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James Madison University

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Examination of cue-induced nicotine withdrawal among humans

An Honors Program Project Presented to

the Faculty of the Undergraduate

College of Health and Behavioral Studies

James Madison University

by Kathleen Ryan Owens

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FACULTY COMMITTEE:

Project Advisor: Jessica Irons, Ph. D.
Associate Professor, Department of Psychology

Reader: Kethera Fogler, Ph. D.
Assistant Professor, Department of Psychology

Reader: Bryan Saville, Ph. D.
Professor, Department of Psychology

HONORS PROGRAM APPROVAL:

Bradley R. Newcomer, Ph.D.,
Director, Honors Program

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The Examination of Cue-Induced Nicotine Withdrawal Among Humans

Kathleen R. Owens

James Madison University

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Abstract

There is copious research investigating the effect of environmental cues on the maintenance of drug behavior in animals, but sparse data exist with regard to humans. In our study, we examined 6 dependent cigarette smokers from James Madison University. We paid participants to use novel lighters that served as audible/tactile cues. After 2 weeks, participants returned to the lab satiated with nicotine for their testing session in which they were presented with the same cue and immediately completed a multiple-choice procedure (MCP) that measured their preferences by offering choices regarding money or the ability to take a cigarette break. Results showed no significant relationship between cue presentation and choice preference across the three conditions until current craving state was withheld as a covariate.

Keywords: environmental cues, behavior, nicotine, multiple-choice procedure

Examination of Cue-Induced Nicotine Withdrawal Among Humans

Effective behavioral intervention has long been a goal of clinical practice and psychological research (both basic and applied). Indeed, behavioral principles have been applied to effect change for a variety of targeted maladaptive behaviors. For example, behavioral interventions have been employed to change substance use, treatment compliance, physical activity, obesity, self-injury, and criminal activity, among others (Foxx, 2013). Behaviors are typically targets of change for reasons related to individual and/or community health and safety. Research has demonstrated that operant conditioning factors such as consequences of target behaviors, consequences of alternative behaviors, and other changes in the environment may all influence behavior change (Cooper, Heron, & Heward, 2007). Though changing target behaviors is critical to improving health or safety (and intervention strategies have been successful to that end), it is also important to examine effective strategies to *maintain* behavior change and prevent relapse of improved conditions. Two areas have been most studied with respect to attempting to understand variables that contribute to relapse: relapse of criminal behavior post-release (i.e., crime recidivism) and substance use lapse and relapse.

Most research on crime recidivism has examined the correlations of crime recidivism with an individual's criminal history and mental health background, socioeconomic status and class, and demographic information including age, gender, and ethnicity (Gendreau, Little, & Goggin, 1996). Other factors such as incarceration sentence length and other legal sanctions with rate of recidivism have also been considered (Kristen & Desmond, 2014). Despite copious correlational research, there are sparse data examining environmental influences on the maintenance of improved criminal behavior (i.e., reduced or lack of criminal behavior).

In contrast, the substance use literature is rich with data examining how the consequences of behavior may help to understand relapse in addition to extensive work examining risk and protective factors for relapse (e.g., Contingency Management; Hartzler, Lash, & Roll, 2012). Though many studies have supported the use of operant behavioral interventions for behavior change, fewer studies offer follow-up data showing maintenance of change after intervention. Conducting follow-up studies and observing demographic predictors offer important information about under what conditions changes in target behaviors are maintained; however, these strategies do not provide insight on how environmental cues affect behavior change. Given that operant conditioning phenomena do not occur in a vacuum, but rather as some of many simultaneously acting and interacting processes, it is important to consider other environmental influences on lapse and relapse. For example, operant conditioning and classical conditioning, or relations between and among environmental cues (intero- and exteroceptive), often function both independently and in tandem with one another. Thus, in addition to demographic variables (e.g., risk and protective factors) and operant processes, understanding classical conditioning phenomena may play a role in setting occasions for relapse—both about how cues may help maintain new behavior, and how they may encourage relapse.

Classical conditioning occurs when an unconditioned stimulus (US), a stimulus that produces an automatic response (UR), is paired with a neutral stimulus (NS), a stimulus that elicits no particular response, leading to an association between the two stimuli. Through this pairing, the conditioned stimulus begins to produce a conditioned response (CR) —a response similar to the UR—even in the absence of the US; however, this association between environment and response operates coincidentally to operant processes (Rescorla, 1988). Using nicotine use as an example, a potential association is created between the nicotine of the cigarette

(US) and the immediate environmental cues (CS). The environmental cues (CS) elicit a smoker's craving for a cigarette (CR). In terms of operant conditioning, environmental cues are discriminated stimuli for the behavior of smoking, and in the presence of the cues, the smoking behavior will be followed by certain consequences (i.e., the euphoric buzz from the nicotine). In other words, a CS gains reinforcing properties, revealing a combined process of both classical and operant conditioning as opposed to two separate phenomena (Rescorla & Solomon,1967).

Most evidence to date regarding the role of environmental cues on behavior focuses on operant conditioning models and their involvement in substance use relapse; however, previous research examining cue association and drug use suggests a potential relation between environmental stimuli and drug-use phenomena. Specifically, several studies have considered the relevance of environmental stimuli and their associations to substance acquisition and maintenance among rats.

Cagguila and colleagues (2001) studied the effects of environmental cues on self-administration of nicotine in rats. Rats were repeatedly given access to self-administration of nicotine in the presence of a cue (chamber light). After associations between nicotine and the chamber light seemed to be established, rats were given access to nicotine without the presence of the chamber light. This led to a decrease in nicotine self-administration. When the chamber light was re-introduced, rates of self-administration increased significantly. These findings suggest that the presence of an environmental cue became associated with the effects of nicotine and thus enabled higher rates of self-administration of nicotine (Cagguila et al., 2001).

As a follow-up, Cagguila and colleagues (2002) compared rates of self-administration of nicotine in rats that were repeatedly given the drug while in the presence of a cue light and rats that received the drug in the absence of any cues (controls). All of the rats were first observed on

continuous reinforcement schedules under which they gained access to nicotine every instance of lever pressing. Rats in the nicotine-plus-cue group exhibited high rates of responding when presented with the conditioned cue, whereas the rats in the control group maintained low levels of responding. When the schedule demand increased, these discrepancies in behavior were maintained, suggesting the cues promoted the acquisition of self-administered nicotine. There is a multitude of data that support these findings suggesting that environmental cues play a meaningful role in nicotine use and maintenance in rats (Caggiula, et al. 2002; Chaudhri, et al., 2006; Liu, et al., 2006; Neugebauer, Cortright, Sampedro, & Vezina, 2014; Ramos, Siegel, & Bueno, 2002).

As noted, cue-induced withdrawal has been well documented in rats (Cagguila et. al, 2001; Cagguila et. al, 2002) but has not yet been fully elucidated among humans. Limited research exists examining the cue-induced withdrawal phenomenon among humans; however, several studies have demonstrated that cue-exposure can influence acquisition among current smokers (e.g., Conklin, Parzynski, Salkeld, Perkins, & Fonte, 2012; Juliano, & Brandon, 1998; Oliver, & Drobes, 2012; Payne, Schare, Levis, & Colletti, 1991; Raymond, Rohsenow, Binkoff, & Monti, 1988**)**.Waters and colleagues (2004) measured cue-provoked craving levels across 158 smokers. Participants were randomly assigned to one of two conditions: high-dose nicotine patch or placebo patch. Once assigned, researchers examined cue-evoked craving across both groups during a cessation procedure. Findings showed that the presentation of smoking cues predicted subsequent relapse. King and colleagues (2016) tested 40 young adult smokers and found that visual exposure to the electronic device induced urges for a combustible cigarette. These findings suggest that cue-induced withdrawal is possible among humans.

One particularly important phenomenon to consider with respect to the role of environmental cues in substance relapse is known as the biological compensatory effect or a compensatory response. A physiological compensatory response occurs when environmental stimuli have been paired repeatedly with the physiological effects of a drug such that when the organism comes in contact with the conditioned environmental stimuli, a compensatory withdrawal syndrome is induced (which may effectively occasion drug use). After repeated associations between environmental cues and drug effects, the body undergoes a compensatory response in preparation for exposure to the drug effects; typically, the compensatory response will include opposing effects from those of the drug. For instance, if the drug increases heart rate, the compensatory response will compensate for the drug by decreasing the heart rate in the presence of the conditioned environmental stimuli. The compensatory response functionally models both a withdrawal syndrome and cue-induced withdrawal (Siegel, 1976).

Few studies have examined cure-induced withdrawal among humans. Dawkins and Munafo (2016) studied 63 cigarette smokers in order to test the efficacy of e-cigarettes in decreasing withdrawal and craving among users. Researchers found that participants who were naïve to e-cigarettes experienced less withdrawal and craving symptoms after e-cigarette use than those who were familiar with the device. These findings suggest that e-cigarettes take on the same conditioned properties as cigarettes, and therefore users become more tolerant to the drug after frequent e-cigarette delivery.

Another potential feature of conditioning that may help to inform understanding of relapse that researchers should investigate is the formation of establishing operations. According to Michael (1993), an establishing operation (EO) is a stimulus, antecedent, or environmental condition that alters the reinforcing effects of a consequence, usually through satiation or

deprivation, therefore enabling a greater increase or decrease in responding. There are two types of establishing operations: unconditioned and conditioned (Laraway, Snycerski, Michael, & Poling, 2003). An unconditioned establishing operation (UEO) is a condition that has the ability to affect the reinforcing effectiveness of a consequence without any learning (e.g., thirst, hunger, tiredness); on the contrary, a conditioned establishing operation (CEO) requires a learning process in order to change the effectiveness of a reinforcer. When an EO increases the effectiveness of a reinforcer, conditioned or unconditioned, it is called a motivating operation (MO) (Laraway et al., 2003). Conditioned motivating operations (CMOs) may have an effect on problem behaviors including substance use (McGill, 1999). Through classical conditioning, a neutral stimulus (e.g., a sound) becomes a conditioned stimulus that elicits a particular response (e.g., engaging in substance use); the CS also serves as a CMO such that it induces withdrawal as well as evokes the behavior of acquiring the substance. Therefore, the cue (both a CS and a CMO) is potentially responsible for the action of the response. This phenomenon potentially influences smoking behaviors. For example, if a dependent smoker is deprived of cigarettes then they will experience withdrawal (UEO). When this withdrawal is paired with a cue (i.e., cigarette lighter), the behavior of smoking becomes more reinforcing, (the UEO then becoming a CMO). This suggests that, in the presence of a conditioned environmental cue, CMOs may influence the problem behavior of smoking.

Given that cue-induced nicotine withdrawal has been most well studied and that the prevalence of cigarette smoking remains a socially important issue, the current study will examine cue-induced nicotine withdrawal among humans. Although the health threats associated with cigarette smoking (i.e., various forms of cancer, cardiovascular and pulmonary diseases, reduced lung function, dependence; Julien, Advokat, & Comaty, 2011) have been known

publicly for many years, nicotine dependence remains prevalent (CDC, 2015). Current treatment options, including nicotine patches, gum, and other forms of nicotine replacement therapy (NRT), produce low success rates, and lapse and relapse continue to be problematic when these products are used for intervention (Waters et. al, 2004). Studies suggest that many cessation procedures (Cognitive Behavioral Therapy, Contingency Management, and NRT) are only effective short-term, and relapse tends to occur following the termination of treatment programs (Etter & Stapleton, 2006). Given the high rates of relapse associated with smoking interventions, it seems reasonable to consider further the role of environmental cues in relapse as a method of improving quit success.

The current study replicated the model put forth by Caggiula et al. (2002) by inducing a cue association between a novel stimulus and nicotine exposure and testing the effects of the cue on nicotine withdrawal. Specifically, we paired a novel stimulus (a lighter with a sound/tactile cue) with smoking so that, over repeated pairing, the cue may become associated with the effects of nicotine. Behavioral theory and aforementioned literature suggested that the association between the novel stimulus cue and the effects of nicotine will lead to subsequent cue exposure eliciting nicotine withdrawal symptoms (e.g., craving). If cue associations lead to withdrawal then, in theory, we should have been able to induce new cue associations or to re-associate existing cues to combat nicotine withdrawal. Further, this model may be applicable to other substances as well as other behaviors that are subject to unwanted relapse.

Method

Participants

Participants included 6 staff members from James Madison University (male = 2; M_{age} = 45, *SD* = 13.93), and self-reported smoking at least 10 cigarettes per day through an online

survey and an in-person Time Line Follow Back (see Materials for description). We excluded individuals who self-report using marijuana (or other substances that are ingested through smoking) more than once a month in order to prevent any associations being made with a substance other than nicotine. We screened 29 participants total, but only 7 qualified to continue the study. One participant quit smoking during the study and was discontinued. Additionally, we excluded those currently enrolled in a nicotine cessation program of any kind in order to assure the lighters would be used consistently.

Materials

Biological Measures

***Urine cotinine* – NicCheck strips (**NicCheck™ I; Mossman Associates, Blackstone, MA) were used to measure the presence of nicotine and cotinine (a nicotine metabolite that has a half-life of 20 hr, permitting a greater opportunity for detection) in urine samples. Multiple validation studies have produced evidence that urinalysis is both a valid and reliable indicator of smoking behavior (e.g., Murray, Connett, Lauger, & Voelker, 1993; Parker et al., 2002). Immunoassay test strips (ITS; NicCheck™ I; Mossman Associates, Blackstone, MA) that provide a semi-quantitative analysis of cotinine levels over the last 5-7 days produced scores and strip colors that ranged from white (0), representing no smoking, to dark pink (14), representing frequent smoking. Validation studies have been done to assess this measure (Bernards, Twisk, van Mechelen, Snel, & Kemper, 2004; Lesichow, Merikle, Cook, Newman, & Muramoto, 1999). Two researchers conducted color assessment of the strips so that interobserver agreement could be calculated and any disagreement could be dealt with by averaging scores.

***Expired breath carbon monoxide (CO)* – A Vitalograph Carbon Monoxide Breath Monitor** (Vitalograph Inc., Quivira, KS), a handheld device that reports CO levels in parts per

million (ppm), was used to measure current smoking status in participants. Expired breath CO has shown high correlation with various self-report measures of smoking including amount of cigarettes smoked per day (Abueg, Colletti, & Kopel, 1985), duration of smoking (Deveci, Deveci, Aski, & Ozan, 2004), and the amount of time since the most recent cigarette (Schmitz, Rhoades, & Grabowski, 1995). Similarly, there is a strong correlation between expired breath CO and other biological measures that have been established as indicators of recent smoking activity such as nicotine and cotinine found in plasma, saliva, and urine (Jarvis, Tunstall-Pedoe, Feyeraband, Vesey, & Saloojee, 1987). Expired breath CO is a relatively accurate measure (± 3ppm) that is preferred due to its noninvasive, cheap, convenient, and immediate characteristics; however, its sensitivity is not as intense as that of other measures such as methods testing urine or saline cotinine.

Self-report Questionnaires

Multiple Choice Procedure - The MCP is a behavioral choice task that allows for assessment of the reinforcing value of a drug relative to concurrently available alternatives (e.g., drug versus money) (Griffiths, Rush, & Puhala, 1996). Participants were asked to make 25 discrete choices between money and some alternative across each of 3 forms. The monetary choices ranged from $0.00 to $10.00, increasing in 25-cent increments. The crossover point served as a value that quantified an alternative to money (i.e., how much the participant valued a smoke break). The first form instructed participants to choose between either one 10-min break (during which they were allowed to smoke a cigarette) or an escalating monetary value (e.g., a smoke break or $2.50). The second form instructed participants to choose between either one standard alcoholic drink or an escalating monetary value. The third form instructed participants to choose between marijuana or an escalating monetary value. The first form was consequated—

all choices were numbered and one choice from the form was randomly drawn, and the preferred consequence was made available immediately. For forms 2 and 3, participants were instructed to make choices as if they were real choices but were told that they are in fact hypothetical choices (shown to be quantitatively different than real choices but qualitatively analogous; Correia & Little, 2006). (See Appendix B for an example.)

Fagerstrom Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 2006) – This 6-item questionnaire was modified from two earlier versions of the Fagerstrom Tolerance Questionnaire (Fagerstrom & Schneider, 1989; Prokhorov, Pallonen, Fava, Ding, & Niaura, 1996) and was designed to assess nicotine dependence of tobacco smoking. Specifically, the FTND assessed dependence as measured by an individual's compulsive smoking behavior, defined in terms of nicotine withdrawal and craving. Items were dichotomous and scored on a 10-point scale, with higher scores corresponding to higher dependence. Despite its use in most smoking cessation research and clinical settings, studies on the psychometric properties of the FTND have produced inconsistent identification of its factor structure (one-factor vs. two-factor; Wellmen et al. 2006; Radzius et al., 2003, respectively) and poor internal consistency (α = .57 - .72). Furthermore, some researchers have criticized its lack of sensitivity and unclear interpretation; however, the FTND does correlate with smoking characteristics (e.g., smoking levels) and may be predictive of long-term abstinence (Breslau & Johnson, 2000). Because of its psychometric limitations, the FTND was included primarily to allow for comparison with previous studies, which frequently report this measure.

Time Line Follow Back (TLFB) – The TLFB is used to assess participants' specific health behaviors (in this case, smoking) with temporal precision. Participants reported their

behaviors on a calendar, quantifying how often they performed a behavior and how much of a substance was consumed per occasion (e.g., how many cigarettes they have smoked per day).

Wisconsin Survey of Withdrawal Symptoms (WSWS; Welsh et al., 1999) – This 28-item questionnaire measures self-reported assessments of severity and type of smoking withdrawal symptoms. Participants responded to phrases (e.g. "I have felt impatient") by rating them on a 5-point Likert scale. (1 = strongly disagree, 5 = strongly agree). The WSWS produced an overall withdrawal score (range = 0 [no withdrawal] – 140 [extreme withdrawal]), as well as individual scores for 7 subscales that correspond with clinical symptoms of nicotine withdrawal (anger, anxiety, sadness, concentration, craving, sleep, and hunger) (APA, 1994). Although the subscales within the WSWS have fairly low internal consistencies (α = .75 - .93), the overall internal consistency is high (α = .90 - .91). Finally, this survey serves as a solid predictor of smoking cessation outcomes (Welsch et al., 1999).

State Trait Anxiety Inventory (STAI) – The STAI consists of two forms; the Trait form is used as a screener for trait-like symptoms of anxiety. The State form is a subjective measure of anxiety used to assess current state-like experiences. Each question (repeated for each form) asked how one feels in the moment using a Likert scale of 1 ("I feel this way almost never") - 4 ("I feel this way almost always"). For example, participants responded to the statement, "I feel secure," based on their current state using a Likert scale of 1 ("not at all") – 4 ("very much so"). The State form of the STAI was used within sessions to assess the amount of anxiety participants feel in the moment (Marteau, & Bekker, 1992).

Cue-association Stimuli

Experimental (Cued) Lighter – Standard BIC lighters were covered with a homemade, snapped cover that surrounds the body of the lighter as well as covers the top (where the flame

exits the device). The cover served as both protection for the lighter as well as a tool for including a sound/tactile cue on the lighter. In order to use the lighter, the snapped cover needed to be unsnapped; similarly, in order to close the cover, the cover needed to be snapped closed. (See Appendix A.)

Control Lighter – Standard BIC lighters were covered with a homemade cover that surrounds the body of the lighters as well as covers the top (where the flame exits the device). Unlike the experimental lighter, the cover of the control lighter did not snap shut; rather the cover easily and inaudibly slid into a slit that kept the cover closed. The slit-cover did not include the same intended tactile/sound cue as the experimental lighter. (See Appendix A.)

Cued Folder – A snap, identical to the one used to make the experimental lighters, was sewn on to a black, plastic accordion folder. In order to open the folder, the snap had to be undone—duplicating the tactile/sound cue. A sticker was used to mask the thread marks on the outside of the folder. (See Appendix A.)

Non-cued Folder – A black, plastic accordion folder was left unaltered and was used without any associated cues. (See Appendix A.)

	Group A	**Group B**	**Controls**
Baseline/Intake	Novel Lighter provided	Novel Lighter provided	Control lighter provided
Testing	Cue exposure	No Cue Exposure	Cue Exposure
Follow-up	Cue exposure	Cue exposure	Cue exposure

Procedure

Participants attended three lab sessions: intake/baseline, testing, and follow-up during which they were asked to complete a series of questionnaires (see Materials), to provide CO breath

samples (Vitalograph must read at least 12ppm), and to provide urine samples (NicCheck must read a score of at least 1). All results were recorded immediately. All sessions were conducted with one participant at a time.

Intake/Baseline. Intake began with informed consent. We verified nicotine use and, if the participants qualified for the study, they were randomly assigned to one of three groups: experimental group A, experimental group B, or control group. Participants were given lighters to use for when they engaged in cigarette smoking. Experimental groups A and B were given experimental lighters that had the tactile/sound cue. The control group was given control lighters that have no associated cue. Lighters were distributed (each person received 4), and participants were asked to use the lighters every time they smoked for the next 2 weeks. Participants were instructed on how to correctly use the lighters, asked not to share the lighters, and told how to contact the researcher with any questions or issues regarding the lighters or the study. In order to maintain the integrity of the study, participants were told that the purpose of the study was to examine the validity of measuring lighter fluid as a means for assessing smoking habits of current smokers (please note the title of the study on the informed consent is consistent with this benign deception).

At the end of the intake session, participants were asked to schedule a testing session approximately 2 weeks from that date. The period of time between the intake session and the testing session was referred to as baseline, and data reflecting behavior that occurred during that time period was referred to as baseline data. Participants were asked to verify lighter use for at least 80% of verification attempts (verification attempts included text messages or emails with time stamped pictures of one of the assigned lighters). The lead researcher sent random requests for picture verification stating how they can send the picture (text message or email) and how

long they have to send the message (2 hours from the time of message delivery). The exact number of verification attempts varied across participants in order to reduce any diffusion affects across participants that could influence response rate (i.e., if participants shared how many verification attempts they experienced, then others might have expected the same and discontinue lighter use). Verification served to ensure that participants used the lighters repeatedly to potentially induce a stimulus-response association. Participants were discontinued from the study if the minimum 80% verification of lighter use was not met. Participants were paid $5.00 for attending the baseline session, regardless of whether they qualified to continue in the study.

Testing. For testing sessions, participants were asked to return to the lab nicotine satiated (having smoked at least one cigarette in the last 10 min). Participants who continued to meet study inclusion criteria provided urine and breath samples and complete self-report measures. Participants who no longer met the requirements of enrollment were thanked, compensated for lighter use, discontinued from further participation, and asked to return their lighters.

During testing sessions, experimental group A and controls were presented with the sound/tactile cue (via the cued-folder stimulus); experimental group B was not presented with the sound/tactile cue (and was exposed to the no-cue folder). The assigned folder held the MCP.

Participants were instructed on how to complete the MCP. Once the directions were understood, the participant was given the assigned folder and was told to open it, prompting the exposure to the cue. The MCP was the first task within the folder that participants had to complete. Participants were not made explicitly aware of the cue presentation. Upon completion of the MCP, the rest of the surveys were administered. At the end of the session participants were asked to return their lighters and schedule a follow-up session. If participants returned all

four lighters, they received monetary bonuses of $5.00. Additionally, if participants successfully verified lighter use at least 80% of the time they received a $35.00 bonus. At the conclusion of the testing sessions, participants were asked to schedule follow-up sessions approximately 1 week from the current date.

Follow up. All three groups were exposed to the cue (using the cued folder) and completed all measures and surveys again. In this session, the MCP was not consequated. Following each follow-up session, researchers emailed participants a list of possible resources for smoking cessation programs. (See Appendix for Figure 1 for a specific illustration of the timeline.)

Results

Participants included 4 females and 2 males all of whom worked as staff members at James Madison University. See Table 1 and 2 for descriptive statistics. A between-subjects ANOVA was used to examine between-group differences with respect to the dependent variable—the MCP crossover points obtained during testing sessions—and revealed no significant differences among the three groups ($p < .05$).

A series of exploratory ANCOVA were conducted to test potential covariates. Covariates were empirically (e.g., craving) and theoretically derived (e.g., gender). A one-way ANCOVA (covariate: current craving state at the time of MCP at testing; $p = .014$) revealed significant differences among the groups (F (2, 5) = 30.795, $p = .031$, $\eta^2 = .969$, *observed power* = .796; See Figure 2). Age, Gender, FTND, current state-anxiety at time of testing, CO at time of testing, number of cigarettes smoked on the day of testing, and number of cigarettes smoked between baseline and testing session did not serve as significant covariates. Post hoc tests revealed that Experimental Group B yielded significantly higher MCP crossover points compared to

Experimental Group A and Controls. Repeated measures ANOVA revealed no significant differences in MCP crossover points between testing and follow-up sessions.

Discussion

The current study sought to investigate potential cue-induced nicotine withdrawal among humans. Participants were exposed to lighters that provided a novel tactile and noise experience during each use in order to create an association between the sound/tactile experience and the reinforcing effects of nicotine. During the testing session, participants were exposed to the same tactile/sound cue and completed a choice procedure intended to assess their current level of nicotine withdrawal. Results revealed participants not exposed to the cue during testing experienced higher levels of withdrawal than those exposed to the cue or controls, but only when controlling for craving. Though cue-induced withdrawal is well documented among animals, the current study is the first to investigate this phenomenon among humans.

Cagguila and colleagues (2001; 2002) conducted a variety of studies that demonstrated cue-induced withdrawal among nicotine-dependent rats. Recent human research suggests that cue-induced withdrawal may occur with e-cigarettes as well (King et al., 2016). Additionally, existing literature suggests that nicotine-dependent human smokers are more sensitive to smoking-related cues compared to nonsmokers (Conklin, Parzynski, Salkeld, Perkins, & Fonte, 2012; Oliver, & Drobes, 2012; Payne, Schare, Levis, & Colletti, 1991; Juliano, & Brandon, 1998; Raymond, Rohsenow, Binkoff, & Monti, 1988**)**. Though previous literature is consistent with respect to evidence for cue-induced withdrawal, current study findings were contrary to expectation. A variety of explanations for inconsistencies should be considered.

A potential explanation for the current study findings may be cue-induced withdrawal does not occur among humans; however, this explanation is unlikely given previous literature. In

addition, it is possible that our dependent variable was not sensitive to acute withdrawal, thus prohibiting our abilities to detect the phenomenon. Alternatively, the tactile/noise experience may not have been salient and/or novel enough to create an association with the reinforcing effects of nicotine. It is possible some participants may not have adhered to our instructions to use (or use properly) the novel lighter when smoking, preventing the development of an association. The small sample size serves as a limitation as well. Although there was sufficient statistical power (*observed power* = .796), one participant not exposed to the cue during testing provided extreme outlying data (~2.5 SD above the mean), likely accounting for the observed effect size (and thus, power).

The finding that craving functions as a significant covariate in the absence of our cue is peculiar. Although craving and withdrawal are related constructs, it is unexpected that craving and withdrawal would have occurred only in the absence of our experimental cue. We offer several possible explanations for this outcome. In the development of our standardized protocol, we neglected to specify at what point during the testing session participants would return our lighters. Even if we had specified to RAs when to ask for the lighters, it is possible that participants may have come in ready to hand them off. If a participant returned lighters at the start of a testing session (prior to measurement of acute withdrawal), the lighters may have served as a withdrawal-inducing cue in the absence of our experimental cue exposure, thus explaining the outlying data. Finally, a smoking-related cue, independent of our manipulation, may have influenced responding for the outlying data (e.g., research assistant who smoked may have smelled like cigarettes). It is unclear whether the outlying data are a result of an associative phenomenon, fluke responding, or some other extraneous variable.

The influence of environmental cues on the development and maintenance of unhealthy behaviors and habits (i.e., smoking) is an area of investigation that deserves further consideration. Research has repeatedly demonstrated the existence of cue-induced withdrawal among animals; however, scant data exist to suggest that cue-induced withdrawal likely occurs among humans. There are several considerations we suggest for future researchers in this area. The use of more salient cues (i.e., loud sounds, bright colors, more intense tactile experience) may be necessary to induce the intended CMO (withdrawal) in humans. Indeed, human environments are exceedingly complex relative to rat operant chambers such that salience of cues is more pronounced in operant chambers. Future research may also consider developing ways to assess individuals' most salient associated cues. For example, a particular ashtray may serve as a conditioned cue that may elicit withdrawal symptoms for one individual.

In addition to cue salience, the duration of the cue-association period may not have been sufficient to allow for the development of cue-associations. Subsequent studies might benefit from longer cue-association duration. Future experimenters may also consider examining cue-induced withdrawal with other substances. Scant research has been conducted with drugs other than nicotine, but what exists supports the notion that environmental cues may influence substance use. For example, Siegel (1976) examined the impact of cue-association between environmental stimuli and the reinforcing effects of morphine and tolerance development in rats. Results showed that rats were tolerant in the cued-experimental environment but not in the alternative environment. Cue-associations may be more readily studied if attempted with substances that cannot be used across such a wide variety of contexts. Nicotine use can, and does, occur across times, places, situations, etc. Some other substance use is more restricted with respect to typical use contexts. For example, alcohol use, for most, does not occur in cars, at

school, at work, etc. (as smoking does for many). Further, many college students use Red Solo Cups at parties. Red Solo Cups may serve as potential salient environmental withdrawal-inducing cues among college students.

An understanding of whether cue-induced withdrawal occurs among humans, and if so, for whom and under what conditions, could be invaluable for informing health interventions and relapse prevention programs for substance use. If cue-induced withdrawal occurs among humans, and researchers are able to harness its effects, there are myriad clinical implications for such data. Currently, 40 to 60% of patients in drug rehabilitation programs experience relapse following treatment (NIDA, 2012). High relapse rates among rehabilitation centers/programs may be explained by the cue-induced withdrawal phenomenon. If substance users are removed from their using contexts, effectively removing themselves from their cue-associations, abstinence would necessarily be less challenging. When returning to previous using contexts upon release from rehabilitation centers/programs, relapse may occur simply because of a re-introduction to the using context (and its cues). Intervention, then, may benefit from including assessment of salient environmental cues and re-association of those cues. Given that substance use parallels other health risk behaviors, it is possible that the cue-induced withdrawal phenomenon may help to understand other cue-related relapse behavior (e.g., relapse in healthy eating; criminal behavior). If research reveals that cue-induced withdrawal occurs, healthcare professionals may be able to help patients change a range of health risk behaviors and crime prevention programs could utilize this knowledge to attempt to mitigate recidivism.

There is an abundance of research that demonstrates the roles environmental cues can play with regard to drug acquisition, tolerance, and withdrawal among animal subjects. Taken together, the literature suggests that cue-induced withdrawal may occur among humans;

however, few studies have examined the possibility experimentally. More research is necessary to fully elucidate the existence of and potential value of understanding cue-induced withdrawal among humans.

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Table 1

Descriptive statistics of the sample

		Minimum	*Maximum*	*Mean*	*Std. Deviation*
1.	CO	11	23	16	4.98
2.	Cigarettes Today	1	5	3.17	1.33
3.	TLFB	145	270	208.17	49.89
4.	FTND	22	89	50.67	30.46
5.	WSWS	47	66	57	8.25

Note: All values denote mean totals derived from testing sessions. TLFB denotes the mean number of cigarettes smoked in between baseline and testing sessions.

Table 2

Descriptive statistics of individuals

	MCP Crossover Point	*Craving*	*CO*	*Cigg. Today*	*TLFB*	*FTND*	*WSWS*
1. Experimental A							
2	1	7	11	5	208	84	85
9	5	6	23	3	145	22	78
2. Experimental B							
6	10	6	21	4	248	56	90
8	2	9	13	3	155	31	73
3. Control							
4	1	7	16	1	270	89	*
7	2	7	12	3	223	22	82

Note: All values denote totals derived from testing sessions. TLFB denotes the mean number of cigarettes smoked in between baseline and testing sessions. * denotes missing data.

Figure 1

Participant timeline

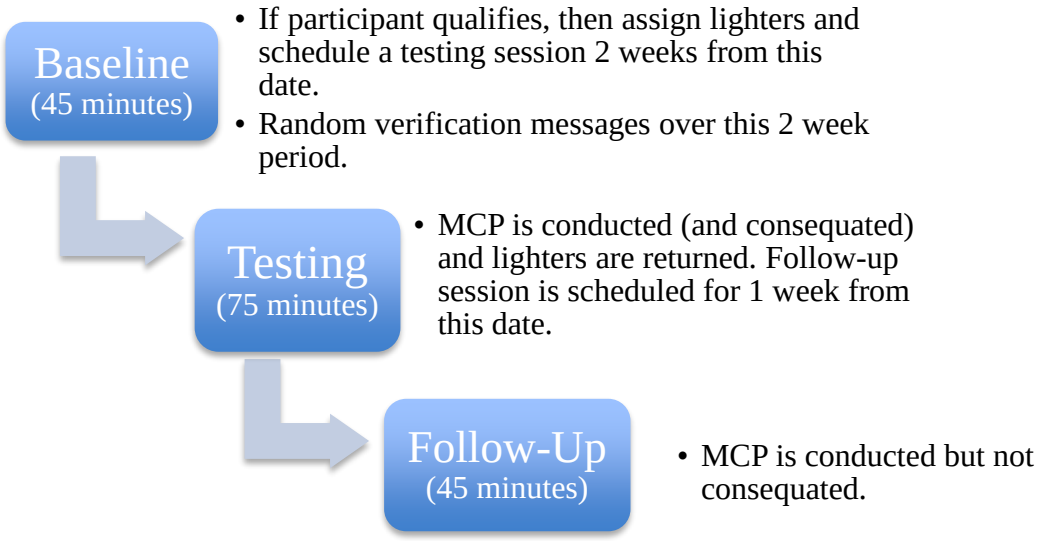

Figure 2

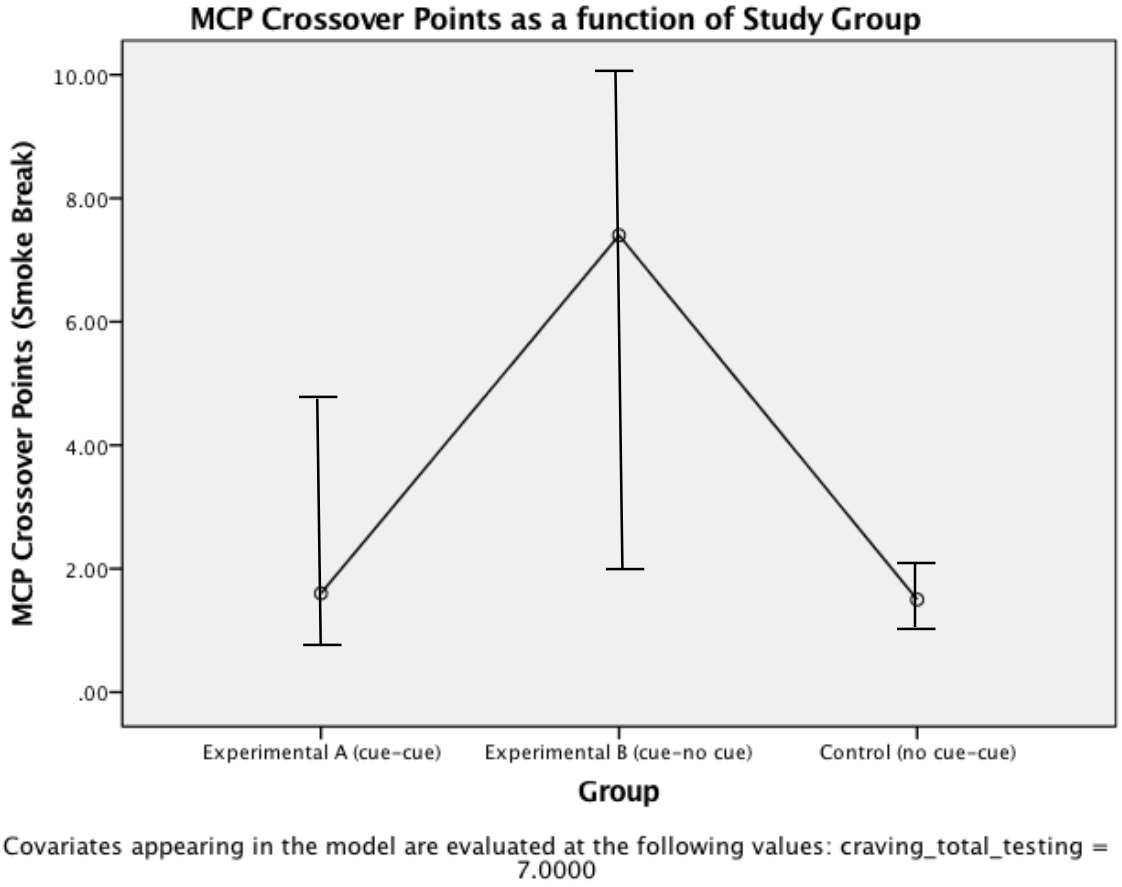

Figure 1. The mean crossover points for the smoke-break MCP (dollar values) as a function of study group while covarying for current craving.

Note: Error bars indicate the spread between the crossover points of the two participants per condition.

Appendix A

Experimental (Cued) Lighter

Control Lighter

Cued Folder

Non-cued Folder

Appendix B

Multiple Choice Form A

Listed below are 25 different choices. For each choice, please indicate your preference by circling either the smoke-break option or the Money option. Remember, we will randomly draw one of the choices below and give you what you indicated you prefer.

Choice #	Smoke Break	Money
1	1 10-minute smoke break	$0.00 received immediately
2	1 10-minute smoke break	$0.25 received immediately
3	1 10-minute smoke break	$0.50 received immediately
4	1 10-minute smoke break	$0.75 received immediately
5	1 10-minute smoke break	$1.00 received immediately
6	1 10-minute smoke break	$1.25 received immediately
7	1 10-minute smoke break	$1.50 received immediately
8	1 10-minute smoke break	$1.75 received immediately
9	1 10-minute smoke break	$2.00 received immediately
10	1 10-minute smoke break	$2.50 received immediately
11	1 10-minute smoke break	$3.00 received immediately
12	1 10-minute smoke break	$3.50 received immediately
13	1 10-minute smoke break	$4.00 received immediately
14	1 10-minute smoke break	$4.50 received immediately
15	1 10-minute smoke break	$5.00 received immediately
16	1 10-minute smoke break	$5.50 received immediately
17	1 10-minute smoke break	$6.00 received immediately
18	1 10-minute smoke break	$6.50 received immediately
19	1 10-minute smoke break	$7.00 received immediately
20	1 10-minute smoke break	$7.50 received immediately
21	1 10-minute smoke break	$8.00 received immediately
22	1 10-minute smoke break	$8.50 received immediately
23	1 10-minute smoke break	$9.00 received immediately
24	1 10-minute smoke break	$9.50 received immediately
25	1 10-minute smoke break	$10.00 received immediately