THE EFFECTS OF NICOTINE ON THE HABITUATION OF REINFORCER EFFECTIVENESS

by

Joshua Lee Karelitz

B. A. in Applied Psychology, The Pennsylvania State University, 2005

M. A. in Research Methodology, University of Pittsburgh, 2011

Submitted to the Graduate Faculty of the

Kenneth P. Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Master of Science in Psychology

University of Pittsburgh

2017

UNIVERSITY OF PITTSBURGH

KENNETH P. DIETRICH SCHOOL OF ARTS AND SCIENCES

This thesis was presented

by

Joshua Lee Karelitz

It was defended on

May 5, 2017

and approved by

Kenneth A. Perkins, PhD, Professor of Psychiatry and Psychology

Eric C. Donny, PhD, Professor of Psychology

Michael A. Sayette, PhD, Professor of Psychology and Psychiatry

Committee Chair: Kenneth A. Perkins, PhD, Professor of Psychiatry and Psychology

THE EFFECTS OF NICOTINE ON THE HABITUATION OF REINFORCER EFFECTIVENESS

Joshua Lee Karelitz, M.S.

University of Pittsburgh, 2017

Beyond its primary and secondary reinforcing effects, nicotine also enhances reinforcement from non-drug stimuli unrelated to smoking. Possibly relevant to that effect, preclinical research has shown that nicotine can maintain the effectiveness of a non-drug operant reinforcer across repeated presentations. Operant reinforcement is a dynamic process in which a reinforcer's ability to promote behavior decreases systematically with each presentation, leading to within-session declines in responding. Habituation to the sensory aspects of a reinforcer is the mechanism underlying declines in its effectiveness. Nicotine's effect on habituation of reinforcer effectiveness has not been demonstrated in humans. The current study was designed as a first step in translating animal research examining nicotine's influence on habituation of reinforcer effectiveness to a human sample. Using a within-subjects design, 30 dependent smokers (14 males, 16 females) participated in two experimental sessions, as part of a larger study. Sessions varied by nicotine condition, no nicotine after overnight abstinence (>12 hr; CO <10 ppm) or ad lib smoking of own cigarette without overnight abstinence (CO > 10 ppm; "nicotine condition"). In each session, participants engaged in a 15-min operant response task to earn time viewing a preferred picture (attractive human model; 7 sec per earned reinforcer; fixed-interval 10 schedule), with unique pictures per session. Overall, reinforced responding and duration of responding were each significantly greater in the nicotine versus no nicotine condition. When examining within-session patterns of responding, rate of reinforced responding declined less

sharply early in the trial and persisted longer under the nicotine versus no nicotine condition. Exploratory analyses suggested that neither self-reported withdrawal levels nor nicotine condition order influenced differences in patterns of responding between conditions. Overall, these results are an initial demonstration of nicotine's (via cigarette smoke) ability to maintain the effectiveness of a reinforcer longer, compared to a no nicotine control. Delaying declines in reinforcer effectiveness may be yet another way in which nicotine promotes smoking behavior.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 INTRODUCTION

Nicotine has been shown to have primary reinforcing effects, such that humans and nonhuman animals will perform a behavioral task (e.g., lever pressing, snout poking, etc.) in order to receive the drug (Donny et al., 1999; Harvey et al., 2004; Henningfield, Miyasato, & Jasinski, 1983). Interestingly, the primary reinforcing effects are relatively weak when compared to other drugs of abuse (e.g., cocaine; Manzardo, Stein, & Belluzzi, 2002). This notion is contrary to the very strong persistence of nicotine use in humans despite adverse health risks, suggesting other factors are involved in developing and maintaining nicotine dependence. In support, secondary reinforcement effects have also been identified. These effects occur when stimuli frequently paired with nicotine intake take on reinforcing properties through either operant or classical conditioning (Caggiula, Donny, Chaudhri, Perkins, Evans-Martin, & Sved, 2002; Rupprecht et al., 2015). Nicotine-associated stimuli may increase the likelihood of engaging in smoking behavior (Rose & Levin, 1991). Such stimuli may be widely varying, including sensory characteristics of smoking (e.g., feel of a cigarette between fingers, taste of smoke, etc.) or environmental conditions where smoking occurs (e.g., specific people also present, smoking locations, etc.). These stimuli can act as discriminative cues (i.e., signaling drug availability), increase craving to smoke (Conklin, 2006; Conklin, Perkins, Robin, McClernon, & Salkeld,

2010; Conklin, Salkeld, Perkins, & Robin, 2013; Stevenson et al., 2017), and can continue to reinforce smoking despite a reduction in nicotine (Donny, Houtsmuller, & Stitzer, 2007).

Additionally, a third reinforcing effect of nicotine has been identified, that of enhancing reinforcement from non-drug stimuli that are unrelated to smoking (Donny et al., 2003). In operant conditioning paradigms, reinforcers are defined as stimuli that follow a behavior and act to increase the likelihood of that behavior in the future (Murphy & Lupfer, 2014). Nonhuman animals have been shown to increase responding for non-drug reinforcers (i.e., light onset, sucrose) following nicotine administration (Donny et al., 2003; Palmatier, O'Brien, & Hall, 2012), despite no contingent association between nicotine and those reinforcers. In humans, very similarly, operant responding for auditory and visual non-drug reinforcers (i.e., preferred music, preferred video clips) increased following acute nicotine administration compared to no nicotine (Perkins & Karelitz, 2013a, 2013b, 2014). Thus, this third manner in which nicotine may increase reinforcement is by enhancing the reinforcing value of other rewarding stimuli in a smoker's environment.

In sum, the psychopharmacological actions of nicotine are directly reinforcing for the user, although the magnitude of such reinforcement is relatively weak when compared to other drugs of abuse. Secondary and tertiary reinforcing effects have been implicated as additional ways in which nicotine can contribute to the persistence of smoking. Elucidating the behavioral influences of nicotine's reinforcing effects may lead to identifying those at increased risk for dependence or give us a better understanding of why smoking behavior is so persistent.

1.1 DYNAMICS OF OPERANT REINFORCEMENT

Reinforcement does not appear to be a static process, but rather a dynamic activity in which a reinforcer's ability to promote behavior may change systematically over relatively short periods of time (e.g., < 1 hour) and as a function of exposure to the reinforcer. Often, there is an underlying assumption that the effectiveness of a reinforcer is consistent across repeated presentations. Yet, studies frequently show rates of responding for a reinforcer initially increase and subsequently decline over time (McSweeney & Hinson, 1992; McSweeney, 2004). McSweeney and Murphy (2009) posited that a reinforcer's effectiveness varies within-session, resulting in the observed uneven rates of responding over time. Sensitization and habituation to the sensory aspects of the reinforcer were implicated as the behavioral processes responsible for changes in its effectiveness. According to the authors, sensitization, or an increase in responsiveness to a stimulus (Groves & Thompson, 1970), occurs early within the session. Habituation, defined in greater detail below, occurs with repeated presentation of the reinforcer to diminish its effectiveness. Of particular interest for the current study is the decline in reinforcer effectiveness due to habituation.

1.1.1 Habituation and operant reinforcement

Habituation can be generally defined as a "decreased response to repeated stimulation" (Groves & Thompson, 1970). However, broad definitions of concepts can lead to misuse and overlapping of otherwise disparate terms. Thompson and Spencer (1966) recognized this issue and developed

Table 1. List of empirical habituation characteristics.

	Habituation Characteristics[1]
1	Repeated application of a stimulus results in a progressive decrease in some parameter of a response to an asymptotic level. This change may include decreases in frequency and/or magnitude of the response. In many cases, the decrement is exponential, but it may also be linear; in addition, a response may show facilitation prior to decrementing because of (or presumably derived from) a simultaneous process of sensitization.
2	If the stimulus is withheld after response decrement, the response recovers at least partially over the observation time ("spontaneous recovery").
3	After multiple series of stimulus repetitions and spontaneous recoveries, the response decrement becomes successively more rapid and/or more pronounced (this phenomenon can be called potentiation of habituation).
4	Other things being equal, more frequent stimulation results in more rapid and/or more pronounced response decrement, and more rapid spontaneous recovery (if the decrement has reached asymptotic levels).
5	Within a stimulus modality, the less intense the stimulus, the more rapid and/or more pronounced the behavioral response decrement. Very intense stimuli may yield no significant observable response decrement.
6	The effects of repeated stimulation may continue to accumulate even after the response has reached an asymptotic level (which may or may not be zero, or no response). This effect of stimulation beyond asymptotic levels can alter subsequent behavior, for example, by delaying the onset of spontaneous recovery.
7	Within the same stimulus modality, the response decrement shows some stimulus specificity. To test for stimulus specificity/stimulus generalization, a second, novel stimulus is presented and a comparison is made between the changes in the responses to the habituated stimulus and the novel stimulus. In many paradigms (e.g. developmental studies of language acquisition) this test has been improperly termed a dishabituation test rather than a stimulus generalization test, its proper name.
8	Presentation of a different stimulus results in an increase of the decremented response to the original stimulus. This phenomenon is termed "dishabituation." It is important to note that the proper test for dishabituation is an increase in response to the original stimulus and not an increase in response to the dishabituating stimulus (see point #7 above). Indeed, the dishabituating stimulus by itself need not even trigger the response on its own.

[1] From Rankin et al., 2009

Table 1 (continued).

9	Upon repeated application of the dishabituating stimulus, the amount of dishabituation produced decreases (this phenomenon can be called habituation of dishabituation).
10	Some stimulus repetition protocols may result in properties of the response decrement (e.g. more rapid rehabituation than baseline, smaller initial responses than baseline, smaller mean responses than baseline, less frequent responses than baseline) that last hours, days or weeks. This persistence of aspects of habituation is termed long-term habituation.

a list of ten empirically validated characteristics of habituation. This list has been refined over time and an updated version from Rankin et al. (2009) is located in Table 1. Identification of these characteristics allows for a more accurate operationalization of habituation: a decreased response to repeated stimulation when it conforms to a list of empirical properties (McSweeney & Murphy, 2000). These characteristics turn into a checklist of sorts, allowing for clear identification of habituation while also separating it from similar terms from other areas of research (e.g., satiation, tolerance, etc.).

Historically, habituation has been examined in classical conditioning paradigms looking at declines in involuntary (i.e., reflexive) responses to repeatedly presented stimuli (e.g., startle response, salivation, neuronal activity, orienting reflex, etc.; for a review see Thompson, 2009). However, preclinical studies by McSweeney and colleagues have applied habituation theory to operant conditioning paradigms. Through this application, empirical support has been established for the explanatory role of habituation in declines in operant reinforced responding. Specifically, McSweeney and colleagues found a large overlap between the within-session patterns of responding and the empirical characteristics of habituation. Examples include declines in operant responding following repeated presentation of a reinforcing stimulus (Table 1, point 1; McSweeney, Hinson, & Cannon, 1996), spontaneous recovery between sessions (Table 1, point 2; Aoyama & McSweeney, 2001a), steeper declines in responding for quickly presented reinforcing stimuli (Table 1, point 4; McSweeney, 1992), and steeper decreases in responding for a less intense reinforcing stimulus (Table 1, point 5; Melville, Rue, Rybiski, & Weatherly, 1997). This line of research established habituation as one of the main mechanisms responsible for within-session declines in operant responding. The researchers also explored alternate explanatory factors and their respective contribution to this behavioral phenomenon.

1.1.2 Alternate explanations

Operant reinforcement paradigms have long assumed that declines in within-session responding are due to factors other than habituation to the stimuli, including changes in attention to the task (Killeen, Hanson, & Osborne, 1978), fatigue from responding (Catania & Reynolds, 1968) or satiation from a consummatory reinforcer (Reese & Hogenson, 1962). Studies completed by McSweeney and colleagues have tested these long-standing assumptions in attempts to identify the mechanism(s) behind within-session declines in operant responding. The researchers systematically tested each factor's contribution to within-session declines in responding.

1.1.2.1 Attention

McSweeney, Weatherly, and Swindell (1996) examined the role of attention on within-session declines in responding using a delayed matching-to-sample task in an animal model (i.e., pigeons). In short, subjects were shown a color (e.g., red) and, after a delay period, were then shown two colors (e.g., red and green). Reinforcement was provided to the subject for correct identification of the first color (i.e., pecking the red stimulus). The authors hypothesized that if attention to the task were to decline within-session, accuracy on the task would also decline. Concurrent examination of within-session declines in operant responding and accuracy on the task revealed decreases in rate of responding as the session went on, whereas accuracy remained stable across the entire session. The results of this study suggest that within-session declines in responding occur independently from attention to the task.

1.1.2.2 Fatigue

The contribution of fatigue to within-session declines in responding was examined by McSweeney, Weatherly, Roll, and Swindell (1995). The researchers utilized an operant task that switched the modality of operant responding (i.e., operandum) after 10, 20, 30, or 40 minutes (depending on condition) into the 60-minute trial. Changing the operanda required the animal to utilize different muscle groups for responding (i.e., lever press versus key press in rats, key peck versus foot peddle press in pigeons), with each operanda requiring a different level of force. The authors hypothesized that different muscle groups would have idiosyncratic rates of fatigue, due the varied amount of force required to produce a response and by simply being separate muscle groups. Any influence of fatigue would result in different patterns of declines in within-session responding across modality of operant responding. However, the patterns of within-session responding did not vary across operanda, suggesting that fatigue contributes minimally to declines in operant responding.

1.1.2.3 Satiation

The difficulty in ruling out satiation as a causal factor in within-session declines in operant responding lies in its definition. As McSweeney (2004) pointed out, the term "satiation" was used to label any within-session decreases in responding by early behaviorists such as B.F. Skinner and Thomas Whelan Reese. Such a broad definition of this term allows for its misuse, especially when applied by those who do not solely study ingestive behavior (e.g., behaviorists). Within the domain of feeding behavior, satiation is often used to describe the decline or cessation of feeding behavior (McSweeney & Murphy, 2000). There are specific elements that contribute to satiation, called "satiety factors". Mook (1995) identified stomach distention, increases in

cholecystokinin (CCK; a hunger suppressing hormone released by the small intestine), and increases in blood sugar levels as satiety factors for feeding. As these factors accumulate or increase within an organism, satiation occurs and feeding behavior either declines or ceases. Understanding how satiety factors contribute to satiation has been crucial in ruling out satiation as a causal factor in within-session declines in operant responding.

Dishabituation is defined as the resumption ("recovery") of a prior high rate of responding after its attenuation due to repeated stimulus exposure, with such recovery resulting from presentation of a strong, different, or extra stimulus (Groves & Thompson, 1970; Brimer, 1970). Recovery following a dishabituating stimulus has been used to test the role of satiation in within-session declines in responding (McSweeney, 2004). Dishabituation in human and animal models has been well documented (Aoyama & McSweeney, 2001a, 2001b; Ernst & Epstein, 2002; McSweeney & Roll, 1998). In this context, once responding for a food reinforcer slows to an asymptotic level, temporary presentation of a strong, different, or extra stimulus (e.g., removing the operanda, dispensing two food pellets instead of one, changing the reinforcement schedule, etc.) will restore responsiveness for the original food reinforcer. If responding decreased due to satiation, consumption of reinforcers earned through resumption of responding would only add to or magnify the existing satiety factors (i.e., greater stomach distention, increases in CCK and blood sugar). As such, resumption of responding following a dishabituating stimulus does not support this satiety hypothesis.

McSweeney and Roll (1998) reviewed studies examining the role of satiation in within-session declines in operant responding for consummatory reinforcers. Studies included in their review manipulated satiety factors to understand their contribution to declines in responding. Across the studies, manipulating caloric density of the reinforcer, prefeeding the subjects, and

prior limitation of food intake did not alter patterns of within-session declines in operant responding. Across these studies, satiety was empirically ruled out as a universal cause of within-session declines in operant responding for consummatory reinforcers. As noted above, the authors further proposed that the patterns of response were consistent with the empirical characteristics of habituation and suggested that this behavioral phenomenon may be responsible for declines in within-session responding. Others have taken this line of research one step further, using the empirical characteristics of habituation to make testable predictions for operant reinforced behavior.

Lloyd, Medina, Hawk, Fosco, and Richards (2014) extended the habituation characteristics to make behavioral predictions for habituation of reinforcer effectiveness in patterns of within-session responding, listed in Table 2. These predictions have been examined in preclinical work (described below). However, there are few clinical studies of habituation of reinforcer effectiveness. Studies examining habituation of reinforcer effectiveness in humans are limited to feeding behavior (for a review see Epstein, Temple, Roemmich, & Bouton, 2009). However, these studies have generated empirically derived interventions for obesity (e.g., limited food variety may lead to reduced food intake) and behavioral interventions for children (e.g., providing a variety of food rewards to maintain reinforcer effectiveness), suggesting that work in this field can have clinical applications.

Table 2. List of predictions for habituation of reinforcer effectiveness, extrapolating from the empirical characteristics of habituation

	Predictions for Habituation of Reinforcer Effectiveness[2]
1	Repeated presentation of a reinforcer will cause a within-session decline in response rate.
2	Subject responding for a reinforcer in 2 consecutive testing sessions with a long break between sessions will show greater responding during the start of the second session than at the end of the first.
3	Subject responding for a reinforcer in once per day sessions for 5 consecutive days will show a faster within-session decline in response rate on the 5th day than on the 1st day of testing.
4	Subject responding for a reinforcer according to a Fixed Interval (FI) 10 sec schedule will show a greater within-session decrease in responding than a subject responding for a reinforcer on a FI 100 sec schedule.
5	Subject responding for a large magnitude reinforcer will show less within-session decline in responding than a subject responding for a smaller magnitude reinforcer.
6	Subject that responds for a reinforcer until an asymptotic baseline (operant) level of responding is reached will show greater initial responding upon retest than a subject that is left in the test situation for additional testing after asymptotic responding is reached.
7	Changing the stimulus properties of the reinforcer after responding has declined (habituated) will increase responding.
8	After responding for a reinforcer has declined (habituated), the introduction of a separate non-contingent novel stimulus will increase responding for the reinforcer.
9	Repeated dishabituation by a non-contingent stimulus (see prediction #8) will have diminished effects on responding with each successive use
10	With repeated testing, total responding during daily test sessions will decrease and that this decrease in responding will be long lasting.

[2] From Lloyd, Medina, Hawk, Fosco, & Richards, 2014

There are clear implications for other behaviors maintained by reinforcement, such as nicotine intake via tobacco smoke. As described above, nicotine has been shown to increase reinforcement from non-drug related stimuli. It may also influence reinforcement by altering habituation to the sensory aspects of reinforcers. Interestingly, in preclinical studies, stimulant drugs (including nicotine) have been shown to slow the rate of habituation of a reinforcer's effectiveness by maintaining persistently higher rates of responding for the reinforcer. Differentiating from nicotine's reinforcement enhancing effects, which focuses on increases in responding as the schedule of responses per reinforcer increases, habituation of reinforcer effectiveness is quantified in relation to the persistence of responding for a reinforcer available on a schedule that does not increase (i.e., fixed ratio schedule). Habituation of reinforcer effectiveness and its implication for drug taking behavior will be described in the next section.

1.2 DRUG EFFECTS ON HABITUATION OF REINFORCER EFFECTIVENESS

Recent preclinical work has shown that stimulant drugs delay habituation of reinforcer effectiveness (Gancarz, et. al, 2012; Lloyd, Hausknecht, & Richards, 2014). Rats receiving either nicotine or methamphetamine had more gradual within-session declines in responding for a visual reward (i.e., turning on a cage light) compared to a sharp reduction in those who received saline. These drug effects may be specific to reinforcers that are sensory in nature (i.e., non-satiating). When receiving methamphetamine, rats showed delayed habituation of reinforcer effectiveness for a sensory (i.e., turning on a light), but not for a consumable (i.e., water),

reinforcer (Lloyd, Hausknecht, & Richards, 2014). Taken together, these preclinical studies suggest that nicotine may have an additional effect on reinforcement: maintaining reinforcer effectiveness across repeated presentations (i.e., attenuating habituation).

Habituation of reinforcer effectiveness has been posited as a contributing factor in drug abuse behavior (Lloyd, Medina, Hawk, Fosco, & Richards, 2014). This process may complement the reinforcement enhancing effects of nicotine to synergistically promote smoking behavior. Following smoking, there is rapid enhancement of reinforcement from stimuli not directly associated with smoking (i.e., sensitization). Nicotine may also delay habituation of reinforcer effectiveness which, in turn, may further sustain the nicotine-enhanced reinforcement (Lloyd, Medina, Hawk, Fosco, & Richards, 2014). Thus, nicotine may both initially increase and subsequently maintain the reinforcing efficacy of some sensory stimuli.

This effect may be a contributing factor in smoking persistence despite the numerous health hazards associated with smoking. Sensory stimuli are ubiquitous in environments in which smokers are allowed to smoke (Van Gucht, Van den Bergh, Beckers, & Vansteenwegen, 2010). Nicotine may acutely increase reinforcement from these stimuli and also delay habituation of such reinforcement. During a quit attempt, these sustained increases in reinforcement due to nicotine intake would be lost with smoking abstinence. This may lead to smoking lapses in cessation as the quitting smoker attempts to regain the greater levels of reinforcement they have come to expect from stimuli in their environment. In support of this hypothesis, early lapses in cessation attempts have been found to be common during preferred activities such as listening to music or watching television (Deiches, Baker, Lanza, & Piper, 2013). However, nicotine's effect on the habituation of reinforcer effectiveness has not been demonstrated in humans.

1.3 THE CURRENT STUDY

The current study was designed as a first step in translating animal research examining nicotine's influence on habituation of reinforcer effectiveness to a human sample. Using a within-subjects cross-over design, I examined whether nicotine via cigarette smoke (versus no smoking) maintained the effectiveness of a reinforcer across repeated administrations during an operant response task. Specifically, I tested the following hypotheses:

1. There will be a main effect of nicotine condition on number of responses and duration (i.e. persistence) of responding for a reinforcer, with a greater number of responses (collapsing across time points) and longer duration responding during the nicotine condition. Earlier studies with human samples have shown increases in operant responding on a progressive ratio schedule (i.e. gradually higher response requirement) for a reinforcing visual stimulus, comparing cigarettes or other substances containing nicotine versus placebo or no nicotine conditions (Perkins & Karelitz, 2013a, 2013b, 2014; Perkins, Karelitz, & Michael, 2015). Because of this, I predicted the increased persistence in responding due to nicotine-maintained reinforcer effectiveness for the visual stimulus would translate to greater responding and time spent responding for the nicotine versus no nicotine condition.

2. There will be a significant time (epoch) X nicotine condition interaction on responding. Preclinical research suggests that nicotine attenuates declines in operant responding attributed to habituation of reinforcer effectiveness, thus leading to greater persistence of responding for the reinforcer (Gancarz, et. al, 2012; Lloyd, Hausknecht, & Richards, 2014). As such, I predicted that a no nicotine condition

would have a sharper rate of decline in operant responding than a nicotine via cigarette smoke condition. This would demonstrate nicotine's (via cigarette smoke) ability to maintain the effectiveness of a reinforcer longer compared to a no nicotine control.

2.0 METHODS

2.1 PARTICIPANTS

The study sample included 30 nicotine dependent smokers (14 males, 16 females), recruited from the Pittsburgh area using flyers and ads on Craigslist and Facebook. All were those who have smoked ≥10 cigarettes per day for the past 12 months and met DSM-V criteria for tobacco dependence, confirmed by a structured interview adapted from Breslau, Kilbey, and Andreski (1994). Mean (SD) sample characteristics were 15.2 (4.0) cigarettes per day, smoking at their current rate for 10.1 (8.2) years, and 33.8 (8.8) years old. The sample self-reported as 70% Caucasian, 23% African American or Black, and 7% more than one ethnicity. Sample characteristics did not vary between genders. Exclusion criteria included current psychiatric diagnosis, current use of psychiatric medications, current nicotine replacement therapy (NRT) use, pregnancy, and currently nursing mothers. All participants underwent a brief physical exam by a physician to confirm they were healthy enough to participate.

2.2 OPERANT RESPONDING TASK

Habituation of reinforcer effectiveness was measured using an updated version of the computer program “Apple Picker” (Norman & Jongerius, 1985). This program has been shown to be an effective method to assess reinforcement from sensory stimuli, including increases due to acute nicotine (Perkins, Karelitz, Jao, & Stratton, 2012; Perkins & Karelitz, 2013a, 2013b, 2014). Participants responded using a keypad to move a cursor around a 19x19 grid on the computer monitor, with tree icons in every other box. Once they placed the cursor over a tree, they pressed a button on the keypad to “check” it for an “apple”, representing a response. Once an apple was found, a brief tone was heard and an apple appeared over the tree for visual and auditory confirmation, followed by appearance of the designated reinforcer (discussed in detail below). The number of responses required to earn a reinforcer, each signified by the appearance of an apple icon, was on a fixed ratio schedule of FR10.

Experimental sessions involved one 15-minute trial of the Apple Picker task, working for a preferred visual stimulus (i.e., picture of attractive model or celebrity; identified in initial session, see below). Each apple found resulted in a 7 second presentation of the reinforcer, presented to the right of the grid. Participants were instructed to work on the task only as long as they wanted to continue viewing the available picture, and they were free to stop responding any time they wanted for the remainder of the 15-minute trial. General interest magazines were available for participants to read when they decided they were finished working on the task to reduce likelihood of continued responding due to boredom. However, these magazines were purposefully “routine” in nature as to not compete with the visual stimulus as a reinforcer.

This version of the Apple Picker task was specifically designed with rudimentary graphics to ensure participants would not find working on the task to be inherently reinforcing. Non-reinforced responding on this task has been shown to be very low (Perkins & Karelitz, 2013a, 2013b, 2014), suggesting that the work task itself is not very intrinsically reinforcing, as intended. Additionally, broadening the use of this task to assess habituation of reinforcer effectiveness was a valid application of this computer program. Previous studies using this program recorded the absolute number of responses as the dependent measure of interest (Perkins, Karelitz, Jao, & Stratton, 2012; Perkins & Karelitz, 2013a, 2013b, 2014). An updated version of the program recorded the time stamp of each response (in seconds since session began), allowing for inspection of within-session patterns of responding. Lending support to the use of this program, previous studies have used similar work tasks to assess habituation of reinforcer effectiveness in humans. Specifically, previous studies reinforced computer mouse clicks in a colored square with small amounts of preferred food (Kenzer, Ghezzi, & Fuller, 2013; Temple et al., 2006; Temple, Giacomelli, Roemmich, & Epstein, 2008a; Temple, Giacomelli, Roemmich, & Epstein, 2008b).

2.3 MEASURES

2.3.1 Nicotine dependence

Nicotine dependence was established during the initial visit using a questionnaire based on current criteria for tobacco use dependence in the DSM-V (American Psychiatric Association,

2013). To meet dependence criteria, participants needed to endorse experiencing two or more substance use disorder criteria within the past 12-month period. Criteria included interpersonal problems related to tobacco use, symptoms of withdrawal (i.e., irritability or fatigue when going without smoking for long periods of time), smoking more than intended to, giving up other activities in order to smoke, and repeated unsuccessful attempts to quit.

2.3.2 Withdrawal

Nicotine withdrawal was measured using the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986). The MNWS is an eight item self-report scale, measured on a 0-100 visual analog scale. This measure of withdrawal has been found to have high internal consistency (Cronbach's alpha $\geq$ 0.85), stability in measurement over time (test-retest correlation of 0.71), and high construct validity (Etter & Hughes, 2006).

2.3.3 Expired-air carbon monoxide

Expired-air carbon monoxide (CO) measurement is an objective, noninvasive method to biochemically assess recent smoking exposure. With an average half-life of 4-hrs, expired-air CO has been shown to be sensitive to recent smoking exposure (i.e., 24 hrs; Benowitz et. al, 2002). Expired-air samples were obtained using BreathCO monitors (Vitalograph, Lenexa KS). According the CO monitor's manual, this device is accurate ±3 ppm (Vitalograph, n.d.). Previous studies have found this device to have high internal consistency, with intraclass correlation coefficients ranging from 0.935 to 0.994 (Javors, Hatch, & Lamb, 2005).

2.4 PROCEDURE

2.4.1 Study Design

Because of the lack of prior human research on habituation with drug use, our main goal was to conduct an initial test of nicotine's influence on maintaining reinforcer effectiveness across repeated presentations. The current study was part of a larger study examining the reinforcement enhancing effects of nicotine replacement therapies. While the larger project had additional testing sessions involving other nicotine conditions (nicotine versus placebo nicotine replacement therapies), the current study only focused on the two most extreme nicotine conditions, ad lib smoking to ensure satiation (i.e., nicotine sufficient to prevent withdrawal) and no smoking following overnight abstinence (i.e., no nicotine for >16 hrs). The preliminary findings from the current study may guide future studies to explore the specific mechanisms behind this process, possibly by manipulating exposure to nicotine per se, separate from smoking behavior, as well as smoking behavior separate from nicotine.

It is important to note that participants did receive a placebo patch and administration of a placebo nasal spray in the no nicotine condition, as part of the larger project. The spray and patch combination placebos provided subjects with some expectation of receiving nicotine (perhaps modestly similar to the expectation of receiving nicotine during the smoking session). However, administration of all products (placebo spray and placebo patch in the "no nicotine" session, as well as smoking behavior in the "nicotine" session) occurred at least 20 mins prior to the operant responding trial of interest for the current study, partly to lessen the acute influence of such

expectations on task responding. This is a possible limitation in the current study (discussed below), but was necessary to integrate the project into the larger research study.

2.4.1.1 Initial screening

Participants were screened over the phone to determine initial eligibility (i.e., smoking habits and general health). Those meeting such criteria were scheduled for an introductory session during which they provided informed consent, filled out forms to further determine eligibility (e.g., DSM-V tobacco dependence), and provided demographic information.

Reinforcer selection

At this initial screening session, participants were shown 40 pictures of attractive models, from among those publicly available and collected from the Internet (20 male, 20 female, mixed ethnicity). They rated each picture on a 0-100 visual analog scale (VAS) of how much they liked seeing it, anchored by "not at all" to "extremely". Two pictures scoring $\geq$50 were used as reinforcers, with no repetition between sessions. Participants indicating less than two preferred models (i.e., rated $\geq$50) were shown another 40 pictures of celebrities (20 male, 20 female), obtained in the same manner, to rate using the same VAS form. Participants still unable to identify a total of two preferred pictures, were excluded from the study, as has been done in previous studies of operant responding in humans (Ernst & Epstein, 2002; Temple et al., 2008b). Following successful identification of reinforcers, participants were introduced to the Apple Picker task and completed one trial working without a reinforcer in order to acclimate them to the task and procedures.

Pictures of attractive models (similar to what were available in the current study) have been used in previous studies, one that examined habituation and another exploring nicotine's effect on reward perception (Attwood, Penton-Voak, & Munafo, 2009; Carretie, Hinojosa, & Mercado, 2003). Positively valenced (i.e., preferred) pictures were used for three reasons. First, participants responded on an operant task to earn time viewing the picture. In order to motivate responding (i.e., serve as a reinforcer), the picture must be intrinsically rewarding to the participant. Second, earlier preclinical studies examining habituation of reinforcer effectiveness each used a visual stimulus as a reinforcer (Gancarz, et. al, 2012; Lloyd, Hausknecht, & Richards, 2014). As this study was designed to be a direct translation from a preclinical to clinical sample, a visual stimulus was selected to maintain consistency. Finally, because this was not a consummatory reinforcer, satiation (as defined above) was not possible.

2.4.1.2 Experimental sessions

The habituation trial followed earlier trials of testing nicotine's effects on responding for other, separate reinforcers. This trial consistently followed the completion of the other testing, which was identical across sessions, controlling for testing behavior prior to the main trial of interest.

As noted above, in this within-subjects cross-over design, sessions were identical, varying only in the nicotine dosing earlier in the session (no nicotine versus smoking of own cigarette), the order of which was randomized and counterbalanced across sessions. For the no nicotine condition, participants were required to abstain from all nicotine or tobacco products overnight (>12 hours). In order to verify abstinence, expired-air carbon monoxide was measured upon arrival, using a Vitalograph BreathCO monitor. Expired-air carbon monoxide levels $\leq$10

ppm was used to confirm compliance with overnight abstinence (Benowitz et. al, 2002). As a part of the larger research study, participants received a placebo patch and were administered a placebo nasal spray. Administration of the nasal spray occurred four times, with four sprays each, once every 20 minutes over a period of 80 minutes, with the last spray occurring 20 mins prior to engaging in the Apple Picker task for the current study.

For the nicotine smoking condition, participants were instructed to smoke normally before the session. Expired-air carbon monoxide levels (again measured using Vitalograph BreathCO monitor) ≥10 ppm confirmed typical and recent smoking behavior upon arrival. As a part of the larger research study, participants took a total of 24 puffs (six puffs across four cigarettes, once every 20 minutes) from their preferred brand of cigarette over a period of 80 minutes to ensure no loss of satiation, again with the last puff occurring 20 mins prior to engaging in the Apple Picker task for the current study.

2.5 ANALYSIS PLAN

2.5.1 Dependent variable

The time of each operant response was collected (in seconds since trial onset) and binned into ninety 10-second epochs. The number of responses per 10-second epoch was the main dependent variable for this study. Previous studies have used a single composite measure to quantify the within-session habituation rate (Lloyd, Medina, Hawk, Fosco, & Richards, 2014). However, this composite measure of habituation rate (expressed as the percent decline per epoch per minute)

assumes a linear decline in within-session responding, despite evidence for non-linear patterns of within-session responding (McSweeney, 1992; McSweeney, 2004). Thus, using the number of responses per 10-second epoch allowed non-linear patterns of responding to emerge and for comparisons of such patterns between conditions to be performed.

2.5.2 Analyses

All analyses were performed using SPSS 23.0 (IBM, Chicago, IL). Two separate paired-samples t-tests were conducted to test my first hypothesis, comparing the number of operant responses and duration responding between nicotine conditions. To test my second hypothesis, multi-level modeling (MLM) was performed using the MIXED command in SPSS. This analysis is typically used to examine data arranged in a hierarchical structure (Ciarleglio & Makuch, 2007; Raudenbush & Bryk, 2001; Singer & Willett, 2003). Hierarchical data consists of lower-level observations nested within higher-level groups (the higher-level groups can also be nested within even higher-level groups and so on). For the current study, lower-level within-session time-points (i.e., epochs) were nested within higher-level nicotine conditions. MLM analysis is able to examine influences on the dependent variable at the lower-level (i.e., differences between time-points), between upper-level groups (i.e., differences between nicotine conditions), or at the cross-level interaction where relationships within the lower-level vary as a function of the higher-level group (Mathieu, Aguinis, Culpepper, & Chen, 2012). The cross-level interaction between Level-1 epoch and Level-2 nicotine condition was the main outcome of interest. This tested whether the within-session pattern of operant responding across epochs varied as a function of nicotine condition.

This analysis method required estimation of several models (Raudenbush & Bryk, 2001; Singer & Willett, 2003). The models examined inter-individual differences in responding (Model 1), determined whether the rate of change in responding was linear or curvilinar across epochs (Models 2-4)[3], examined whether inclusion of a time-invariant nicotine condition covariate would further reduce proporitonal variance (Model 5), and identified the covariance structure model that best assessed the error covariance structure of the data (Models 6-8). This model estimation process facilitated the identification of the appropriate rate of change (e.g., linear, quadratic, or cubic), error covariance structure, and parsimonious set of factors to be included in the final model (Model 9). As an indirect test for effects of withdrawal relief, MNWS withdrawal scores were included as a time-invariant covariate without random effects in a separate analysis, using the same parameters as Model 9. The goal of this additional exploratory model was to determine whether patterns of responding were related to self-reported withdrawal. Akaike Information Criterion (AIC; Akaike, 1974) was used to determine the best model. Smaller AIC values indicated the better fitting model. All models were computed using restricted maximum likelihood (REML) estimation.

[3] Because within-session patterns of operant responding have been shown to be non-linear (i.e., quadratic and cubic; McSweeney, 1992; McSweeney, 2004), Models 3 and 4 were used to determine which growth trajectory best fit the data. A linear slope would indicate that the rate of change in responding across epochs was constant. When graphed out, this would look like a straight line across epochs (either increasing, decreasing, or flat). For a quadratic slope, the rate of change in responding would not have been constant across epochs. Instead, the rate of change in responses would increase (or decrease) to a peak (or trough) after which it would decrease (or increase). When graphed out, this would look like a parabola (i.e., U-shaped curve), either first increasing or decreasing depending on the nature of the data. A cubic slope has two stationary points (i.e., one peak and one trough), which form an S-shaped curve when graphed.

3.0 RESULTS

As expected, expired-air CO values were significantly greater upon arrival to the nicotine condition (M = 16.9, SEM = 1.3) than the no nicotine condition (M = 3.9, SEM = 0.4), $t(29) = 9.52$, $p < .001$. Similarly, MNWS withdrawal scores upon arrival were significantly lower during the nicotine condition (M = 9.0, SEM = 3.0) than the no nicotine condition (M = 21.7, SEM = 3.4), $t(29) = 3.70$, $p < .001$.Together, these differences indicate participant compliance to instructions for both sessions--to smoke as normal and to abstain overnight.

Figure 1 shows mean number of responses and duration responding (in seconds) by nicotine and no nicotine conditions. Responding was greater during the nicotine condition (M = 187.4, SEM = 35.0) compared to the no nicotine condition (M = 132.3, SEM = 18.8). The mean difference in number of operant responses between nicotine conditions was significant (mean (SE) difference of 55.1 (25.1) responses), $t(29) = 2.20$, $p < .05$. Similarly, duration of responding was longer during the nicotine condition (M = 186.1 seconds, SEM = 37.0) compared to the no nicotine condition (M = 123.7 seconds, SEM = 18.5; mean (SE) difference of 62.4 (27.6) seconds), $t(29) = 2.26$, $p < .05$. As described in the Analysis section, multiple models were estimated using MLM analysis to determine which best explained observed differences in the pattern of within-session responding for the visual reinforcer as a function of nicotine condition.

The model building process (Models 1-8) is described in the Appendix and the final model (Model 9) is described and interpreted below.

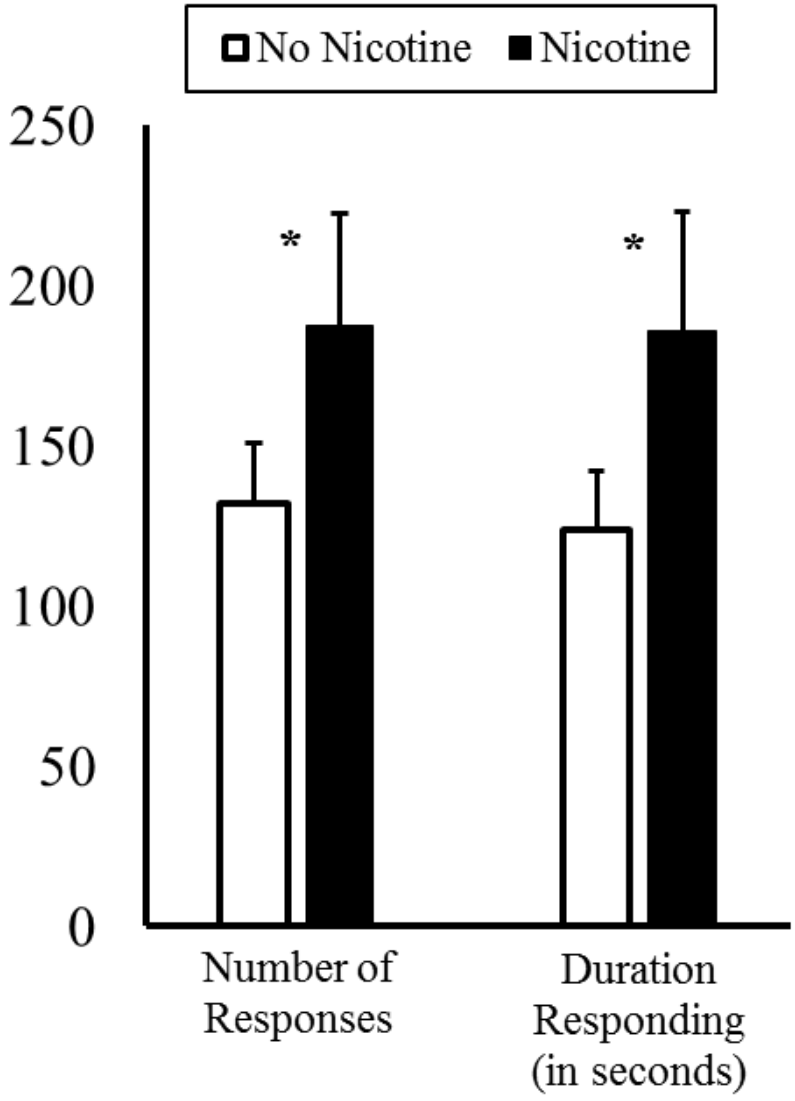

Figure 1. Mean (+SE) number of responses and duration responding (in seconds) by nicotine condition. * p < .05 for the within-subjects comparison between nicotine conditions

3.1 MODEL 9: FINAL MODEL INTERPRETATION

Table 3 contains the estimated parameters for Model 9. As suggested by Singer and Willett (2003), the estimated parameters from the final model were used to create prototypical plots of the data to demonstrate the moderating effect of nicotine condition on rate of change in responding across epochs, displayed in Figure 2. Parameters for the fixed effects, γ_{00}, γ_{10}, γ_{20} and γ_{30}, were interpreted as relating to the no nicotine condition (Singer & Willett, 2003). Estimated mean responding in the first epoch in the no nicotine condition was 10.08, γ_{00}= 10.08, $p < .001$, which declined across subsequent epochs, γ_{10}= -0.56, $p < .001$. The decline in responding over the course of the session is consistent with Rankin and colleagues' (2009) first characteristic of habituation, see Table 1. The rate of decline in responding in the no nicotine condition slowed as the session continued, γ_{20}= 0.01, $p < .001$. However, the rate of decline increased once more later in the session, γ_{30}= -0.00006, $p < .001$.

There was no difference in responding in the first epoch between nicotine conditions, γ_{01}= -0.07, p = .86. Compared to the no nicotine condition, responding in the nicotine condition had a relatively slower rate of linear change over time, γ_{11} = 0.08, $p < .005$. The decline in responding was more gradual later in the session during the nicotine condition relative to the no nicotine condition, γ_{21} = -0.002, $p < .05$. Responding increased late in the session marginally more during the nicotine condition, γ_{31} = 0.00001, p = .059. Differences in the patterns of within-session responding are illustrated in Figure 2.

The estimated variance components indicated significant within-session variability in responding, σ_ε^2 = 6.69, $p < .001$, significant individual differences in responding within the first epoch, σ_0^2 = 21.12, $p < .01$, and significant individual differences in rate of linear (σ_1^2 = 0.03, p <

.001) and quadratic rates of change (σ_2^2 = 0.000002, $p < .001$). There was also significant variance in responding between nicotine conditions, σ_3^2 = 2.19, $p < .001$. The covariance components showed significant relationships between responding in the first epoch and both linear (σ_{01}^2 = -0.73, $p < .001$) and quadratic (σ_{02}^2 = 0.006, $p < .01$) changes in responding over epochs. These relationships suggest that higher amount of responding within the first epoch was associated with a steeper linear decline in responding but increased quadratic change in responding. In other words, the response rate for those who responded more in the first epoch initially decreased more quickly than those who responded less in the first epoch. Additionally, change in responding over time was different between those with initially higher rates of responding and those starting with lower rates of responding. The rate of responding for initially high responders declined at a relatively steep rate which became less steep as the session went on, whereas those with initially lower rates of responding did not have this dampening effect on their rates of responding. Quadratic change in responding was significantly associated with linear change in responding (σ_{12}^2 = -0.0003, $p < .001$), indicating an inverse relationship between these two growth parameters.

To address whether these effects of nicotine on responding for reward may have been due to negative reinforcement (relief of withdrawal) rather than positive reinforcement, exploratory analysis examined the effect of controlling for baseline MNWS withdrawal. When added to the final model as a fixed time-invariant covariate, participants' withdrawal scores did not make a

Table 3. Results of final multi-level modeling analysis model with illustrative data

		Parameter	Model 9 Final Model
Fixed Effects			
Composite Model	Intercept	γ_{00}	10.08***
	Epoch (linear term)	γ_{10}	-0.56***
	Epoch^2 (quadratic term)	γ_{20}	0.01***
	Epoch^3 (cubic term)	γ_{30}	-0.00006***
	NIC	γ_{01}	-0.07
	NIC x Epoch	γ_{11}	0.08***
	NIC x Epoch^2	γ_{21}	-0.002*
	NIC x Epoch^3	γ_{31}	0.00001†
Variance Components			
Level 1:	Within-session	σ_ε^2	6.69***
Level 2:	Intercept	σ_0^2	21.12***
	Linear term		
	variance	σ_1^2	0.03***
	covar with intercept	σ_{01}^2	-0.73***
	Quadratic term		
	variance	σ_2^2	0.000002***
	covar with intercept	σ_{02}^2	0.006**
	covar with linear term	σ_{12}^2	-0.0003***
	NIC		
	variance	σ_3^2	2.19***

Table 3 (continued)

	covar with intercept	σ^2_{03}	0.33
	covar with linear term	σ^2_{13}	0.05
	covar with quadratic term	σ^2_{23}	-0.0008†
Pseudo R^2 Statistics			
		R^2_ε	0.59
Goodness-of-fit			
	AIC		26023.43
	ΔAIC		-384.15

† p < .10, *p < .05, ** p < .01, *** p < .001

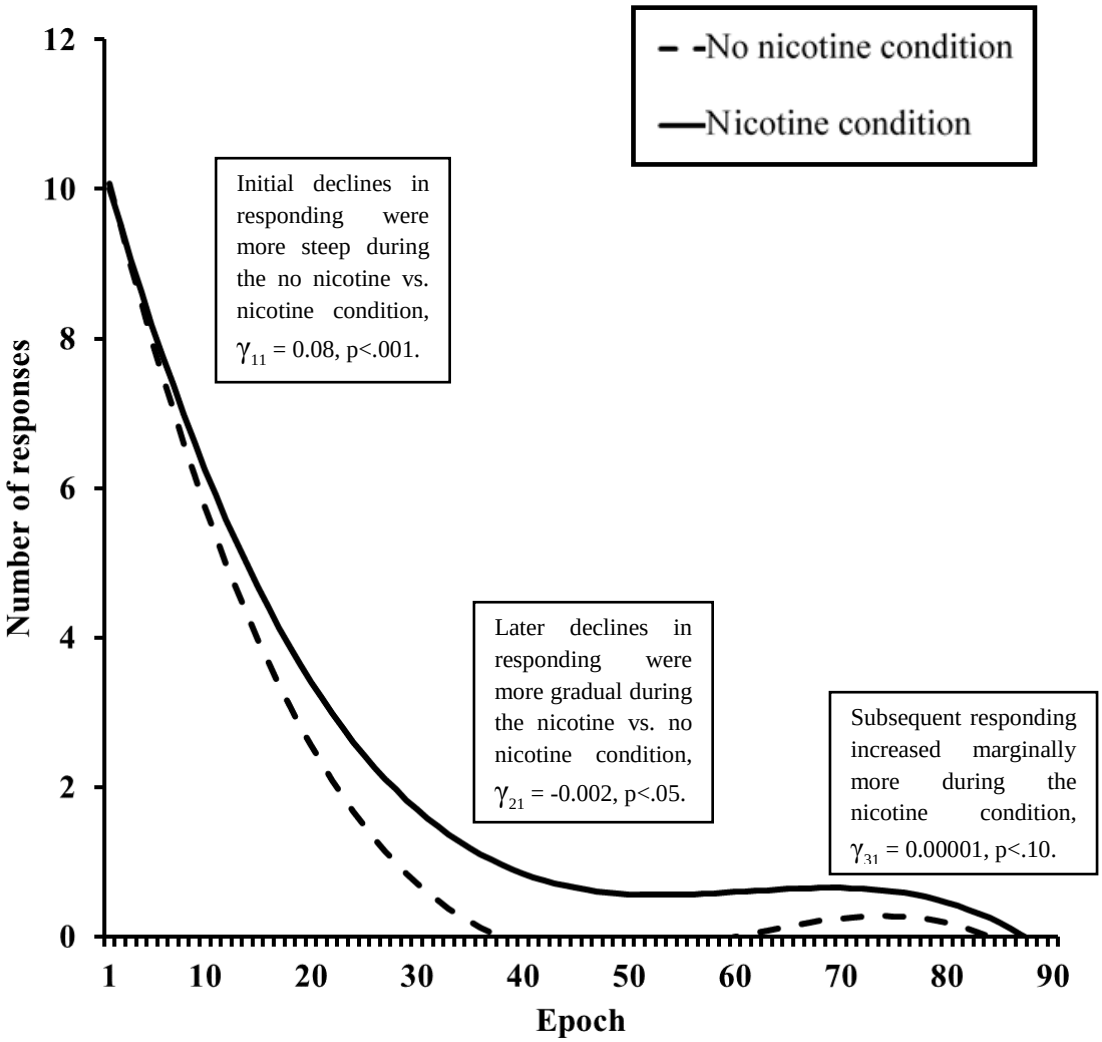

Figure 2. Plot of the moderating effect of nicotine condition on the number of responses across epochs

significant contribution to the model, $\beta = .002$, ns, and other parameters in the model were unchanged. A secondary exploratory analysis tested for order effects on responding. A binary nicotine condition order (no nicotine first/nicotine first) variable as a fixed time-invariant covariate did not make a significant contribution to the model, $\beta = .39$, ns. Controlling for effects of nicotine condition order did not change any other parameters in the model. Results of these exploratory analyses suggest that neither self-reported withdrawal levels nor nicotine condition order influenced differences in the observed patterns of responding between sessions.

4.0 DISCUSSION

The purpose of this study was to examine whether recent exposure to nicotine (via cigarette smoke) versus no nicotine would attenuate declines in operant responding for a visual reinforcer (viewing an attractive photo) attributed to habituation of reinforcer effectiveness. To my knowledge, this may have been the first specific test of this notion in humans, and thus the first to translate the animal research examining nicotine's influence on habituation of reinforcer effectiveness to a human sample. Overall, reinforced responding and duration of responding were each significantly greater in the nicotine condition compared to the no nicotine condition. Together, these results confirmed my first hypothesis: Participants responded more and spent a longer time responding for the reinforcer in the nicotine condition relative to the no nicotine condition. When examining the within-session patterns of responding, the rate of reinforced responding declined less sharply early in the trial and persisted longer under the nicotine versus no nicotine condition. Overall, these results are an initial demonstration of nicotine's (via cigarette smoke) ability to maintain the effectiveness of a reinforcer longer, when compared to a no nicotine control.

There was evidence to support an explanatory role of habituation of reinforcer effectiveness for the observed declines in responding over time. Responding for the available reinforcer declined over the course of the session. This is consistent with the first point on Table

1, which stated that responding would decrease as a function of "repeated application of a stimulus" (Rankin et al., 2009). Also consistent with this point, observed declines in responding were exponential over time. As predicted by Lloyd and colleagues (2014), and demonstrated in Figure 2, there was greater responding during the first epoch of a session than at the last epoch of the preceding session. Taken together, these results lend preliminary support for participants' declines in responding due to habituation of reinforcer effectiveness.

4.1 LIMITATIONS

The current study was part of a larger project designed to assess the reinforcement enhancing effects of nicotine replacement therapies. While there was a nonabstinent cigarette smoking condition, there was no specifically matched placebo (i.e., denicotinized or very low nicotine cigarette) condition to compare. Results of the current study could have been influenced by simple smoking behavior per se. Inclusion of a matched "placebo" cigarette condition would have controlled for smoking behavior between groups, limiting between group differences to nicotine per se. Additionally, the no nicotine condition was not simply a no smoking condition; participants received a placebo patch (at least five hours earlier) and administration of a placebo nasal spray (at least 20 minutes earlier) before the habituation trial of interest, as part of the larger project. Although unlikely, it is conceivable that receiving this no-nicotine patch and/or spray could alter within-session patterns of reinforced responding for the visual reinforcer. On the other hand, if so, such a "control" procedure may have narrowed the difference in responding between the "no nicotine" and "nicotine" conditions, and thus underestimated the magnitude of

nicotine's effects. Thus, follow up studies should include better matched comparison groups to allow for clearer causal relationships to be identified.

The role of withdrawal as an explanatory factor for the observed differences between conditions appears unlikely. As discussed above, self-reported withdrawal did not make a significant contribution to the model and its inclusion in the model did not change other estimates of other parameters from the previous model. Yet, future studies in this line of research should consider including a group of nondependent smokers (i.e., occasional smokers who do not experience withdrawal; Shiffman, 1989) to more directly examine the influence of nicotine withdrawal on habituation of reinforcer effectiveness. We have found similar effects of nicotine on enhancing reinforcement from non-drug rewards in nondependent, as well as dependent smokers (Perkins & Karelitz, 2013), but it is still possible that habituation effects may differ due to level of dependence.

Although this study examined declines in operant reinforced responding due to habituation of reinforcer effectiveness, there was limited demonstration of habituation as operationalized through some of the empirical characteristics of habituation (Table 1; Rankin et al., 2009; McSweeney & Murphy, 2000). However, the first empirical characteristic of habituation (Table 1; Rankin et al., 2009) and Lloyd et al.'s (2014) first and second predictions for habituation of reinforcer effectiveness (see Table 2) were demonstrated, suggesting habituation occurred within each session. Additional studies would be needed to confirm habituation (i.e., meet additional habituation characteristics) and rule out alternate explanations. As noted earlier, satiation is unlikely with a non-consummatory reinforcer (the visual reward), but the individual roles of attention to the task and fatigue may need to be examined. Also, fatigue seems unlikely given the modest response requirement for receipt of each reinforcer.

(The FR10 typically took only 13 seconds to complete, in contrast to other research with progressive ratio schedules, often requiring more than 170 responses for each reinforcement later in a trial before most participants stop responding; e.g., Perkins, Karelitz, & Michael, 2015). Following McSweeney and colleagues' lead, the inclusion of a dishabituating stimulus, changing the operanda following declines in responding, and the use of a delayed matching-to-sample task are examples for future studies in this line of research.

The current study used a within-subjects design, which introduced the possibility of carry over effects. However, as previously discussed, the order of sessions (i.e., nicotine first vs. no nicotine first) did not have a significant effect on within-session patterns of responding in the current study. To more directly address this possible issue in future studies, utilizing a fully between-subjects study design would eliminate the possibility of any carry over effects, although that design also has its own serious practical limitations (e.g., reduced statistical power, increased sample size, etc.; Greenwald, 1976).

4.2 STRENGTHS

The within-subjects design used in the current study provided specific advantages over a between-subjects design. First, each participant acts as their own control, increasing statistical power (Cohen, 1988). In addition, the internal validity of studies utilizing a within-subjects design depends less on random assignment than those using a between-subjects design (Charness, Gneezy, & Kuhn, 2012).

The simplicity of the operant response task, Apple Picker, and participant-specific reinforcers were additional strengths of the current study's design. Responding on the task was simplified to highlighting and selecting boxes on a grid (simulating lever pressing in preclinical research; e.g., Caggiula, Donny, Palmatier, Liu, Chaudhri, & Sved, 2008). Additionally, each participant selected their preferred visual stimulus in the initial screening session. This ensured that the visual stimulus would intrinsically motivate operant responding rather than assuming a universally reinforcing visual stimulus across all participants.

4.3 IMPLICATIONS

The current study was the first to directly demonstrate nicotine via cigarette smoke's ability to maintain a reinforcer's effectiveness across repeated presentations in a human sample. This outcome has implications for better understanding nicotine dependence, smoking prevalence, and cessation treatment efficacy.

My findings were consistent with preclinical research suggesting that nicotine attenuates declines in operant responding attributed to habituation of reinforcer effectiveness (Gancarz, et. al, 2012; Lloyd, Hausknecht, & Richards, 2014). The consistency between preclinical and clinical paradigms lends further support to the translation of the behavioral effects of nicotine across species (O'Dell & Khroyan, 2009). This cross-species validation is important for demonstrating how findings from preclinical studies apply to human samples in clinical research.

Nicotine has modest primary reinforcing effects, suggesting its secondary and tertiary reinforcing effects likely have significant roles in supporting smoking behavior. Declines in

reinforcer effectiveness over time within one session are typically attributed to habituation to the sensory aspects of stimuli, as outlined in the Introduction. Delaying such declines may be yet another way in which nicotine exerts reinforcement enhancing effects and promotes smoking behavior. People smoke in situations rich in sensory stimuli (e.g., while watching television, listening to the radio, socializing with other people, while working or commuting, etc.; Ven Gucht et al., 2010), and over time, stimuli in the smoker's drug taking environment would be expected to become less salient as they habituate to the sensory aspects of the various stimuli. However, following nicotine intake, these stimuli would maintain their reinforcing properties for longer periods of time, which may lead to a perceived richer environment for the smoker.

Lloyd and colleauges (2014) hypothesized that a more rapid habituation of reinforcer effectiveness contributes to difficulty concentrating in those diagnosed with attention deficit hyperactivity disorder (ADHD). Interestingly, the link between cigarette smoking and ADHD is quite strong. Children and adolescents diagnosed with ADHD are more likely to start smoking (Milberger, Biederman, Faraone, Chen, & Jones, 1997), smoking prevalence is higher in adults with ADHD (Pomerleau, Downey, Stelson, & Pomerleau, 1995), and ADHD smokers experience more intense withdrawal symptoms when trying to quit (Liebrenz et al., 2016). Nicotine and nicotine receptor agonists have each shown efficacy in treating symptoms of ADHD (Levin et al., 1996; Potter, Dunbar, Mazzulla, Hosford, & Newhouse, 2014; Potter, Schaubhut, & Shipman, 2014).

Looking at ADHD through the lens of rapid habituation suggests that this subpopulation of smokers may be trying to use nicotine to attenuate rapid declines in reinforcer efficacy. A self-medication hypothesis was proposed by Gehricke et al. (2007), positing that those diagnosed with ADHD "may use cigarettes as a stimulant drug" to alleviate common symptoms such as

attention deficit, impulsivity, and hyperactivity. However, this hypothesis has yet to be adequately tested and empirical support is limited (Glass & Flory, 2010). The current study did not directly test nicotine's ability to attenuate loss of reinforcer effectiveness due to habituation in smokers with ADHD. This is a subpopulation of smokers at an increased risk of becoming dependent, through mechanisms which may be related to nicotine's effects on habituation of reinforcer effectiveness. Future studies within this subpopulation of smokers may help to explain the high smoking prevalence in those diagnosed with ADHD.

Perhaps similarly, a more rapid habituation of reinforcer effectiveness may be experienced when smokers attempt to quit, contributing to difficulty concentrating, a common symptom of nicotine withdrawal (West, Ussher, Evans, Rashid, 2006). Drugs that slow habituation of reinforcer effectiveness (e.g., stimulant medications, and possibly NRT), may aid cessation by restoring these cognitive deficits during a quit attempt. Additional research would be required to test whether cessation treatments (such as bupropion, varenicline, or NRT) delay habituation of reinforcer effectiveness.

The current study was an initial test of nicotine's ability to maintain a visual stimulus' reinforcing effectiveness across repeated presentations using a human sample. Specifically, I hypothesized that nicotine (compared to no nicotine) would lead to increased persistence in responding (i.e., greater responding and time spent responding) and a more gradual decline in responding. Results of this study supported both hypotheses, suggesting that nicotine maintains the reinforcing effectiveness of a preferred visual stimulus by attenuating declines in reinforcement attributed to habituation. Additional research is needed to more fully understand the mechanisms underlying nicotine's role in this dynamic reinforcement process.

APPENDIX A

MULTI-LEVEL MODELING ANALYSES

A.1 MODEL 1: UNCONDITIONAL MEANS MODEL

An unconditional means model was fit without predictors from either level, equivalent to a one-way ANOVA model with a random effect (Raudenbush & Bryk, 2001; Shek & Ma, 2011; Singer & Willett, 2003). This model estimated the overall mean in responding (collapsing across epochs and nicotine conditions; γ_{00}) and the residual variance in responding observed in Level-1 (σ_ε^2) and Level-2 (σ_0^2) units. Because this model does not contain a variable for time, it is also known as a "no change model" (Singer & Willett, 2003). Each residual variance component was tested for significance and the intraclass correlation coefficient was calculated using the formula described below.

The intraclass correlation coefficient (ICC) was computed using parameters estimated in Model 1. The ICC determined the proportion of variance in within-session responding that is due to differences between nicotine conditions (Level-2 units) and the stability of within-session responding (Level-1 units; Mathieu, Aguinis, Culpepper, & Chen, 2012). The equation used for calculating the ICC was:

$$ICC = \frac{\sigma^2}{\sigma^2 + \sigma_\varepsilon^2}$$

Model 1 facilitated computation of the ICC by partitioning the total variance in responding into variation within session (Level-1 units) and variation between sessions or nicotine conditions (Level-2 units).

Table 4 contains estimated coefficients for Models 1 through 5. There was significant within-session residual variability to be explained at Level-1 ($\sigma_\varepsilon^2 = 16.38$, $p < .001$), significant between-session residual variability to be explained at Level-2 ($\sigma_0^2 = 2.26$, $p < .01$), and an ICC of 0.12. Overall, 12% of the variability in responding was due to differences between sessions (i.e., nicotine conditions).

A.2 MODELS 2-4: UNCONDITIONAL GROWTH MODEL TESTING

A series of unconditional growth models were estimated to test whether change in responding was linear (Model 2), quadratic (Model 3), or cubic (Model 4) across epochs. The variable epoch (originally ranging from 1 to 90) was centered at 0 (now ranging from 0 to 89) allowing the Level-1 intercept to represent the true initial status (i.e., number of responses in the first epoch). Introduction of epoch into the model allowed for estimation of individual changes in responding over time. Epoch was used to model linear change over time in Model 2, $Epoch^2$ was added to Model 3 to assess quadratic change in responding, and $Epoch^3$ was added to Model 4 to test cubic change. Each model was nested within the subsequent model (e.g., the unconditional means model nested was within the unconditional linear growth model; the unconditional linear

growth model was nested within the unconditional quadratic growth model, etc.). Models were tested for fit, relative to the prior model, by comparing AIC values, with lower values indicating the better fitting model. Proportional reduction in variance components (i.e., Pseudo R^2) was computed between sequential models to quantify the amount of variation in responding explained by adding additional covariates to the model.

Models 2 and 3 were fit using fixed and random slopes for the intercept and epoch variables. Model 4 was fit without random slopes for the cubic change variable, $Epoch^3$, due to convergence issues with random slopes for this variable. In short, fixed slopes would not allow growth rates to vary across participants whereas random slopes do allow for variation in growth rates across participants (Singer & Willett, 2003).

A.2.1 Model 2

Both fixed effects in the model were significant, $\gamma_{00} = 5.26$, $p < .001$, $\gamma_{10} = -0.08$, $p < .001$, indicating that responding was not constant over time. Estimated mean responding in the first epoch (collapsing across conditions) was 5.26 responses, which declined as the session went on. Those with higher initial values for responding had a lower linear decrease and those with lower initial values had faster linear decreases in responding over time, $\sigma_{01}^2 = -0.16$, $p < .001$. Random error terms for the intercept (σ_0^2) and linear change (σ_1^2) were significant, indicating between-

Table 4. Results of multi-level modeling analysis model building process with illustrative data

		Parameter	Model 1 No change	Model 2 Linear change	Model 3 Quadratic change	Model 4 Cubic change	Model 5 Conditional Cubic Growth
Fixed Effects							
Composite Model	Intercept	γ_{00}	1.78***	5.26***	8.31***	10.04***	10.08***
	Epoch (linear term)	γ_{10}		-0.08***	-0.29***	-0.53***	-0.56***
	Epoch^2 (quadratic term)	γ_{20}			0.002***	0.009***	0.01***
	Epoch^3 (cubic term)	γ_{30}				-0.00005***	-0.00006***
	NIC	γ_{01}					-0.07
	NIC x Epoch	γ_{11}					0.08***
	NIC x Epoch^2	γ_{21}					-0.002*
	NIC x Epoch^3	γ_{31}					0.00001†
Variance Components							
Level 1:	Within-session	σ_ε^2	16.38***	10.65***	7.83***	7.34***	6.69***
Level 2:	Intercept	σ_0^2	2.26***	11.90***	21.95***	21.97***	21.12***
	Linear term variance	σ_1^2		0.002***	0.03***	0.03***	0.03***

Table 4 (continued).

	covar with intercept	σ^2_{01}		-0.16***	-0.70**	-0.70**	-0.73***
	Quadratic term						
	variance	σ^2_2			0.000002***	0.000002***	0.000002***
	covar with intercept	σ^2_{02}			0.005**	0.005**	0.006**
	covar with linear term	σ^2_{12}			-0.0003***	-0.0003***	-0.0003***
	NIC						
	variance	σ^2_3					2.19***
	covar with intercept	σ^2_{03}					0.33
	covar with linear term	σ^2_{13}					0.05
	covar with quadratic term	σ^2_{23}					-0.0008†
Pseudo R^2 Statistics							
		R^2_ε		0.35	0.52	0.55	0.59
Goodness-of-fit							
	AIC		30524.49	28301.45	26732.26	26407.58	26023.43
	ΔAIC			-2223.04	-1569.19	-324.68	-384.15

† $p < .10$, *$p < .05$, ** $p < .01$, *** $p < .001$

session predictors may be able to explain variability in these parameters. Between Model 1 and Model 2, within-session variance decreased from 16.38 to 10.65. This suggested that linear rate of change explained 35% of within-session variance in responding. Inspection of AIC values indicated that Model 2 was a better fit to the data than Model 1, 28301.45 vs. 30524.49, respectively, so the linear growth term was retained in the subsequent model.

A.2.2 Model 3

All fixed effects for this model were significant, $\gamma_{00} = 8.31$, $p < .001$, $\gamma_{10} = -0.29$, $p < .001$, $\gamma_{20} = 0.002$, $p < .001$. Mean responding (γ_{00}) in the first epoch was estimated to be 8.31 which declined linearly over time (γ_{10}). The significant quadratic growth term (γ_{20}) was positive, indicating a deacceleration of the linear decrease. Overall, responding decreased as time went, with the trend for linear decline weakening after the 61st epoch, or just over ten minutes into the trial ($-\gamma_{10}/(2*\gamma_{20})$; Singer & Willett, 2003). Model 3 was a better fit to the data than Model 2, with AIC values of 26732.26 and 28301.45, respectively. The quadratic and linear growth terms were included in the subsequent model.

A.2.3 Model 4

A cubic growth term (Epoch^3) was included as a fixed effect only, due to a non-converging model when included as both fixed and random effects. Fixed effects for the intercept and the linear, quadratic, and cubic growth terms were significant. Estimated mean responding for the

first epoch was 10.04, γ_{00} = 10.04, p < .001. The negative linear growth term, γ_{10} = -0.53, p < .001, indicated that responding initially decreased from the intercept value. The positive quadratic growth term, γ_{20} = 0.009, p < .001, suggested that trend for decline in rate of responding diminished over time. However, the negative cubic growth term, γ_{30} = -0.00005, p < .001, indicated that the deceleration in responding lessened later in the session. As no new random effects were added, the random effects in Model 4 were unchanged from Model 3. Inspection of the AIC values show that Model 4 improved model fit over Model 3, with a decline in AIC of 324.68. Subsequent model testing retained the equation used in Model 4.

A.2.4 Model 5: Conditional Growth Model Testing

A dichotomous variable, "NIC" was added as a fixed and random effect, time-invariant covariate to test for differences in change in responding across epochs between nicotine conditions. This variable was coded as '0' for the no nicotine condition and '1' for the nicotine condition. Specifically, this model tested whether nicotine condition predicted the intercept, linear change, quadratic change, and cubic change terms. Cross-level interactions between NIC x Epoch, NIC x Epoch^2, and NIC x Epoch^3 were also included in Model 5. Initial plans were to remove nonsignificant interaction terms one at a time, starting with the highest order polynomial interaction (West, 2009). However, as discussed below, all interaction coefficients were retained from Model 5.

As shown in Table 4, all fixed main effects (except for NIC) were significant. The cross-level interactions between NIC and the linear and quadratic change terms were also significant. The interaction between NIC and the cubic change term was marginally significant (p = .059).

This model was retained for further testing to determine the appropriate error covariance structure. These coefficients are interpreted and discussed in in relation to Model 9.

A.2.5 Models 6-8 Covariance Structure Testing

Multilevel modeling analysis allows for specifying error covariance structure to ensure the model best fits the data. The error covariance structure is the embodiment of the random effects included in the analysis (Singer & Willett, 2003). Specifying an error covariance structure imposes limitations upon the covariance between the random factors. If the incorrect covariance structure is used, parameter estimates are likely to be biased and inconsistent across the repeated measures (Shek & Ma, 2011). Thus, three error covariance structures were compared, unstructured, compound symmetry, and first-order autoregressive.

An unstructured covariance structure allows the error parameters to take on any value the data demand (Singer & Willett, 2003), often offering the best fit to the data (Shek & Ma, 2011). The compound symmetry structure holds error variance and covariance constant across timepoints and the first-order autoregressive structure assumes a relationship between adjacent timepoints that grows weaker as time increases (Singer & Willett, 2003). Models 6 through 8 were estimated using one of each of these error structures. Inspection of the AIC values across models indicated that the unstructured covariance structure (AIC = 26023.43) was a better fit than either the compound symmetry (AIC = 26799.89) or first-order autoregressive (AIC = 26799.47) structures. The unstructured covariance structure was used for the final model, Model 9.

BIBLIOGRAPHY

Akaike, H. (1974). A new look at the statistical model identification. *IEEE Transactions on Automatic Control*, *19*(6), 716-723. https://doi.org/10.1109/TAC.1974.1100705

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.

Aoyama, K., & McSweeney, F. K. (2001a). Habituation contributes to within-session changes in free wheel running. *Journal of the Experimental Analysis of Behavior*, *76*(3), 289-302. https://doi.org/10.1901/jeab.2001.76-289

Aoyama, K., & McSweeney, F. K. (2001b). Habituation may contribute to within-session decreases in responding under high-rate schedules of reinforcement. *Animal Learning & Behavior*, *29*(1), 79-91. https://doi.org/10.3758/BF03192817

Attwood, A. S., Penton-Voak, I. S., & Munafò, M. R. (2009). Effects of acute nicotine administration on ratings of attractiveness of facial cues. *Nicotine & Tobacco Research*, *11*(1), 44-48. https://doi.org/10.1093/ntr/ntn006

Benowitz, N. L. (1999). Nicotine Addiction. *Primary Care: Clinics in Office Practice*, *26*(3), 611–631. https://doi.org/10.1016/S0095-4543(05)70120-2

Benowitz, N. L., Iii, P. J., Ahijevych, K., Jarvis, M. J., Hall, S., LeHouezec, J., … Velicer, W. (2002). Biochemical verification of tobacco use and cessation. *Nicotine & Tobacco Research, 4*(2), 149–159. https://doi.org/10.1080/14622200210123581

Breslau, N., Kilbey, M., & Andreski, P. (1994). DSM-III-R nicotine dependence in young adults: prevalence, correlates and associated psychiatric disorders. *Addiction, 89*(6), 743-754. https://doi.org/10.1111/j.1360-0443.1994.tb00960.x

Brimer, C. J. (1970). Disinhibition of an operant response. *Learning and Motivation, 1*(4), 346-371. https://dx.doi.org/10.1016/0023-9690(70)90100-1

Caggiula, A. R., Donny, E. C., Chaudhri, N., Perkins, K. A., Evans-Martin, F. F., & Sved, A. F. (2002). Importance of nonpharmacological factors in nicotine self-administration. *Physiology & behavior*, 77(*4*), 683-687. https://doi.org/10.1016/S0031-9384(02)00918-6

Caggiula, A. R., Donny, E. C., Palmatier, M. I., Liu, X., Chaudhri, N., & Sved, A. F. (2008). The role of nicotine in smoking: a dual-reinforcement model. In R.A. Bevins & A.R. Caggiula (Eds), *The motivational impact of nicotine and its role in tobacco use* (pp. 91-109). New York, NY: Springer. https://doi.org/10.1007/978-0-387-78748-0_6

Caggiula, A. R., Donny, E. C., White, A. R., Chaudhri, N., Booth, S., Gharib, M. A., … Sved, A. F. (2001). Cue dependency of nicotine self-administration and smoking. *Pharmacology Biochemistry and Behavior, 70*(4), 515–530. http://doi.org/10.1016/S0091-3057(01)00676-1

Carretié, L., Hinojosa, J. A., & Mercado, F. (2003). Cerebral patterns of attentional habituation to emotional visual stimuli. *Psychophysiology, 40*(3), 381-388. https://doi.org/10.1111/1469-8986.00041

Catania, A. C., & Reynolds, G. S. (1968). A quantitative analysis of the responding maintained by interval schedules of reinforcement. *Journal of the Experimental analysis of behavior*, *11*(3S2), 327-383. https://doi.org/10.1901/jeab.1968.11-s327

Charness, G., Gneezy, U., & Kuhn, M. A. (2012). Experimental methods: Between-subject and within-subject design. *Journal of Economic Behavior & Organization*, *81*(1), 1-8. https://doi.org/10.1016/j.jebo.2011.08.009

Ciarleglio, M. M., & Makuch, R. W. (2007). Hierarchical linear modeling: An overview. *Child abuse & neglect*, *31*(2), 91-98. https://doi.org/10.1016/j.chiabu.2007.01.002

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: L. Erlbaum Associates.

Conklin, C. A. (2006). Environments as cues to smoke: Implications for human extinction-based research and treatment. *Experimental and Clinical Psychopharmacology*, *14*(1), 12–19. https://doi.org/10.1037/1064-1297.14.1.12

Conklin, C. A., Perkins, K. A., Robin, N., McClernon, F. J., & Salkeld, R. P. (2010). Bringing the real world into the laboratory: Personal smoking and nonsmoking environments. *Drug and Alcohol Dependence*, *111*(1–2), 58–63. https://doi.org/10.1016/j.drugalcdep.2010.03.017

Conklin, C. A., Salkeld, R. P., Perkins, K. A., & Robin, N. (2013). Do people serve as cues to smoke? *Nicotine & Tobacco Research*, *15*(12), 2081-2087. http://doi.org/10.1093/ntr/ntt104

Deiches, J. F., Baker, T. B., Lanza, S., & Piper, M. E. (2013). Early lapses in a cessation attempt: lapse contexts, cessation success, and predictors of early lapse. *Nicotine & Tobacco Research*, *15*(11), 1883-1891. https://doi.org/10.1093/ntr/ntt074

Donny, E. C., Caggiula, A. R., Mielke, M. M., Booth, S., Gharib, M. A., Hoffman, A., … McCallum, S. E. (1999). Nicotine self-administration in rats on a progressive ratio schedule of reinforcement. *Psychopharmacology*, *147*(2), 135–142. https://doi.org/10.1007/s002130051153

Donny, E. C., Chaudhri, N., Caggiula, A. R., Evans-Martin, F. F., Booth, S., Gharib, M. A., ... & Sved, A. F. (2003). Operant responding for a visual reinforcer in rats is enhanced by noncontingent nicotine: implications for nicotine self-administration and reinforcement. *Psychopharmacology*, *169*(1), 68-76. https://doi.org/10.1007/s00213-003-1473-3

Donny, E. C., Houtsmuller, E., & Stitzer, M. L. (2007). Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. *Addiction*, *102*(2), 324-334. https://doi.org/10.1111/j.1360-0443.2006.01670.x

Epstein, L. H., Temple, J. L., Roemmich, J. N., & Bouton, M. E. (2009). Habituation as a determinant of human food intake. *Psychological Review*, *116*(2), 384–407. https://doi.org/10.1037/a0015074

Ernst, M. M., & Epstein, L. H. (2002). Habituation of responding for food in humans. *Appetite*, *38*(3), 224-234. https://doi.org/10.1006/appe.2001.0484

Etter, J. F., & Hughes, J. R. (2006). A comparison of the psychometric properties of three cigarette withdrawal scales. *Addiction*, *101*(3), 362-372. https://doi.org/10.1111/j.1360-0443.2005.01289.x

Gancarz, A. M., Ashrafioun, L., San George, M. A., Hausknecht, K. A., Hawk Jr., L. W., & Richards, J. B. (2012). Exploratory studies in sensory reinforcement in male rats: Effects of methamphetamine. *Experimental and Clinical Psychopharmacology*, *20*(1), 16–27. https://doi.org/10.1037/a0025701

Gehricke, J. G., Loughlin, S. E., Whalen, C. K., Potkin, S. G., Fallon, J. H., Jamner, L. D., Belluzzi, J. D., & Leslie, F. M. (2007). Smoking to self-medicate attentional and emotional dysfunctions. *Nicotine & Tobacco Research, 9*(Suppl 4), S523-S536. https://doi.org/10.1080/14622200701685039

Glass, K., & Flory, K. (2010). Why does ADHD confer risk for cigarette smoking? A review of psychosocial mechanisms. *Clinical child and family psychology review*, *13*(3), 291-313. https://doi.org/10.1007/s10567-010-0070-3

Greenwald, A. G. (1976). Within-subjects designs: To use or not to use? *Psychological Bulletin*, *83*(2), 314. https://doi.org/10.1037/0033-2909.83.2.314

Groves, P. M., & Thompson, R. F. (1970). Habituation: A dual-process theory. *Psychological Review, 77*(5), 419–450. https://doi.org/10.1037/h0029810

Harvey, D. M., Yasar, S., Heishman, S. J., Panlilio, L. V., Henningfield, J. E., & Goldberg, S. R. (2004). Nicotine serves as an effective reinforcer of intravenous drug-taking behavior in human cigarette smokers. *Psychopharmacology*, *175*(2), 134–142. https://doi.org/10.1007/s00213-004-1818-6

Henningfield, J. E., Miyasato, K., & Jasinski, D. R. (1983). Cigarette smokers self-administer intravenous nicotine. *Pharmacology Biochemistry and Behavior*, *19*(5), 887-890. https://doi.org/10.1016/0091-3057(83)90099-0

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Archives of general psychiatry*, *43*(3), 289-294. https://doi.org/10.1001/archpsyc.1986.01800030107013

Javors, M. A., Hatch, J. P., & Lamb, R. J. (2005). Cut-off levels for breath carbon monoxide as a marker for cigarette smoking. *Addiction*, *100*(2), 159–167. https://doi.org/10.1111/j.1360-0443.2004.00957.x

Kenzer, A. L., Ghezzi, P. M., & Fuller, T. (2013). Stimulus specificity and dishabituation of operant responding in humans. *Journal of the Experimental Analysis of Behavior*, *100*(1), 61–78. https://doi.org/10.1002/jeab.29

Killeen, P. R., Hanson, S. J., & Osborne, S. R. (1978). Arousal: its genesis and manifestation as response rate. *Psychological Review*, *85*(6), 571. https://doi.org/10.1037/0033-295X.85.6.571

Levin, E. D., Conners, C. K., Sparrow, E., Hinton, S. C., Erhardt, D., Meck, W. H., ... & March, J. (1996). Nicotine effects on adults with attention-deficit/hyperactivity disorder. *Psychopharmacology*, *123*(1), 55-63. https://doi.org/10.1007/BF02246281

Liebrenz, M., Fisher, C. E., Nellen, R., Frei, A., Biechl, A. C., Hiestand, N., ... & Eich, D. (2016). Adult attention-deficit/hyperactivity disorder and nicotine withdrawal: a qualitative study of patient perceptions. *BMC psychiatry*, *16*(1), 1. https://doi.org/10.1186/s12888-016-0911-9

Lloyd, D. R., Medina, D. J., Hawk, L. W., Fosco, W. D., & Richards, J. B. (2014). Habituation of reinforcer effectiveness. *Frontiers in Integrative Neuroscience*, *7*, *1-20*. https://doi.org/10.3389/fnint.2013.00107

Lloyd, D. R., Hausknecht, K. A., & Richards, J. B. (2014). Nicotine and methamphetamine disrupt habituation of sensory reinforcer effectiveness in male rats. *Experimental and Clinical Psychopharmacology*, *22*(2), 166–175. https://doi.org/10.1037/a0034741

Manzardo, A. M., Stein, L., & Belluzzi, J. D. (2002). Rats prefer cocaine over nicotine in a two-lever self-administration choice test. *Brain research*, *924*(1), 10-19. https://doi.org/10.1016/S0006-8993(01)03215-2

Mathieu, J. E., Aguinis, H., Culpepper, S. A., & Chen, G. (2012). Understanding and estimating the power to detect cross-level interaction effects in multilevel modeling. *Journal of Applied Psychology*, *97*(5), 951. https://doi.org/10.1037/a0028380

McSweeney, F. K. (1992). Rate of reinforcement and session duration as determinants of within-session patterns of responding. *Animal Learning & Behavior*, *20*(2), 160-169. https://doi.org/10.3758/BF03200413

McSweeney, F. K. (2004). Dynamic changes in reinforcer effectiveness: Satiation and habituation have different implications for theory and practice. *The Behavior Analyst*, *27*(2), 171-188.

McSweeney, F. K., & Hinson, J. M. (1992). Patterns of responding within sessions. *Journal of the Experimental Analysis of Behavior*, *58*(1), 19-36. https://doi.org/10.1901/jeab.1992.58-19

McSweeney, F. K., Hinson, J. M., & Cannon, C. B. (1996). Sensitization–habituation may occur during operant conditioning. *Psychological Bulletin*, *120*(2), 256-271. https://doi.org/10.1037/0033-2909.120.2.256

McSweeney, F. K., & Murphy, E. S. (2000). Criticisms of the Satiety Hypothesis as an Explanation for Within-Session Decreases in Responding. *Journal of the Experimental Analysis of Behavior*, *74*(3), 347-361. https://doi.org/10.1901/jeab.2000.74-347

McSweeney, F. K., & Murphy, E. S. (2009). Sensitization and habituation regulate reinforcer effectiveness. *Neurobiology of Learning and Memory*, *92*(2), 189-198. https://doi.org/10.1016/j.nlm.2008.07.002

McSweeney, F. K., Murphy, E. S., & Kowal, B. P. (2001). Dynamic changes in reinforcer value: Some misconceptions and why you should care. *The Behavior Analyst Today*, *2*(4), 341-349. https://doi.org/10.1037/h0099952

McSweeney, F. K., & Roll, J. M. (1998). Do animals satiate or habituate to repeatedly presented reinforcers? *Psychonomic Bulletin & Review*, *5*(3), 428-442. https://doi.org/10.3758/BF03208818

McSweeney, F. K., Weatherly, J. N., Roll, J. M., & Swindell, S. (1995). Within-session patterns of responding when the operandum changes during the session. *Learning and Motivation*, *26*(4), 403-420. https://doi.org/10.1016/S0023-9690(05)80004-9

McSweeney, F. K., Weatherly, J. N., & Swindell, S. (1996). Within-session changes in responding during delayed matching-to-sample and discrimination procedures. *Animal Learning & Behavior*, *24*(3), 290-299. https://doi.org/10.3758/BF03198977

Melville, C. L., Rue, H. C., Rybiski, L. R., & Weatherly, J. N. (1997). Altering reinforcer variety or intensity changes the within-session decrease in responding. *Learning and Motivation*, *28*(4), 609-621. https://doi.org/10.1006/lmot.1997.0984

Milberger, S., Biederman, J., Faraone, S. V., Chen, L., & Jones, J. (1997). ADHD is associated with early initiation of cigarette smoking in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(1), 37-44. https://doi.org/10.1097/00004583-199701000-00015

Mook, D. G. (1995). *Motivation: The organization of action* (2nd ed.). New York: W. W. Norton.

Murphy, E. S., & Lupfer, G. J. (2014). Basic Principles of Operant Conditioning. *The Wiley Blackwell Handbook of Operant and Classical Conditioning*, 165-194. https://doi.org/10.1002/9781118468135.ch8

Murphy, E. S., McSweeney, F. K., Smith, R. G., & McComas, J. J. (2003). Dynamic changes in reinforcer effectiveness: Theoretical, methodological, and practical implications for applied research. *Journal of Applied Behavior Analysis*, *36*(4), 421–438. https://doi.org/10.1901/jaba.2003.36-421

Norman, W. D., & Jongerius, J. L. (1985). Apple Picker: Computer software for studying human responding on concurrent and multiple schedules. *Behavior Research Methods, Instruments, & Computers*, *17*(2), 222–225. https://doi.org/10.3758/BF03214387

O'Dell, L. E., & Khroyan, T. V. (2009). Rodent models of nicotine reward: what do they tell us about tobacco abuse in humans? *Pharmacology Biochemistry and Behavior*, *91*(4), 481-488. https://doi.org/10.1016/j.pbb.2008.12.011

Palmatier, M. I., O'Brien, L. C., & Hall, M. J. (2011). The role of conditioning history and reinforcer strength in the reinforcement enhancing effects of nicotine in rats. *Psychopharmacology*, *219*(4), 1119–1131. https://doi.org/10.1007/s00213-011-2439-5

Perkins, K. A., & Karelitz, J. L. (2013a). Reinforcement enhancing effects of nicotine via smoking. *Psychopharmacology*, *228*(3), 479–486. https://doi.org/10.1007/s00213-013-3054-4

Perkins, K. A., & Karelitz, J. L. (2013b). Influence of reinforcer magnitude and nicotine amount on smoking's acute reinforcement enhancing effects. *Drug and Alcohol Dependence*, *133*(1), 167–171. https://doi.org/10.1016/j.drugalcdep.2013.05.016

Perkins, K. A., & Karelitz, J. L. (2014). Sensory reinforcement-enhancing effects of nicotine via smoking. *Experimental and Clinical Psychopharmacology*, *22*(6), 511–516. https://doi.org/10.1037/a0037823

Perkins, K. A., Karelitz, J. L., Jao, N. C., & Stratton, E. (2012). Possible reinforcement enhancing effects of bupropion during initial smoking abstinence. *Nicotine & Tobacco Research*, *15*(6), 1141-1145. https://doi.org/10.1093/ntr/nts224

Perkins, K. A., Karelitz, J. L., & Michael, V. C. (2015). Reinforcement enhancing effects of acute nicotine via electronic cigarettes. *Drug and alcohol dependence*, *153*, 104-108. https://doi.org/10.1016/j.drugalcdep.2015.05.041

Pomerleau, O. F., Downey, K. K., Stelson, F. W., & Pomerleau, C. S. (1995). Cigarette smoking in adult patients diagnosed with attention deficit hyperactivity disorder. *Journal of Substance Abuse*, *7*(3), 373-378. https://doi.org/10.1016/0899-3289(95)90030-6

Potter, A. S., Dunbar, G., Mazzulla, E., Hosford, D., & Newhouse, P. A. (2014). AZD3480, a novel nicotinic receptor agonist, for the treatment of attention-deficit/hyperactivity disorder in adults. *Biological psychiatry*, *75*(3), 207-214. https://doi.org/10.1016/j.biopsych.2013.06.002

Potter, A. S., Schaubhut, G., & Shipman, M. (2014). Targeting the nicotinic cholinergic system to treat attention-deficit/hyperactivity disorder: rationale and progress to date. *CNS drugs*, *28*(12), 1103-1113. https://doi.org/10.1007/s40263-014-0208-9

Rankin, C. H., Abrams, T., Barry, R. J., Bhatnagar, S., Clayton, D. F., Colombo, J., … Thompson, R. F. (2009). Habituation revisited: An updated and revised description of the behavioral characteristics of habituation. *Neurobiology of Learning and Memory*, *92*(2), 135–138. https://doi.org/10.1016/j.nlm.2008.09.012

Raudenbush, S. W., & Bryk, A. S. (2001). *Hierarchical linear models: Applications and data analysis methods*. SAGE publications.

Raudenbush, S. W., et al. (2011). Optimal Design Software for Multi-level and Longitudinal Research (Version 3.01) [Software]. Available from www.wtgrantfoundation.org.

Reese, T. W., & Hogenson, M. J. (1962). Food satiation in the pigeon. *Journal of the Experimental Analysis of Behavior*, *5*(2), 239-245. https://doi.org/10.1901/jeab.1962.5-239

Roll, J. M., & McSweeney, F. K. (1999). Within-session changes in response rate: Implications for behavioral pharmacology. *The Psychological Record*, *49*(1), 15-32.

Rose, J. E., & Levin, E. D. (1991). Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. *British journal of addiction*, *86*(5), 605-609. https://doi.org/10.1111/j.1360-0443.1991.tb01816.x

Rupprecht, L. E., Smith, T. T., Schassburger, R. L., Buffalari, D. M., Sved, A. F., & Donny, E. C. (2015). Behavioral mechanisms underlying nicotine reinforcement. In *The Neuropharmacology of Nicotine Dependence* (pp. 19-53). Springer International Publishing. https://doi.org/10.1007/978-3-319-13482-6_2

Shek, D. T., & Ma, C. (2011). Longitudinal data analyses using linear mixed models in SPSS: concepts, procedures and illustrations. *The Scientific World Journal*, *11*, 42-76. https://doi.org/10.1100/tsw.2011.2

Shiffman, S. (1989). Tobacco “chippers” individual differences in tobacco dependence. *Psychopharmacology*, *97*(4), 539-547. https://doi.org/10.1007/BF00439561

Singer, J. D., & Willett, J. B. (2003). *Applied longitudinal data analysis: Modeling change and event occurrence*. Oxford university press.

Stevenson, J. G., Oliver, J. A., Hallyburton, M. B., Sweitzer, M. M., Conklin, C. A., & McClernon, F. J. (2017). Smoking environment cues reduce ability to resist smoking as measured by a delay to smoking task. *Addictive Behaviors*, *67*, 49-52. https://doi.org/10.1016/j.addbeh.2016.12.007

Stolerman, I. P., & Jarvis, M. J. (1995). The scientific case that nicotine is addictive. *Psychopharmacology*, *117*(1), 2–10. https://doi.org/10.1007/BF02245088

Temple, J. L., Giacomelli, A. M., Roemmich, J. N., & Epstein, L. H. (2008a). Dietary variety impairs habituation in children. *Health Psychology*, *27*(1S), S10. https://doi.org/10.1037/0278-6133.27.1

Temple, J. L., Giacomelli, A. M., Roemmich, J. N., & Epstein, L. H. (2008b). Habituation and within-session changes in motivated responding for food in children. *Appetite*, *50*(2), 390-396. https://doi.org/10.1016/j.appet.2007.09.005

Temple, J. L., Kent, K. M., Giacomelli, A. M., Paluch, R. A., Roemmich, J. N., & Epstein, L. H. (2006). Habituation and recovery of salivation and motivated responding for food in children. *Appetite*, *46*(3), 280-284. https://doi.org/10.1016/j.appet.2006.01.012

Thompson, R. F. (2009). Habituation: a history. *Neurobiology of learning and memory*, *92*(2), 127-134. https://doi.org/10.1016/j.nlm.2008.07.011

Thompson, R. F., & Spencer, W. A. (1966). Habituation: a model phenomenon for the study of neuronal substrates of behavior. *Psychological review*, *73*(1), 16. https://doi.org/10.1037/h0022681

Van Gucht, D., Van den Bergh, O., Beckers, T., & Vansteenwegen, D. (2010). Smoking behavior in context: where and when do people smoke? *Journal of behavior therapy and experimental psychiatry*, *41*(2), 172-177. https://doi.org/10.1016/j.jbtep.2009.12.004

Vitalograph BreathCO Quick Start User Training Manual [Internet]. Lenexa, KS: Vitalograph; [Date unknown; cited 2015 Jan 5]. Available from: http://vitalograph.com/downloads/view/07323

West, B. T. (2009). Analyzing longitudinal data with the linear mixed models procedure in SPSS. *Evaluation & the Health Professions*, *32*(3), 207-228. https://doi.org/10.1177/0163278709338554

West, R., Ussher, M., Evans, M., & Rashid, M. (2006). Assessing DSM-IV nicotine withdrawal symptoms: a comparison and evaluation of five different scales. *Psychopharmacology*, *184*(3-4), 619-627. https://doi.org/10.1007/s00213-005-0216-z