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Evidence for greater cue reactivity among low dependent vs. high dependent smokers

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Abstract

Introduction—Cue reactivity paradigms are well-established laboratory procedures used to examine subjective craving in response to substance-related cues. For smokers, the relationship between nicotine dependence and cue reactivity has not been clearly established. The main aim of the present study was to further examine this relationship.

Methods—Participants (N=90) were between the ages 18–40 and smoked ≥ 10 cigarettes per day. Average nicotine dependence (Fagerström Test for Nicotine Dependence; FTND) at baseline was 4.9 (SD=2.1). Participants completed four cue reactivity sessions consisting of two in vivo cues (smoking, neutral) and two affective imagery cues (stressful, relaxed), all counterbalanced. Craving in response to cues was assessed following each cue exposure using the Questionnaire of Smoking Urges—Brief (QSU-B). Differential cue reactivity was operationally defined as the difference in QSU scores between the smoking and neutral cues, and between the stressful and relaxed cues.

Results—Nicotine dependence was significantly and negatively associated with differential cue reactivity scores in regards to hedonic craving (QSU factor 1) for both in vivo and imagery cues, such that those who had low FTND scores demonstrated greater differential cue reactivity than those with higher FTND scores ($\beta = -.082$; $p = .037$; $\beta = -.101$; $p = .023$, respectively). Similar trends were found for the total QSU and for negative reinforcement craving (QSU factor 2), but did not reach statistical significance.

Discussion—Under partially sated conditions, less dependent smokers may be more differentially cue reactive to smoking cues as compared to heavily dependent smokers. These findings offer methodological and interpretative implications for cue reactivity studies.

Keywords

cue reactivity; craving; dependence; smoking; nicotine

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1. INTRODUCTION

Cue reactivity paradigms are well-established and specific laboratory procedures to examine craving in response to drug-paired cues. Cue-specific craving is most commonly measured with various self-report indices of craving (Carter & Tiffany, 1999; Ferguson & Shiffman, 2009) and is commonly viewed as a form of stimulus control (i.e., the ability of environmental cues to elicit craving) that develops following repeated pairings between drug administration and specific environmental and/or affective stimuli.

Cue reactivity methods are valid methods to experimentally test the likelihood of relapse and treatment outcome (Donny, Griffin, Shiffman, & Sayette, 2008; Ferguson & Shiffman, 2009; Payne, Smith, Adams, & Diefenbach, 2006; Swan, Ward, & Jack, 1996; Waters et al., 2004). Also, to the extent that treatments are designed with the purpose of diminishing craving, cue reactivity methodology could serve as an early method to test the potential efficacy of treatments prior to large clinical trials (Davies, Willner, & Morgan, 2000; Waters et al., 2004). Some investigators have proposed that cue reactivity could be used as treatment itself, (i.e., through cue exposure/extinction), though the therapeutic significance of this approach as a stand-alone intervention has been questioned elsewhere (Brandon, Piasecki, Quinn, & Baker, 1995; Conklin & Tiffany, 2002a, 2002b).

Numerous studies have examined factors that may influence cue reactivity among smokers, including perceived drug availability (Wertz & Sayette, 2001), affect (Taylor, Harris, Singleton, Moolchan, & Heishman, 2000), level of nicotine deprivation (Geier, Mucha, & Pauli, 2000; Payne, Smith, Sturges, & Holleran, 1996), gender (Niaura et al., 1998; Saladin, Carpenter, Gray, LaRowe, DeSantis, & Upadhyaya, under review; Waters et al., 2004), and manipulation of cues (Conklin & Tiffany, 2001). Another important factor that has been examined is the relationship between nicotine dependence and cue reactivity (Davies et al., 2000; Donny et al., 2008; Knott et al., 2008; McClernon, Kozink, & Rose, 2008; Payne et al., 1996; Shadel, Shiffman, Niaura, Nichter, & Abrams, 2000; Shiffman & Paty, 2006; Smolka et al., 2006). However, results from these studies are equivocal and no clear relationship exists. On one hand, heavily dependent smokers could be more cue reactive than minimally dependent smokers, since greater nicotine/cigarette exposure in the former group should lead to greater neuroadaptations in brain reward systems that would, in turn, augment sensitivity to smoking-related cues (Robinson & Berridge, 1993). Indeed, evidence for this relationship exists. Two studies of treatment (Payne et al., 1996) and non-treatment seeking (Donny et al., 2008) smokers have shown a positive correlation between dependence and craving in response to smoking-related cues, suggesting that heavier smokers are more cue reactive. Corroborating evidence also comes from two imaging studies that demonstrated increased responding to cues among smokers with greater levels of dependence (McClernon et al., 2008; Smolka et al., 2006), though one of these studies also found a negative correlation between dependence and fMRI reactivity in other brain areas (McClernon et al., 2008).

Alternatively, other models of addiction (Stewart, de Wit, & Eikelboom, 1984) allow, at least under some conditions, that nicotine dependence would be inversely associated with cue reactivity. For example, low dependent smokers smoke less frequently and often within a relatively narrow range of stimuli, whereas heavily dependent smokers smoke more frequently and irrespective of specific environmental cues. Thus, for heavily dependent smokers, few stimuli become unique predictors of nicotine administration. Support for this notion comes from literature on “chippers,” i.e., people who smoke no more than five cigarettes per day on at least four days per week (Shiffman, Paty, Kassel, Gnys, & Zettler-Segal, 1994). Recent research by Shiffman and Paty (2006) suggest that “chippers”, are under significantly *greater* stimulus control than are heavy smokers. These researchers were

able to correctly predict smoking (yes or no) on the basis of distinct situational stimuli more so among chippers (83% of the time) than heavy smokers (65%). Though chippers represent a distinct group of smokers towards an extreme end on the continuum of regular smoking, an inverse relationship between stimulus control and level of dependence may still hold among more frequent smokers. For example, Hogarth and colleagues (2003) demonstrated that light daily smokers (people who smoke fewer than 20 cigarettes per day) have a higher attentional bias to cigarette cues than do heavy smokers, again suggesting that it is possible that lower dependent individuals are under greater stimulus control than their high dependent counterparts (Hogarth, Mogg, Bradley, Duka, & Dickinson, 2003). Finally, indirect data from our own lab suggest that cue reactivity procedures could be most sensitive among smokers low in dependence and thus under greater stimulus control (Carpenter et al., 2009).

The purpose of the present study was to further examine the relationship between nicotine dependence and cue-elicited craving. With few exceptions (Davies et al., 2000), previous literature in this area has largely ignored the possibility that craving is multidimensional (Shadel, Niaura, Brown, Hutchison, & Abrams, 2001), and is frequently thought to include both hedonic craving (i.e., anticipation of positive outcomes) and craving as a function of negative reinforcement (i.e., anticipation of withdrawal relief) (Davies, P. Willner, & Morgan, 2000; King & Epstein, 2005; Tiffany & Drobes, 1991). Given the possibility that low-dependent smokers often do not experience withdrawal (Shiffman, Kassel, Paty, Gnys, & Zettler-Segal, 1994; Shiffman, Paty, Kassel, Gnys, & Zettler-Segal, 1994) but rather smoke under tightly bound and usually positively-valenced stimuli, it follows that the conditioned response for low-dependent smokers would likely be limited to hedonic craving only. We specifically examined whether nicotine dependence and cue reactivity are inversely related, and whether this relationship is specific to hedonic craving, withdrawal craving, or both. Data from this report derive from a larger study examining gender and menstrual cycle phase effects on craving and cue reactivity, tested among non-treatment seeking smokers.

2 METHODS

2.1. Participants

Participants (N=90) between 18 and 40 years of age and smoking at least 10 cigarettes per day were eligible for study entry. Participants were excluded if they had any major psychiatric or medical disorder, had used any psychotropic medicine in the past month, or had a medical condition or were taking a medication that could potentially affect craving or cue reactivity (e.g., beta blockers, benzodiazepines). Additionally, since the parent study examined the effects of menstrual phase on cue reactivity, women were excluded from the study if they were currently taking contraception or hormone replacement, met criteria for Premenstrual Dysphoric Disorder (PMDD), were pre-menarcheal or post-menopausal, had an irregular menstrual cycle, had a hysterectomy, were pregnant or were within three months of giving birth or breast feeding.

2.2. Procedures

Following a baseline visit, eligible participants were scheduled for four cue reactivity sessions which were conducted in the outpatient General Clinical Research Center (GCRC) of MUSC. To control for time since last cigarette, participants were instructed to bring a pack of their own cigarettes and to smoke a cigarette upon arrival (verified via a carbon monoxide breathalyzer 30 minutes after last cigarette). Prior to initiating the cue reactivity sessions, participants were required to provide a negative urine drug screen, a blood alcohol level of .000 and a negative pregnancy test. The cue reactivity sessions took approximately

120 minutes. During each session, participants were exposed to each of four cues (described below) in a counterbalanced order. Each cue was presented for a duration of 90 s with a 10 min nature slide show presented between each cue in an attempt to reduce possible carry-over effects. Subjective measures of craving were taken immediately prior to and immediately following each cue presentation. See LaRowe et al., 2007 for a comprehensive description of the cue reactivity session (LaRowe, Saladin, Carpenter, & Upadhyaya, 2007).

2.3. Cues

A total of four counterbalanced cues (90-seconds each) were used: two in vivo cues and two personalized affective imagery scripts. Standardized instructions were given via headphones for handling of cues. The active smoking cue consisted of in vivo manipulation of the participant's own brand of cigarettes and a lighter. The corresponding neutral cue was a similar manipulation of a pencil and eraser. The personal imagery cues (one stressful, one relaxed) were both idiographic to and prepared by each participant. The stressful script was based on a recent stressful event at work or home. The control for this affective script was a neutral, relaxed script also prepared by the participant him/herself. All imagery cues were recorded and presented to the participants via headphones.

2.4. Measures

Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) at the initial baseline visit. During the cue reactivity procedure, subjective craving was assessed using the Questionnaire of Smoking Urges—Brief (QSU-B; Cox, Tiffany, & Christen, 2001). The QSU-B is a 10-item, self-report measure of craving that yields a total score as well as scores for two factors. Factor 1 assesses hedonic craving; i.e., craving in anticipation of positive response. Factor 2 assesses craving through negative reinforcement; i.e., alleviation of withdrawal. Items are based on a Likert scale ranging from one (“strongly disagree”) to seven (“strongly agree”) Items are averaged and thus the total as well as factor scores all have a possible range of 1–7.

2.5. Analyses

Differential cue reactivity was operationally defined as the difference in QSU scores between the in vivo cues (smoking minus neutral) and between the imagery cues (stressful minus relaxed), and thus represents an index of craving in response to smoking related cues per se. The relationship between dependence and differential cue reactivity, across all four cue reactivity sessions (controlling for session effects), was examined via generalized estimating equations (GEE), wherein dependence was entered as a predictor and all measures of craving (QSU total, factors 1 & 2) were entered as criterion variables. For purposes of the GEE analysis, FTND was entered as a continuous variable. Significance level was set at $\alpha = .05$.

3. RESULTS

The participants ($N=90$; 53 males, 74 white) had a mean age of 30 ($SD=6$), had been smoking for an average of 11.3 (5.9) years, and had an average of 3.4 (5.7) prior quit attempts. Participants reported smoking an average of 19.3 (7.9) cigarettes per day, with a mean FTND score of 4.9 (2.1). Absolute and differential QSU data can be found in Table 1. In an effort to describe cue-elicited craving across the range of dependence, a median split was conducted to differentiate between low ($FTND < 5$; $n = 37$) and high dependent ($FTND \geq 5$; $n = 53$) smokers. Low dependent smokers smoked an average of 14.9 (4.1) cigarettes per day, vs. 22.4 (8.4) among high dependent smokers. All smokers, including those both high and low in dependence, reported significantly greater craving (total and within each factor)

in response to both the active in vivo and imagery cues ($p < .001$) as compared to their respective control cues, thus demonstrating that our procedures effectively elicited craving.

For all cues, absolute craving (craving in response to each cue alone) was higher among smokers with greater nicotine dependence (see Table 1). However, differential, cue-elicited craving (i.e., the difference between active and control cues) was higher for all cues among smokers with lower nicotine dependence. The relationship between overall differential cue-elicited craving (Total QSU) and FTND was non-significant, for both the in vivo cue ($\beta = -.041$; $p = .253$) and the stressful imagery cue ($\beta = -.059$; $p = .153$). In support of our hypotheses, FTND was significantly and negatively associated with differential hedonic craving (QSU factor 1) for both in vivo ($\beta = -.082$; $p = .037$; see Figure 1) and imagery cues ($\beta = -.101$; $p = .023$; see Figure 2). There was no relationship between dependence and negative reinforcement craving (QSU Factor 2) for any cue. We considered the possibility of a ceiling effect among high dependent smokers; i.e., that high dependent smokers could not significantly respond to cues because their ambient craving (i.e., in response to neutral/relaxed cues) was high. This does not appear to be the case. As Table 1 shows, all smokers, including those both high and low in nicotine dependence, demonstrated heightened cue elicited craving in response to each active cue, as compared to each inactive cue.

4. DISCUSSION

This study examined the relationship between nicotine dependence and differential cue reactivity; i.e., cue reactivity in response to active vs. inactive cues. While overall (absolute) craving was higher among high dependent smokers, differential cue reactivity was inversely associated with nicotine dependence across all cues tested, but specifically with respect to hedonic craving only (QSU factor 1). In other words, smokers low in dependence evinced greater differential cue reactivity (in the form of hedonic craving) than did their counterparts with greater dependence.

Our study is conceptually similar to, but methodologically different from, a prior study by Shiffman and Paty (2006). Whereas our study tested lab-based measures of cue reactivity among a sample entirely comprised of daily smokers, including those with both high and low dependence, Shiffman and Paty used ecological momentary assessment (EMA) methods comparing chippers (occasional smokers) and heavier smokers. Although chippers are similar to low dependent daily smokers, there are also important differences. Chippers by definition smoke no more than five cigarettes per day on at least four days per week (Shiffman & Paty, 2006), and are unlikely to experience physiological withdrawal (Shiffman, et al., 1994). In contrast, daily smokers, even those smoking at a low rate, are susceptible to withdrawal. Despite this key difference, our findings are largely congruent. That prior study found heavy smokers, i.e., those with greater nicotine dependence, demonstrated higher levels of ambient craving, diminishing the effect of cue-specific craving. By contrast, chippers were under greater stimulus control than heavy smokers in all situational dimensions examined. For example, chippers were greater than four times more likely to smoke while engaging in indulgent activities (e.g., relaxation, socializing, eating, drinking, or doing nothing that involved work) than any other activity. Because of the association with smoking and indulgent activities, the authors suggested a “reinforcement-enhancement” hypothesis in which chippers may smoke during indulgent activities to enhance the already pleasurable rewards (Shiffman & Paty, 2006). This interpretation may help explain the negative association between nicotine dependence and hedonic craving (QSU factor 1) that we observed in the present study.

Our findings are also partially consistent with those of Davies and colleagues (2000). Results from their study demonstrated that chippers’ reward cravings significantly increased

in response to smoking-related cues. Regular smokers, on the other hand, exhibited craving primarily induced by negative reinforcement (Davies et al., 2000), a finding that was not replicated in the present study. The authors suggest that smoking-related cues act predominantly on reinforcement-induced craving in chippers, and on withdrawal-induced craving among regular smokers. Additionally, prior research (Knott et al., (2008) have shown that regular smokers, compared to chippers, exhibit greater overall (i.e., unadjusted) craving as determined by the reward factor of the QSU (Factor 1), a finding replicated here. However, while our study demonstrates potentially greater differential (i.e., adjusted) craving (response to active cues while adjusting for inactive cues) among low dependent smokers, Knott and colleagues did not report on this outcome.

The present findings can also be interpreted in the context of prior research on tonic vs. phasic craving (Tiffany, Warthen, and Goedeker, 2009). The former may primarily be a function of abstinence or withdrawal, while the latter may be associated with exposure to smoking- and/or emotion-related cues. Since heavily dependent smokers are more likely to experience the effects of withdrawal (compared to low dependent smokers), it follows that tonic rather than phasic craving will dominate the craving experience of heavily dependent smokers. As a result, high dependent smokers are likely less responsive to cues. Conversely, the relatively minimal withdrawal experienced by low dependent smokers, together with the narrow range of stimulus conditions under which smoking occurs, results in the dominance of phasic craving. Thus, low dependent smokers are more cue reactive, and under greater stimulus control, than are their heavily dependent counterparts.

Results from recent brain imaging studies suggest that there may be different pathways to cue-elicited reactivity between low versus high dependent smokers (McClernon et al., 2008; Smolka et al., 2006). More specifically, McClernon and colleagues (2008) found negative associations between dependence scores (FTND) and reactivity in five brain regions as well as positive associations with five other brain regions. An earlier study by Smolka and colleagues (2006) also found positive correlations between dependence scores (FTND) and reactivity in seven brain regions. Results from these studies may help explain the discrepancies that have been reported about the relationship between level of nicotine dependence and cue reactivity in that the correlation may be, at least partially, dependent on what brain regions are being targeted. It may also be that there are multiple individual differences affecting this relationship that have yet to be accounted for.

As this study was part of a larger study, and therefore was not optimally designed to address our core research question, there are limitations herein, and results should be interpreted with caution. First, the results are derived from a sample consisting only of daily smokers smoking at least 10 cigarettes per day. This eligibility criterion may have truncated the range of responding. To further elucidate the relationship between nicotine dependence and cue reactivity, future studies should include a broader spectrum of dependence, including occasional smokers and smokers who smoke less than 10 cigarettes per day. Additionally, the overall cue-elicited response within our sample was modest. It would be helpful to include other cue types and reactivity measures (e.g., a visual analog measure of craving, which could be more sensitive to cue elicited craving).

Our data offer further evidence that smokers with lower levels of nicotine dependence may be under greater stimulus control, and thus more cue reactive, than smokers high in nicotine dependence. The finding that this relationship was restricted to hedonic craving only offers further evidence that low dependent smokers may crave cigarettes as a result of positive reinforcement (instead of smoking to alleviate withdrawal symptoms/negative reinforcement). Our findings may help begin to offer insight into the role of craving, cue reactivity and nicotine dependence varies by how cue-elicited craving is conceptualized. It is

clear however that more research is needed on the role of smoking reinforcement, and its relationship to cue-elicited craving in different subgroups of smokers.

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Figure 1.
Differential cue reactivity elicited by *in vivo* cues (QSU F1) by nicotine dependence

Figure 2.
Differential cue reactivity elicited by *imagery* cues (QSU F1) by nicotine dependence

Table 1
Absolute and Differential Cue Reactivity Responding by Level of Dependence (Mean (SD))

	IN VIVO CUES			IMAGERY CUES		
	Neutral	Smoking	Difference *	Relaxed	Stressful	Difference *
Overall (N=90)						
Total	3.44 (1.48)	3.98 (1.51)	0.54	3.23 (1.91)	3.85 (1.49)	0.62
QSU F1	4.56 (1.81)	5.19 (1.72)	0.63	4.26 (1.91)	4.99 (1.69)	0.73
QSU F2	2.32 (1.45)	2.76 (1.62)	0.44	2.19 (1.46)	2.71 (1.60)	0.52
Low FTND (n=37)						
Total	2.93 (1.17)	3.61 (1.34)	0.68	2.68 (1.22)	3.43 (1.29)	0.75
QSU F1	4.03 (1.61)	4.91 (1.67)	0.88	3.65 (1.72)	4.58 (1.59)	0.93
QSU F2	1.83 (0.99)	2.31 (1.31)	0.48	1.71 (1.00)	2.27 (1.33)	0.56
High FTND (n=53)						
Total	3.81 (1.56)	4.25 (1.58)	0.44	3.62 (1.59)	4.16 (1.54)	0.54
QSU F1	4.94 (1.85)	5.41 (1.72)	0.47	4.69 (1.93)	5.28 (1.17)	0.59
QSU F2	2.67 (1.61)	3.09 (1.75)	0.42	2.55 (1.63)	3.03 (1.71)	0.48

* **Note:** $p < .001$ for all comparisons between in vivo cues (smoking vs. neutral) and imagery cues (stressful vs. relaxed)