models in which measures of dependence were included and grouped as a variable set, we examined variable inflation factor (VIF) values for each predictor, in order to assess the potential influence of multicollinearity, or excessive shared variance across predictors, on results. Since multicollinearity can potentially distort estimates of effects and standard errors, and is common when variables may be highly correlated, this was a serious concern. For all cues, VIF scores for the dependence variables were below 10, meaning they fell within the conventionally acceptable range (Smoking: Appetitive: VIF Range = 1.12-8.55; Distress-relief: VIF Range = 1.12 – 8.54; Negative Affect: Appetitive: VIF Range = 1.11-8.73; Distress-relief: VIF Range = 1.12 – 8.71; Positive Affect: Appetitive: VIF Range = 1.11-8.92;

Distress-relief: VIF Range = 1.14 – 8.92), suggesting that the validity of the results for the multivariate regression models was not compromised by effects of multicollinearity.

### 3.5.7 Ceiling Effects

Reactivity was measured as change in craving on a fixed scale, and investigators using similar methods have expressed concern over ceiling effects influencing results. One concern regarding ceiling effects was that more dependent individuals would be selectively affected, such that elevated baseline craving scores would constrain the degree to which the most dependent smokers could report increases in craving. To assess whether ceiling effects might have precluded observation of craving increases among the most dependent smokers, we examined all tests with and without individuals in the top 10% of QSU scores (Total score>43). There were no differences in results.

In addition, within cue type there were no differences in *change in craving* between individuals with higher dependence (top quartile) and those with lower dependence scores (all others), and there was no evidence that more dependent individuals "maxed out" reported craving on the scale. In other words, cue-induced craving was not constrained or skewed because the most dependent smokers could not sufficiently report increases in craving. It is thus unlikely that ceiling effects influenced subsequent results.

### 3.5.8 Neutral-Active Cue Difference

Finally, in an attempt to understand whether the use of a pre-post cue change score may have limited our ability to detect a relationship between dependence and cue-induced craving for the active cues, we *also* conducted analyses in which cue-induced craving was conceptualized as the difference between *post-cue* craving in response to the active cues and *post-cue* craving in

response to the neutral cue. The pattern of results for the multiple regression models (i.e., including all dependence measures in the model) did not change.

## 4.0 Discussion

This study examined the relationship between several self-report measures of nicotine dependence and cue reactivity – the change in craving in response to different types of visual cues, in a sample of daily smokers. As in previous studies (e.g., Donny et al., 2008) dependence was a significant predictor of background (pre-cue) craving but was largely unrelated to reactivity, per se (i.e., *changes* in craving in response to cues considered to be smoking-relevant). This pattern of results for the active cues (smoking, negative affect, positive affect) remained largely consistent regardless of whether or not we controlled for reactivity in response to the neutral cue and time since last cigarette.

One interpretation of these findings is that reactivity to smoking-relevant cues and dependence are distinct, largely unrelated constructs. This conclusion has important implications for the way in which dependence and reactivity are conceptualized. A variety of factors, including physiological, psychological, social, legal, environmental, and others, can influence smoking behavior. Dependence and reactivity may simply reflect different factors that function in concert with many others to shape a person's smoking. Dependence may be one (perhaps particularly important) contributor to a persistent pattern of drug use, but one that does not encompass the way in which a person's smoking is affected by the environment. While more recent 'dependence' scales, such as the WISDM-68 have chosen to include reactivity to cues as a facet of nicotine dependence (Piper et al., 2004), cue-reactivity *is not* included in many other definitions and measures of dependence, which tend to emphasize features of escalated compulsive use, tolerance and/or withdrawal (e.g., APA, 1994). If dependence and reactivity

can be disentangled, perhaps they capture, respectively, 'internal' and 'external' influences on smoking behavior. The concept of nicotine dependence –absent cue reactivity – may more closely represent internal drivers of smoking, such as tolerance/withdrawal and regulation of blood nicotine levels. If the way in which a person responds to environmental cues is unrelated to 'dependence', cue-reactivity may uniquely capture the extent to which smoking is affected by the outside world. In this respect, dependence and cue reactivity may be viewed as complementary but conceptually distinct contributors to smoking behavior. Perhaps, similar to Herman & Kozlowski's (1984) boundary model for smoking behavior, dependence plays a significant role in perpetuating a stable or global pattern of smoking within certain parameters. That is, dependence may reflect the drive to smoke regularly in order to maintain nicotine levels within certain limits. In contrast, reactivity to environmental cues may account for moment-to-moment variations in smoking behavior within this basic framework of average smoking behavior. The two need not be correlated in order for both constructs to be relevant to smoking, and for both constructs to inform our understanding of why people continue to smoke- and fail to quit.

Alternatively, that reactivity and dependence were consistently unrelated in this study may suggest that *laboratory cue-induced craving* does not generalize to a smoker's experience in the real world. First, laboratory cue-induced craving as a phenomenon may not generalize to the majority of smoking occasions. Tiffany's (1990) perspective posits that drug *use* is largely automatic. In contrast, *craving* requires non-automatic, conscious processing, and is only experienced when automatic smoking patterns are interrupted (e.g., when smoking is not allowed or when individuals are asked to consciously reflect on their craving state). Thus, while a smoker might report a robust increase in craving in response to laboratory cues, that process does not

necessarily represent the majority of instances in which a person smokes, at least when cigarettes are readily available and the person is not trying to quit. In addition, in a review of 4 studies employing the cue-availability paradigm, Tiffany and colleagues report a fairly weak association between cue-induced craving and latency to smoke ($r = 0.23$; 5% of variance; Tiffany, Warthen, & Goedeker2009). Consequently, cue-induced craving in the laboratory may represent a very unique and context-specific phenomenon that does not adequately reflect typical smoking behavior, and may not even strongly correlate with *immediate* smoking behavior. Dependence measures, however, are intended to describe global and behaviorally relevant aspects of real-life smoking behavior (e.g., persistence of smoking, success during a quit attempt). If cue-induced craving in the laboratory is not strongly correlated to real-life smoking experiences, it is thus not surprising that cue-induced craving would be unrelated to dependence scores.

Another possible interpretation of null findings is that laboratory cue-induced craving is simply an insufficient gauge of cue reactivity *in the real world*, due to poor ecological validity of smoking-relevant cues. Of note, some of the most compelling evidence demonstrating a relationship between environmental cues, craving and actual smoking behavior (cessation outcome) comes from studies using EMA to examine smoking in real-world environments (Shiffman et al., 1996; 1997). In contrast, as summarized by Perkins (2009), laboratory studies of cue reactivity consistently fail to observe any relationship between cue-induced craving in the laboratory and clinical outcomes during a quit attempt. Thus, ecological validity of the cue exposure (i.e., real environment vs. cues in the laboratory) might be an important factor in assessing the relationship between cue-reactivity and dependence. As noted above, dependence measures seek to capture global information about an individual's smoking behavior in the *real world*, not in response to laboratory manipulations. Our use of visual cues to induce cigarette

craving in the laboratory –while seemingly effective at generating significant craving change– may simply not capture how the individual responds to real-world smoking cues (e.g., seeing a friend light a cigarette in a favorite bar). This disconnect between the context of the assessment (the lab) and the outcome of interest (e.g., smoking persistence in real life) may preclude the detection of any potential relationship between cue reactivity and dependence. Future studies may benefit from examining this relationship using more robust and ecologically valid smoking cues, such as virtual reality cues (e.g., Baumann & Sayette, 2006) or personalized environmental cues (Conklin, 2006), in order to determine whether or not ecological validity of the smoking cue influences the relationship between laboratory cue-induced craving and dependence.

Relative to previous work, the current study demonstrates some important similarities and differences. In a sample of heavy smokers culled from different subsamples, Donny et al. (2008) reported no relationship between dependence and laboratory cue reactivity (pre-post change score). Of note, this study examined heavier, deprived smokers and utilized a different type of smoking cue (in vivo) than the present study. Despite important differences in sample and paradigm across the two studies, the similar patterns of null findings may suggest that dependence and reactivity to laboratory smoking cues are truly unrelated. Another more recent study (Watson et al., 2010) examined the relationship between FTND and cue-induced appetitive craving in response to in vivo smoking cues and affective imagery cues. The study reported that less dependent individuals demonstrated greater changes in appetitive (QSU F1) craving in response to cues compared to more dependent smokers. While the current study differs in many important ways from Watson et al. (e.g., use of a pre-post cue change score, use of visual smoking cue), the two share a number of commonalities. For example, both focused on a sample of moderate *ad lib* smokers and examined the relationship between dependence measures

(FTND) and QSU scores in response to cues. It is unclear why results differ across the two studies. The use of differential post-cue craving (Post-cue Smoking- Post-cue Neutral) rather than a change score does not appear to account for the discrepant results, as conceptualizing cue-reactivity as differential post-cue craving in the current student yielded similar null findings. In addition, it is unclear whether or not the use of an in vivo (vs. visual) smoking cue may account for these differences, as the visual smoking cue *did* produce significantly higher changes in craving compared to the neutral cue. Furthermore, Donny et al. (2008) report similar null findings in response to an in vivo smoking cue, suggesting that the use of a less robust smoking cue in the current study may not entirely explain our null findings. Additional work is needed in order to understand how the relationship between dependence and cue-induced craving may differ across different types of cues.

This study had several limitations, which may have influenced results. First, while participants were instructed to smoke "as usual" prior to the session and were required to remain abstinent for at least 30 minutes prior to cue exposure, considerable variability existed both between and within individuals (across sessions) with regard to the reported duration of abstinence. Because this study was part of a larger study on cue-reactivity and ad lib smoking patterns, which included non-daily and daily smokers, it was impractical to require all individuals to smoke at the outset of each session, as this may have represented a significant deviation from "ad lib" smoking, particularly for non-daily smokers. However, controlling for reported duration of abstinence did not affect results. Future studies investigating the relationship between dependence and cue reactivity in daily smokers should seek to standardize the period of deprivation more rigidly across all participants, in order to control for potential variations in abstinence-induced craving during cue exposure. This is particularly important, given that many

measures of dependence incorporate abstinence induced craving and withdrawal symptoms (and ability to tolerate them) in conceptualizing dependence. Participants also provided answers to all dependence measures within a single questionnaire packet. It is possible that the repetition of questions may have systematically limited variability in dependence scores, clouding any potential relationship between dependence and cue induced craving. This seems unlikely however, as nearly all measures of dependence demonstrated a normal distribution, and mean scores were comparable to those described in previous studies. In addition, the dependence scores were related to background craving, so reduced variability does not appear to be a problem.

Similarly, limited variability in craving change may have reduced our ability to detect a relationship with dependence. The levels of pre-cue, post-cue, and change in craving observed in this study were relatively modest. However, there was no evidence of ceiling or floor effects in craving reports; subjects reported cravings that tended to fall within the middle of the craving scale. Despite this, craving reports spanned the entire range of the craving scale. In addition, findings were consistent with prior studies, in that the 'proximal' smoking cue provoked increases in craving that were significantly larger than those observed in the neutral cue condition. Moreover, the study had sufficient power to detect even very modest relationships (change in model $R^2$) between dependence and change in craving. Thus, it seems unlikely that insufficient change in craving in response to cues obscured any relationship between dependence and reactivity. In addition, it is also possible that the use of two controls (pre-cue craving, neutral reactivity) may have reduced the 'available' variance in craving change left to be explained by dependence, and thus diminished our ability to detect a relationship. However, results were largely unchanged even when neutral reactivity was not included as a covariate, and when only

differential post-cue reactivity was examined, so over-control does not appear to explain our null findings.

This study also had several notable strengths. As noted above, our sample size (n=207 smokers, k=840 reactivity sessions) provided sufficient power to detect even modest effect sizes. This sample is larger than any comparable study that has examined the relationship between dependence and cue induced craving. Thus, we were well-positioned to detect any relationship between dependence and cue-induced craving had one existed. In addition, our sample was not limited to moderate- heavy smokers, but included individuals who smoked as little as 5 CPD. Thus, we were able to examine this relationship across a broad range of smokers. Finally, we examined a number of different measures of dependence. While type I error was a concern, due to multiple tests, the absence of any significant relationship across tests suggests that truly no relationship between dependence and cue-induced craving was present in our data.

## 5.0 Future Studies

While the current study addresses an important step in better understanding the meaning and utility of laboratory cue-induced craving, many important questions remain unanswered. For example, the current study only examined visual (pictoral) smoking and affect cues, which may be less robust/effective in provoking craving (Carter et al., 2006). As noted above, it is unclear whether or not the relationship between dependence and cue-induced craving may differ across different types of distal smoking cues (e.g., in vivo, visual), as previous studies using in vivo cues report inconsistent findings (i.e., Donny et al., 2008; Watson et al., 2010). Future studies may want to explore the relationship between dependence and cue-induced craving in response to different types of smoking cues. Also, the current study only examined this relationship

among a sample of daily smokers. It is unclear whether or not this relationship may differ among individuals who smoke only intermittently. Future studies may wish to examine the relationship between dependence and cue-induced craving in non-daily smokers. In addition, the relationship between dependence and actual *smoking behavior* in response to laboratory cues is unclear. Additional work examining the complex relationship between cue exposure, craving, and smoking behavior will contribute to a better understanding of how –*if at all*- laboratory cue-reactivity may be related to smoking behavior.

## 6.0 Conclusion

In short, this study supports **did not** support the notion that nicotine dependence and laboratory cue-induced craving in response to smoking and affect cues are related. This may suggest that dependence and reactivity to environmental stimuli reflect distinct aspects of addictive behavior. Alternatively, it may suggest that reactivity –as assessed in the laboratory- is simply unrelated to smoking behavior in the real world. Future studies should examine the relationship between reactivity to cues, dependence, and actual smoking behavior, in order to better understand how reactivity to cues and nicotine dependence may function independently or synergistically to influence smoking behavior.

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