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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 and neutral) and two affective imagery cues (stressful and 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 regard 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.

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 and Tiffany, 1999; Ferguson and 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 and Sayette, 2008; Ferguson and Shiffman, 2009; Payne, Smith, Adams and Diefenbach, 2006; Swan, Ward and 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 and 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 and Baker, 1995; Conklin and Tiffany, 2002a,b).

Numerous studies have examined factors that may influence cue reactivity among smokers, including perceived drug availability (Wertz and Sayette, 2001), affect (Taylor, Harris, Singleton, Moolchan and Heishman, 2000), level of nicotine deprivation (Geier, Mucha and

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Pauli, 2000; Payne, Smith, Sturges and Holleran, 1996), gender (Niaura et al., 1998; Saladin et al, under review; Waters et al., 2004), and manipulation of cues (Conklin and 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 and Rose, 2008; Payne et al., 1996; Shadel, Shiffman, Niaura, Nichter and Abrams, 2000; Shiffman and 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 and 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 and 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 and 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, Mogg, Bradley, Duka and Dickinson (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 et al., 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 and 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 et al., 2000; King and Epstein, 2005; Tiffany and Drobes, 1991). Given the possibility that low-dependent smokers often do not experience withdrawal (Shiffman, Kassel, Paty, Gnys and Zettler-Segal, 1994; Shiffman, Paty, et al., 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 and 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 min 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 min. 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 slideshow 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, Saladin, Carpenter and Upadhyaya, 2007 for a comprehensive description of the cue reactivity session (LaRowe et al., 2007).

2.3. Cues

A total of four counterbalanced cues (90 s 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 and 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 and Fagerstrom, 1991) at the initial baseline visit. During the cue reactivity