ARE ALL SMOKERS THE SAME? THE IMPACT OF NICOTINE AND NON-NICOTINE FACTORS ON CIGARETTE SMOKING AMONG LIGHT AND INTERMITTENT, AND DAILY DEPENDENT SMOKERS

by

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ABSTRACT

Light and/or intermittent smokers (LITS) and daily dependent smokers (DDS) differ in their smoking patterns and motivations, but the role of nicotine in such differences is unclear. This study assessed the independent and combined influences of nicotine and non-nicotine factors on subjective and behavioural smoking-related outcomes. Forty-one non-treatment seeking smokers (18 LITS) administered nicotine-containing cigarettes (NC), denicotinized cigarettes (DC), nicotine inhalers (NI), or placebo inhalers (PI) across four laboratory sessions following overnight abstinence. Subjects rated their subjective state throughout each session and engaged in a smoking lapse task to assess their smoking behaviour. LITS experienced lower craving and withdrawal, self-administered fewer cigarette puffs ($p \leq .001$) and tended to delay the onset of smoking for longer ($p = .04$, FDR>5%) than DDS. Pre-administration of NC and DC decreased craving and smoking behaviour across participants ($p < .001$), suggesting that a combination of nicotine and non-nicotine factors contribute to modulating cigarette smoking in LITS and DDS alike.

LIST OF ABBREVIATIONS USED

DDS	Daily Dependent Smokers
LITS	Light and Intermittent Smokers
cpd	Cigarettes per day
CO	Carbon monoxide
ppm	Parts per million
DSM	Diagnostic and Statistical Manual of Mental Disorders
MNWS	Minnesota Nicotine Withdrawal Scale
VAS	Visual Analogue Scale
FTCD	Fagerström Test for Cigarette Dependence
NC	Nicotine cigarettes
DC	Denicotinized cigarettes
NI	Nicotine inhaler
PI	Placebo inhaler
NRT	Nicotine replacement therapy
PR	Progressive ratio
mg	Milligram
SPSS	Statistical Package for Social Sciences
n	Sample size
p	p-value for significance testing
F	F-value from linear mixed models
M	Mean
SD	Standard deviation
SE	Standard error
FDR	False detection rate
T1	Time 1
T2	Time 2
T3	Time 3
T4	Time 4

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CHAPTER 1. INTRODUCTION

1.1 Cigarette Smoking

Tobacco smoking has steadily declined over the past several decades. According to 2015 estimates, 10-15% of North American adults are current cigarette smokers, dropping by nearly a third since 1965 (Schiller, Lucas, & Peregoy, 2012; World Health Organization [WHO], 2015). Despite substantial decreases in regular daily smoking (i.e. daily dependent smokers; DDS), the number of light and intermittent smokers (LITS) has increased over the last twenty years (for a review, see Reyes-Guzman et al., 2017). In fact, LITS are thought to encompass approximately one third to half of all adult smokers in North America (Centers for Disease Control and Prevention [CDC], 2011; Jamal et al., 2015; WHO, 2015).

Although there is some degree of consensus about what constitutes DDS (i.e. regular daily smoking, often upwards of 5 or 10 cigarettes per day; Leeman, O'Malley, White, & McKee, 2010; Sweitzer, Denlinger, & Donny, 2013), there is less agreement about what constitutes LITS. For example, some reports have examined intermittent smokers separate from all other daily smokers (e.g. Shiffman, Dunbar, Tindle, & Ferguson, 2015; Tindle & Shiffman, 2011), while others group light daily and non-daily smokers together (e.g. Coggins, Murrelle, Carchman, & Heidbreder, 2009). Notably, studies including light smokers have defined this group by their consumption patterns, including individuals who report consuming anywhere between 1-4, up to 10 cigarettes per day (cpd) (Hajek, West, & Wilson, 1995; Reyes-Guzman et al., 2017; Shiffman, Paty, Kassel, Gnys, & Zettler-Segal, 1994; Zhu, Sun, Hawkins, Pierce, & Cummins, 2003). However, it has been proposed that the number of cpd alone may not be a reliable marker

of smoking status, as cigarettes are heterogenous in content and individuals tend to vary in their rate of drug metabolism (Husten, 2009). Thus, a range of other measures should also be used in combination with cigarette consumption quantities to define smoking subgroups (i.e. biomarkers, standardized dependence assessments).

Despite varying definitions of LITS (e.g. non-daily smoker, up to 10 cpd), the aforementioned studies have found commonalities among other factors, including demographic and smoking characteristics that differ from typical DDS. In fact, many reports show that the majority of LITS have relatively extensive smoking histories, yet smoke infrequently and show little evidence of dependence through traditional measures (i.e. tolerance, withdrawal; Coggins et al., 2009; Reyes-Guzman et al., 2017; Shiffman, 2009). In contrast to the withdrawal-avoidance motives common among DDS (Al-Delaimy et al., 2007), LITS are often motivated by the immediate rewarding effects of smoking (i.e. 'peak-seekers'; Russell, 1971). LITS also tend to be younger, are more likely to start smoking later, and to have a higher educational status, relative to DDS (Reyes-Guzman et al., 2017). Indeed, they likely represent a unique sub-population of smokers, as many LITS do not transition to DDS, even after years of smoking (Shiffman et al., 1994).

1.2 Factors Associated with Smoking

1.2.1 Nicotine Factors

Cigarette smoking tends to be resistant to change. In addition to relatively stable patterns of smoking behaviour, the majority of smokers relapse within one year of a serious quit attempt (Hughes, Keely, & Naud, 2004). The persistence of cigarette smoking has often been attributed to tobacco dependence, wherein the maintenance (i.e.

homeostasis) of plasma nicotine levels is key to avoiding unpleasant symptoms associated with abstinence. Thus, negative reinforcement processes, such as craving and withdrawal avoidance, become primary motivators driving continued cigarette smoking (Benowitz, 2010). Considering the short 2-3 hour half-life of nicotine (Benowitz, 2010), individuals would need to smoke frequently throughout the day to maintain nicotine homeostasis.

Indeed, DDS often engage in regular smoking to avoid symptoms of withdrawal (typically every hour or so; Al-Delaimy et al., 2007), and nicotine replacement therapy (NRT) tends to decrease craving (Niaura et al., 2005) and improve quit rates (Stead et al., 2012), particularly among the highly dependent (Gourlay, Forbes, Marriner, Pethica, & McNeil, 1995). Among LITS however, NRTs appear to be ineffective at curbing cigarette craving (McGrath, Peloquin, Ferdinand, & Barrett, 2015) and at delaying and/or decreasing smoking behaviour (i.e. smoking lapse and relapse; Shiffman et al., 2019). Thus, while traditional theories of smoking that emphasize nicotine dependence account for the majority cigarette smoking among DDS, they tend to account for little variability in smoking behaviour among LITS as many of them do not smoke frequently enough to maintain consistent levels of nicotine (Benowitz, 2010). It is also unlikely that differences in smoking behaviour between DDS and LITS are attributable to variations in nicotine's pharmacokinetic properties, as intermittent smokers absorb and metabolize nicotine in a similar way to DDS (Shiffman, Dunbar, & Benowitz, 2014). Moreover, the extent to which LITS experience and are motivated by symptoms of cigarette withdrawal or craving following extended periods of abstinence remains contested.

A small number of survey-based self-report studies have documented symptoms of dependence, including craving and withdrawal, among LITS (DiFranza et al., 2002; 2007; Fernando, Wellman, & DiFranza, 2006). Specifically, symptoms of cigarette withdrawal have been reported within 1-3 days of abstinence in individuals smoking less than 5 cpd (Fernando et al., 2006), and in individuals who smoke as infrequently as one day per week (DiFranza et al., 2002).

In contrast to these self-report findings, an early experimental study demonstrated an absence of withdrawal symptoms among intermittent smokers following 58 hours of abstinence (Shiffman, Paty, Gnys, Kassel, & Elash, 1995). Similar results were found in naturalistic environments using ecological momentary assessment, such that LITS reported a lack of craving and withdrawal-related symptoms following numerous days of abstinence (Shiffman et al., 2015).

Nicotine may nevertheless serve as a key reinforcer for LITS, despite evidence suggesting that these occasional smokers are not motivated by nicotine maintenance and withdrawal avoidance. As would be expected given the traditional theory of nicotine dependence, when DDS were provided with low nicotine-containing cigarettes, their cigarette craving and consumption reduced relative to higher nicotine-containing cigarettes after six weeks (Donny et al., 2015). Interestingly, a similar finding was observed for LITS, with notable decreases in overall cigarette consumption and cigarette smoking days following a two-week period (Shiffman, Kurland, Scholl, & Mao, 2018). Since LITS do not smoke frequently enough to maintain nicotine levels, this adds support to the idea that they are ‘peak-seekers’ (Russell, 1971), smoking for positive reinforcement to achieve the acute hedonic effects of nicotine (Shiffman, 2009).

In summary, these cumulative findings suggest that LITS are not primarily motivated by nicotine-seeking or nicotine-withdrawal factors in the same way that DDS appear to be. In contrast to DDS, NRTs appear to be ineffective at decreasing smoking behaviour and curbing symptoms of craving among LITS (Shiffman et al., 2019). However, low nicotine-containing cigarettes appear to decrease the motivation to smoke, observed through a reduction of smoking behaviour in LITS (Shiffman et al., 2018) and DDS (Donny et al., 2015). Thus, nicotine is implicated in the reinforcing effects of smoking among all smokers, at least to some extent.

1.2.2 Non-Nicotine Factors

1.2.2.1 Context and Stimuli

If LITS are motivated by the positive pharmacological effects of nicotine, and not by withdrawal avoidance associated with traditional dependence (Shiffman, Dunbar, Tindle, & Ferguson, 2015; Shiffman et al., 1995), then they should theoretically be able to quit smoking relatively easily. However, LITS are persistent smokers and often have difficulty quitting (Tindle & Shiffman, 2011). In fact, LITS make nearly twice as many quit attempts compared to DDS (Reyes-Guzman et al., 2017) and are only slightly more likely to be successful (22% vs. 13%; Tindle & Shiffman, 2011). This bolsters the case to examine other non-nicotine factors that may underlie LITS smoking behaviour such as situational stimuli, sensorimotor components, and perceptions around smoking.

Indeed, situational stimuli are thought to exert a greater influence on smoking behaviour in LITS compared to DDS (e.g. Shiffman & Paty, 2006; Thrul, Bühler, & Ferguson, 2014). The idea that a certain behaviour is influenced by the presence (or absence) of particular stimuli can be explained by the phenomenon of stimulus control.

Through various learning processes, continued smoking can be driven by a range of internal (e.g. mood) and external (e.g. environmental) stimuli (Bickel & Kelly, 1988). If LITS smoking behaviour is limited to certain situations or environments, this would imply that exposure to such stimuli would likely facilitate continued smoking (e.g. strong stimulus control). Indeed, strong stimulus control tends to be pervasive among individuals engaging in occasional, non-dependent substance use (Bickel & Kelly, 1988; Russell, 1971). However, stimulus control is thought to diminish in the transition to dependence (Shiffman & Paty, 2006), as substance using behaviour becomes more habitual and motivated by maintenance.

Consistent with this view, a retrospective self-report study found that LITS tend to endorse cue-exposure and social factors as primary motivators for smoking. This is in contrast to DDS who more frequently endorsed motives associated with dependence, such as tolerance and craving (Shiffman, Dunbar, Scholl, & Tindle, 2012). Comparable results were obtained using ecological momentary assessment in naturalistic environments. Relative to DDS, LITS smoking was often associated with numerous contextual cues, such as socializing, being around other smokers, and being at a bar (Shiffman et al., 2014b). A follow-up study using similar methodology found that LITS experienced significantly stronger stimulus control compared to DDS across all contexts measured, including mood, location, activity, social setting, food/drink consumption, and time of day (Shiffman, Dunbar, & Ferguson, 2015).

Craving also appears to be more closely tied to cigarette smoking among LITS compared to DDS (Shiffman, Dunbar, & Ferguson, 2015; Shiffman et al., 2014b; Shiffman & Paty, 2006; Thrul et al., 2014). This is likely because LITS show very little

craving when they are not smoking, whereas DDS are prone to elevated craving between cigarettes (Shiffman et al., 2014a). Notably, DDS also experienced a significant amount of craving and stimulus control in the aforementioned investigations, however their relationship to smoking behaviour was weaker than that observed among LITS.

The idea that stimulus control can facilitate continued smoking behaviour and explain smoking patterns among both LITS and DDS seems to extend beyond traditional theories of nicotine dependence. To account for both withdrawal avoidance and stimulus control, Shiffman et al. (2015) propose a two-factor model of smoking behaviour. Researchers argue that all smoking is initially motivated by stimulus control, but as dependence develops, smoking becomes primarily driven by withdrawal avoidance. Importantly, the transition to dependence does not simply erase the impact of stimulus control on smoking, rather it is thought to mute these external processes in favour of internal homeostasis (i.e. nicotine maintenance, withdrawal avoidance). This explains why DDS lapse or relapse in the presence of smoking cues even when their nicotine requirements have been satiated and their withdrawal symptoms are suppressed (Shiffman, Ferguson, Gwaltney, Balabanis, & Shadel, 2006). Thus, while stimulus control is likely motivating and maintaining smoking behaviour to some extent among LITS, DDS appear to be influenced by both withdrawal avoidance and stimulus control.

In addition to contextual stimuli, the perception of smoking opportunities can also influence craving and drive smoking behaviour (Schlagintweit, Perry, Darredeau, & Barrett, 2019). Drug use opportunities comprise multiple factors, including (1) beliefs about drug availability, (2) beliefs about drug effects, (3) intention to use the drug, and (4) some desire to use the drug (Wertz & Sayette, 2001). It is hypothesized that the

anticipation of an impending smoking opportunity would increase craving, whereas the absence of an opportunity would impede craving (Wertz & Sayette, 2001).

Indeed, laboratory-based studies that have directly manipulated the availability of smoking opportunities found impacts on subjective, behavioural, and physiological responses. In these investigations, smokers reliably report increased craving and withdrawal in anticipation of an imminent smoking opportunity relative to an absent or delayed opportunity (Carter & Tiffany, 2001; Gloria et al., 2009; Juliano & Brandon, 1998). Naturalistic investigations of smoking behaviour demonstrate comparable findings. Specifically, the odds of smoking reduced by approximately 60% among both DDS and LITS when it was forbidden (Shiffman et al., 2014a). On the other hand, LITS were particularly more likely to smoke when cigarettes were readily available, a 28-fold increase compared to an 11-fold increase for DDS (Shiffman et al., 2014a).

The sensorimotor components of smoking (i.e. taste, smell, tracheobronchial sensations, handling, puffing, and inhaling) can also facilitate continued smoking behaviour (Rose, 2006). In fact, smoking reinforcement is thought to be driven by the combined influence of sensorimotor components and removing some of these factors tends to decrease liking and satisfaction (Breland, Evans, Buchhalter, & Eissenberg, 2002). For example, anesthetizing portions of the respiratory tract decreases cigarette craving (Rose, Tashkin, Ertle, Zinser, & Lafer, 1985), and removing olfactory/taste sensations decreased the reinforcing effects of smoking (Perkins et al., 2001). Additionally, ritualistic behaviours associated with smoking (e.g. taking the cigarette out, holing it and inhaling repeatedly for 5-10 minutes) are often experienced as relaxing (McClernon, Westman, & Rose, 2004), particularly for DDS who smoke multiple times

throughout the day and thus develop strong associations between smoking rituals and reward. This also lends support to the role of stimulus control that drives cigarette smoking among both LITS and DDS to some extent. Lastly, a host of pharmacological factors are also implicated in the rewarding sensorimotor components of smoking.

1.2.2.2 Pharmacology

Nicotine largely facilitates the reinforcing 'scratching' sensation associated with smoking by stimulating nerve endings located throughout the respiratory system (Ginzel, 1975). In line with this finding, nicotine-containing cigarettes are consistently rated as stronger than denicotinized cigarettes (Rose & Behm, 2004a, 2004b), and blocking peripheral nicotinic receptors results in lower ratings of strength and desirability (Rose, Westman, Behm, Johnson, & Goldberg, 1999). While cigarette strength tends to be positively associated with desirability, excessive harshness produced by nicotine is often aversive (Rose, Turner, Murugesan, Behm, & Laugesen, 2010).

Despite the fact that NRTs can significantly improve quit rates among DDS, they tend to be unpleasant (e.g. high ratings of harshness; Rose et al., 2010), and their long-term success rate after 6 months rarely exceeds 20% (Stead et al., 2012). High rates of smoking lapse and relapse can partly be explained by the two-factor model of smoking, where smokers become more reactive to smoking-related cues and stimuli following periods of abstinence even when withdrawal symptoms are satiated (e.g. increased stimulus control; Shiffman et al., 2015). Importantly, continued smoking behaviour can also be motivated by other non-nicotine constituents of cigarette smoke. For instance, tar in cigarettes can interact with nicotine to dampen harshness associated with nicotine

vapors, making smoking more acutely reinforcing than the use of NRTs (Rose et al., 1999).

To assess the relative impacts of nicotine and non-nicotine pharmacology on craving and smoking behaviour, Barrett (2010) conducted a laboratory-based study with a group of low and highly dependent smokers (as measured through the Fagerström Test for Cigarette Dependence (FTCD; Fagerström, 2012)). Participants were administered four products (nicotine cigarettes (NC), denicotinized cigarettes (DC), nicotine inhalers (NI), and placebo inhalers (PI)) in counterbalanced order followed by an ad libitum smoking task where subjects had the opportunity to earn puffs of their preferred brand of cigarette. Overall, NC and DC were rated as more subjectively satisfying, and the pre-administration of either tobacco product significantly reduced craving compared to the NI. Yet, only NC reduced the amount of preferred cigarette self-administration, with no differences between high and low dependence groups. Other laboratory-based studies found similar results. Notably, DC and low-dose nicotine cigarettes alleviated craving, but their ability to reduce withdrawal symptoms was less consistent (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005; Rose & Behm, 2004).

These cumulative findings allude to a fundamental role for both nicotine and non-nicotine factors in maintaining cigarette smoking among all smokers. Numerous studies suggest that DDS smoke frequently to maintain nicotine levels and avoid withdrawal. Importantly, they also tend to experience strong stimulus control and recurrent cravings that makes abstinence difficult, even when nicotine levels are maintained. On the other hand, LITS often smoke for the reinforcing effects of nicotine and appear be primarily driven by stimulus control and craving. However, the extent to which pharmacological

factors (e.g. nicotine vs. non-nicotine tobacco) influence craving, withdrawal, and smoking behaviour in LITS compared to DDS remains unclear. This prompts the need for laboratory-based studies that allow careful investigations into the mechanisms facilitating smoking behaviour among these heterogeneous subgroups of smokers.

1.3 Laboratory-Based Models of Cigarette Smoking

Although naturalistic studies such as ecological momentary assessment have a high degree of ecological validity and far-reaching implications, they lack internal control, making it difficult to attribute outcomes to one particular variable. Thus, modeling what has been observed in naturalistic studies in a controlled laboratory setting is key to informing knowledge and future investigations, including costly clinical trials. Indeed, human laboratory models of smoking behaviour can be used to bridge the gap between pre-clinical animal studies, naturalistic observation, and clinical trials.

In addition to providing basic insight into mechanisms facilitating smoking behaviour, laboratory models can also be used to examine medication efficacy for relapse prevention. A single smoking lapse is considered to be one of the best predictors of smoking relapse (Marlatt, Curry, & Gordon, 1988; Norregaard, Tonnesen, & Petersen, 1993). While lapses tend to occur shortly after abstinence and are defined as any amount of smoking (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996), relapses are defined as a return to typical smoking over multiple days (Hughes et al., 2003). Notably, the first lapse represents the important transition from abstinence to smoking (Shiffman et al., 1996). Thus, in addition to quantifying cigarette smoking, examining the ability to resist the first cigarette (i.e. smoking lapse) is necessary to provide insight into smoking lapse behaviour (McKee, 2009).

McKee (2009) developed and validated (McKee, Weinberger, Shi, Tetrault, & Coppola, 2012) a laboratory smoking lapse task comprising the ability to resist the first cigarette, and subsequent smoking behaviour. In the paradigm, participants are initially exposed to a known antecedent of smoking, such as nicotine deprivation or stress. They are then presented with their preferred brand of cigarette, an ashtray, and a lighter, and are instructed that they can begin a self-administration period or receive monetary reinforcement in exchange for certain intervals of time that they delay smoking (e.g. every 5-minutes). When participants choose to smoke or the delay period ends, they engage in the self-administration period. Importantly, this provides participants with standard smoking cues and a perceived smoking opportunity, both of which are related to craving and smoking behaviour (Carter & Tiffany, 2001; Shiffman et al., 2014b). Previous investigations employing this task typically use a 50-minute delay period followed by a 60-minute self-administration period. Monetary reinforcement has ranged from $0.20-$1.00 per every 5-minute delay, and smoking behaviour is measured in whole cigarettes (e.g. McKee et al., 2012; Pang & Leventhal, 2013; Roche et al., 2014).

Studies have found that known predictors of smoking lapse, including nicotine deprivation, dependence severity, withdrawal, and cue-exposure reduced participants ability to delay smoking (McKee, 2009; McKee et al., 2012; Roche et al., 2014; Stevenson et al., 2017). Additionally, pharmacotherapies for smoking cessation tended to improve heavily dependent smokers ability to delay smoking (McKee et al., 2012). These cumulative findings would suggest that the laboratory smoking lapse paradigms are relatively sensitive to factors that predict and inhibit smoking, providing key insight into the mechanisms underlying smoking lapse behaviour among DDS. To my knowledge

however, laboratory-based smoking lapse studies have yet to be conducted with LITS. LITS and DDS tend to vary in their experiences of craving and withdrawal (Shiffman et al., 2014a), smoke for different reasons (Reyes-Guzman et al., 2017), and respond to pharmacotherapies in different ways (Shiffman et al., 2019; Stead et al., 2012). However, it is unclear to what extent nicotine and non-nicotine factors differentially influence smoking lapse and drive cigarette smoking among LITS relative to DDS.

1.4 Study Aims and Hypotheses

This study therefore aimed to clarify the independent and combined influences of nicotine and non-nicotine factors on a number of subjective and behavioural smoking-related outcomes among a heterogeneous sample of non-treatment seeking smokers (LITS, DDS). Following overnight smoking abstinence and different pharmacological manipulations (NC, DC, NI, PI), we were specifically interested in examining (1) cigarette craving and withdrawal, (2) the ability to resist smoking, and (3) subsequent smoking behaviour in the presence of salient smoking cues and a known smoking opportunity using a modified smoking lapse paradigm (McKee, 2009; McKee et al., 2012).

Previous investigations using the McKee smoking lapse paradigm have found that 30-36% of heavily dependent smokers abstained for the entire 50-minute delay period (Roche et al., 2014; Stevenson et al., 2017). Since we are using the task among a range of dependent and non-dependent light smokers, we propose a lengthened 120-minute delay task. This length roughly corresponds with the half-life of nicotine (2-3 hours; Benowitz, 2010) and would allow for the recovery of some previously desensitized nicotinic receptors (i.e. no longer fully satiated; Picciotto, Addy, Mineur, & Brunzell, 2008; Picard

et al., 2013). Whether participants wait the full 120-minutes or decide to smoke immediately (range: 1-3 hours from product administration), this length of time should be sufficient to observe differences between DDS and LITS with regards to withdrawal symptom onset and any enduring effects of acute pharmacological manipulation on cigarette smoking. We also propose a self-administration paradigm that measures smoking behaviour in puffs versus whole cigarettes (Barrett, 2010). It is speculated that this should enhance the sensitivity of the paradigm to detecting medication and other effects of interest.

It has been demonstrated that LITS experience strong stimulus control (Shiffman et al., 2015), and that DDS also experience stimulus control, even when their withdrawal symptoms are supressed (Shiffman et al., 2006). Since the smoking lapse paradigm incorporates smoking cues (cigarettes, lighter, ashtray) and an anticipated smoking opportunity, we expected that none of the products would reliably delay smoking onset (i.e. smoking lapse) in either DDS or LITS. We also hypothesized that DDS would experience higher levels of craving and withdrawal throughout the sessions relative to LITS (Shiffman et al., 2014a), and that they would self-administer more cigarette puffs overall since they generally smoke more than LITS.

We hypothesize that the tobacco products (NC, DC) would reduce cigarette craving among DDS (Barrett, 2010; Buchhalter et al., 2005; Faulkner et al., 2018; Rose & Behm, 2004a), and likely among LITS, relative to nicotine alone. Consistent with nicotine maintenance theories of dependence, only the nicotine products (NC, NI) would decrease cigarette withdrawal among DDS (Shiffman et al., 2006). Lastly, only a combination of nicotine and tobacco (NC) would decrease cigarette self-administration

(Barrett, 2010). Findings from the present study provide key insight into the nicotine and non-nicotine factors motivating smoking behaviour among LITS relative to DDS.

CHAPTER 2. MATERIALS AND METHODS

2.1 Participants

Forty-one (15 female) adult smokers were included in the study. To define smoking subgroups (DDS and LITS), we employed multiple methodologies (the Fagerström Test for Cigarette Dependence (FTCD; Fagerström, 2012) in addition to the number of cpd), as per guidelines proposed by Husten (2009). Twenty-three (8 female) were Daily Dependent Smokers (DDS), defined as smoking daily and scoring ≥3 on the FTCD (Fagerström, 2012), suggesting they were moderately to highly dependent on tobacco. Eighteen (7 female) were Light and Intermittent Smokers (LITS), defined as smoking ≥1 cigarette per month, but ≤10 cpd and scoring zero on the FTCD, indicating they were non-dependent.

During a telephone screening interview, all participants reported being medically healthy, not having any current psychiatric disorder, and not taking prescription medication (with the exception of contraceptives in females). Additionally, participants reported being regular smokers for at least the past year, did not intend to quit smoking within the next 30 days, were not currently using any form of nicotine replacement therapy (NRT), and had no prior experience using nicotine inhalers. Overall, participants ranged in age from 20 to 65 years (mean = 32.51, standard deviation (SD) = 12.56). Table 1 presents details on additional participant demographic characteristics.

Table 1

Means and standard deviations for participant demographic variables

Variable	Mean (SD)		
	Total Sample (n = 41)	Daily Dependent Smokers (DDS; n = 23)	Light & Intermittent Smokers (LITS; n = 18)
Age in years	32.51 (12.56)	**37.26 (14.16)**	**26.44 (6.51)**
Cigarettes per day	7.59 (6.18)	**11.58 (5.06)**	**2.49 (2.72)**[1]
FTCD	2.76 (2.79)	**4.91 (1.76)**	**0 (0)**
Age of first tobacco use	14.96 (3.57)	**13.54 (3.41)**	**16.78 (2.96)**
Number of years as a smoker	12.65 (11.72)	**17.27 (13.34)**	**6.75 (5.19)**
Number of quit attempts	1.78 (2.74)	2.13 (2.85)	1.33 (2.61)
Sex (% female)	36.6%	34.8%	38.9%

Note. Bolded values represent significant group differences (DDS vs. LITS; all $p < .05$).
[1] If non-daily smoker (n = 14), cigarettes per day was calculated from average number of cigarettes per week.

2.2 Materials

Carbon monoxide measurement. A breath carbon monoxide (CO) analyzer (Vitalograph, UK) was used to verify smoking abstinence. This instrument is considered to be a valid and reliable measure of acute tobacco smoke exposure and smoking status (Benowitz et al., 2002).

Cigarettes. The nicotine-containing cigarettes (NC) (Yellow Light Natural American Spirit, Reynolds American, Santa Fe, New Mexico, USA) contained 11.1 mg of tar and 1.32 mg of nicotine, and the denicotinized cigarettes (DC) (Quest 1 Vector Tobacco, Mebane, North Carolina, USA) contained 10 mg of tar and 0.05 mg of nicotine.

Inhalers. Nicotine-containing inhalers (NI) (10mg; 4mg deliverable, Pharmacia, Mississauga, Ontario, Canada) and nicotine-free placebo inhalers (PI) were identical in appearance, however, the PIs contained pharmacologically inert cellulose filters. All inhalers were flavoured differently with citrus or mint solution containing menthol, thymol, and eucalyptol (Johnson & Johnson Inc., Markham, Ontario, Canada).

Heart rate. A Polaris Heart Rate monitor (Polar Electro Canada Inc., Lachine, Quebec, Canada) consisting of a chest strap and digital app was used to assess average heart rate over 60-seconds.

Demographic information and smoking patterns. Demographic information (e.g. sex, age, highest level of education) as well as smoking history and patterns (e.g. age of first cigarette, number of quit attempts, number of cigarettes smoked per day) were assessed with the use of an author-compiled Demographics and Smoking History Questionnaire.

Subjective withdrawal symptoms. The Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986, 1998) was used to assess withdrawal symptoms. The MNWS included eight items corresponding with DSM-5 Tobacco Withdrawal Symptoms (American Psychiatric Association [APA], 2013) in addition to a single 'craving' item. Respondents rated each item on a scale from 0 (not present) to 3 (severe). Since prior research suggests that craving is distinct from other withdrawal symptoms (Hughes & Hatsukami, 1986), it was not included in the total withdrawal score calculation. The remaining eight items were averaged to produce an overall withdrawal score (Hughes & Hatsukami, 1998).

Subjective cigarette craving. A single 'craving' item from the MNWS was analyzed separately to provide a craving score.

Product liking. A Visual Analogue Scale (VAS) consisting of one item ('like product') was used to assess subjective liking of the product participants received (NI, PI, NC, or DC). The item was rated on a 10cm horizontal line with labeled integers 1-10 and endpoints anchored at 'Not at all' and "Extremely'. Similar scales have been demonstrated to be reliable and sensitive to subjective individual experiences (Bond & Lader, 1974).

Product content rating. A five-item questionnaire was used to asses subjective content ratings of the product participants received. Each item (nicotine content, tar content, strength, flavour, harshness) was rated on a scale from 1 to 10 with variable endpoint labels (e.g. 'no nicotine', 'very bad flavour' to 'very high nicotine', 'extremely harsh').

Smoking lapse. A modified laboratory analogue of smoking lapse behaviour (McKee, 2009; McKee et al., 2012) was used to examine the extent to which participants are able to delay smoking. At the onset of the delay period, participants were presented with a lighter, an ashtray, and their preferred brand of cigarette. They were instructed that they could smoke at any time, but that they would earn $0.10 for each minute they delay smoking for a maximum of $12 over 120 minutes. Similar tasks have been demonstrated as sensitive to abstinence-related effects (McKee et al., 2012).

Smoking self-administration. Subsequent smoking behaviour was assessed with the use of a computerized progressive ratio (PR) task. The PR task began immediately following completion of the smoking lapse task (e.g. once participants indicated they wanted to smoke, or the delay period ended). To earn puffs of their preferred cigarette they were required to press keys on a keyboard for a predetermined number of times. The first puff required 10 key presses and the number of presses required to earn subsequent puffs increased by a ratio of 1.3. Participants were instructed that they could smoke as much or as little as they wanted over 60 minutes, but that they would have to remain seated with one of their preferred cigarettes in the ashtray in front of them. Similar PR tasks have been shown to be sensitive to changes in craving (Willner, Hardman, & Eaton, 1995), pharmacological manipulation (Barrett, 2010), and smoking status (Darredeau, Stewart, & Barrett, 2013).

2.3 Procedure

Participants attended four double-blind experimental sessions during which they received one of the four product conditions (NC, DC, NI, PI) in randomized order. After providing written consent to participate, overnight smoking abstinence (≥12 hours) was

verified with the use of a carbon monoxide (CO) analyzer (Vitalograph, UK), with a maximum cut-off of 15 parts per million (ppm). A minimum 12-hour abstinence from alcohol, cannabis, and other drugs, and 2-hour abstinence from caffeine was verified verbally through self-report. Participants then completed a cigarette craving and withdrawal questionnaire (MNWS) and their heart rate was assessed over 60 seconds (Time 1; T1). If it was their first session, participants also completed a demographics and smoking history questionnaire.

Next, participants were presented with either an inhaler (NI, PI) or cigarettes (NC, DC) accompanied by instructions that the product may or may not contain nicotine. An independent blinder prepared and administered the products such that the researchers were unaware of their true nicotine content. In order to standardize product self-administration, participants were instructed to take two second inhaler puffs every ten seconds over the course of 20 minutes, or to take two second cigarette puffs every fifteen seconds over the course of 10 minutes (equivalent to approximately two cigarettes), as prompted by an audio recording (Darredeau & Barrett, 2010a).

Immediately following product self-administration, participants rated how much they liked the cigarette or inhaler they received and filled out a questionnaire assessing their subjective cigarette craving and withdrawal symptoms. Their heart rate was also assessed over the course of 60 seconds (Time 2; T2). To achieve similar nicotine plasma concentrations following the nicotine-containing cigarette and inhaler administration, a 60-minute absorption period followed (Schneider, Olmstead, Franzon, & Lunell, 2001) during which participants had the option to watch a their choice of pre-approved television shows (e.g. no smoking-related cues). Participants then completed an

additional craving and withdrawal questionnaire, and their heart rate was reassessed (Time 3; T3).

Next, participants engaged in a modified smoking lapse task (McKee, 2009; McKee et al., 2012) lasting up to 120 minutes. They were seated comfortably at a table with their preferred brand of cigarette, a lighter, and an ashtray, and were instructed that they could smoke at any time, but they would earn a small amount of money for each minute they delayed. Once participants informed the researcher they wanted to smoke, or the full 120 minutes lapsed, they began a computerized PR task (Barrett, 2010) where they had the option to smoke as much or as little as desired over the subsequent 60 minutes. The experimenter remained with the participants throughout the duration of the delay and self-administration period to ensure compliance with the protocol. Upon completion of the PR task, participants rated the product they received at the beginning of the session in terms of its nicotine and tar content, strength, flavour, and harshness.

2.4 Statistical Analyses

Data were analyzed using linear mixed models in SPSS version 25 (SPSS Inc., Chicago, Illinois, USA). Model simplicity and likelihood ratio tests were conducted to determine the optimal covariance structure for each model. Primary outcomes were subjective product ratings (liking, nicotine and tar content, strength), subjective cigarette craving and withdrawal, heart rate (averaged over 60 seconds), latency to smoking lapse (in minutes), and cigarette self-administration (number of cigarette puffs earned during the PR task). A random intercept was selected for all models to account for individual differences in outcome measures.

For craving, withdrawal, and heart rate models, Time (T1, T2, T3) and Smoking Status (DDS, LITS) were entered with fixed slopes, and Product (NC, DC, NI, PI) was entered with random slopes to account for individual differences in pharmacodynamic responses. Product, Time, and Smoking Status interaction terms were also added as per a priori research questions. Among the plausible covariance structures tested, Compound Symmetry was selected as the optimal matrix for these models.

For subjective product ratings and behavioural outcomes (latency to smoking lapse, cigarette self-administration), Product and Smoking Status were entered with fixed slopes. A Product by Smoking Status interaction term was also included. Since all slopes were fixed, an Identity covariance structure was used for the final models.

Alpha was set at 0.05, and the Benjamini-Hochberg method was used to determine the false detection rate (FDR) within each model tested. To control for type 1 error, the FDR was set at .05 such that there was less than a 5% chance that any finding was a false positive. Thus, when alpha <.05 but FDR >.05, findings were considered to be false positives. Tests of simple main effects were performed on the pairwise comparisons between estimated marginal means. Tests comparing estimated marginal means were adjusted for multiple comparisons using the Sidak procedure. Notably, all means are reported as estimated marginal means.

2.5 Data Screening

Model residuals were screened to assess for normality and influential multivariate outliers. The craving and smoking lapse models appeared to be relatively normally distributed and did not contain any influential multivariate outliers. The cigarette withdrawal and self-administration models both appeared to have moderately high

kurtosis and contained 4 influential outlier cases (3 and 1 respectively). Similarly, the heart rate model appeared to have high kurtosis, a right skew, and contained 3 influential outliers. The product rating models appeared to be relatively normally distributed and did not contain any influential outliers.

It has been demonstrated that logarithmic data transformations rarely improve data variability and/or normality and tend to be challenging to interpret (Feng et al., 2014). Thus, transformation techniques were not applied to the data even in cases where deviation from normality was observed.

All models were run including and excluding influential outliers. Because the identified cases were likely true population outliers and not data entry errors, results are reported including all cases. A supplementary analyses section (see Appendix A) reports statistics on affected models excluding the influential outlier cases. Notably, none of the findings differed between analyses including and excluding outlier cases (i.e. there were no differences between analyses in the statistically significant effects reported).

CHAPTER 3. RESULTS

3.1 Study Completion

Overall, 29 of the 41 participants completed all four experimental sessions, while the remaining 12 participants attended 1-3 sessions. Of the 29 completers (11 LITS, 18 DDS), protocol deviations occurred in six sessions (affecting four participants; e.g. power outage, withdraw from product self-administration early), thus data from the affected sessions was excluded after T1. Additionally, one participant failed to complete the withdrawal symptom questionnaire during two time points. Lastly, due to device malfunction, heart rate data was not available for two sessions for two participants, and one time-point for two participants.

No significant differences were found in average number of cigarettes per day or FTCD score between participants who completed 1-3 session and participants who had completed all 4 sessions. However, males were more likely than females to complete all study sessions. It is possible that female participants found the products they received at the beginning of the sessions more aversive than males. Exploratory analyses examining ratings of product liking and harshness found no sex differences, however, suggesting that other factors may have influenced this discrepancy.

3.2 Subjective Product Ratings

A main effect of Product was found for subjective product liking ($F(3, 94.73)=19.67$, $p<.001$), ratings of nicotine content ($F(3, 91.95)=17.92$, $p<.001$), tar content ($F(3, 92.06)=28.96$, $p<.001$), strength ($F(3, 91.83)=24.11$, $p<.001$), and harshness ($F(3, 90.40)=30.61$, $p<.001$). No main effect of Product was observed for flavour ratings ($p=.131$). See Table 2 for means, standard errors, and pairwise comparisons.

A Product by Smoking Status interaction was also observed for ratings of tar, $F(3, 92.06)=3.30$, $p=.024$, with DDS rating NI significantly higher in tar (M=3.23, SE=.48) compared to LITS (M=1.06, SE=.57, $p=.004$). Additionally, a main effect of Smoking Status was observed for flavour ratings, $F(1, 36.51)=5.15$, $p=.029$, with LITS tending to rate all products higher in flavour (M=4.40, SE=.36) compared to DDS (M=3.31, SE=.32). A Smoking Status by Product interaction was also found, $F(3, 93.31)=3.50$, $p=.018$. Specifically, LITS rated NI and PI significantly higher in flavour (M=4.41, SE=.63; M=5.10, SE=.60 respectively) relative to DDS (M=2.14, SE=.53; M=2.76, SE=.56 respectively; all $p<.006$).

No main effect of Smoking Status was identified for tar ratings ($p=.41$), and no main effects of Smoking Status or interactions were observed for product liking, nicotine content, harshness, and strength (all $p>.10$).

Table 2

Estimated marginal means and standard errors for product ratings by Product

Product ratings	M (SE)				Significant effects (p<.05)
	NC	DC	NI	PI	
Liking	5.60 (.36)	4.32 (.37)	2.49 (.37)	2.66 (.37)	NC, DC > NI, PI NC > DC
Nicotine content	5.92 (.41)	4.15 (.42)	4.62 (.42)	1.75 (.43)	NC, DC, NI > PI NC > DC
Tar content	5.11 (.36)	4.50 (.36)	2.14 (.37)	1.22 (.37)	NC, DC > NI, PI
Strength	5.88 (.39)	3.55 (.40)	4.54 (.40)	1.40 (.41)	NC, DC, NI > PI NC > DC
Harshness	5.63 (.40)	3.64 (.41)	5.29 (.41)	1.16 (.42)	NC, DC, NI > PI NC, NI > DC
Flavour	4.51 (.39)	3.69 (.40)	3.27 (.41)	3.93 (.41)	No effect of Product

3.3 Primary outcomes

3.3.1 Smoking Lapse

On average, participants delayed 71 minutes before smoking (range = 0-120 minutes) and abstained for the full 120 minutes 41.8% of the time. A main effect of Smoking Status was observed for smoking lapse, $F(1, 36.93)=4.54$, $p=.04$, with a tendency for LITS to delay smoking for longer than DDS (M=85.40, SE=10.05; M=56.91, SE=8.82 respectively). However, the FDR for this finding was >5% (adjusted $p=.12$), thus was potential false positive. No main effect of Product ($p=.398$) or interaction between Product and Smoking Status ($p=.60$) was identified.

3.3.2 Smoking Self-Administration

A main effect of Smoking Status was observed for smoking self-administration, $F(1, 35.79)=20.99$, $p<.001$, see Figure 1a. Specifically, DDS self-administered significantly more cigarette puffs during the PR task (M= 16.87, SE=1.11) relative to LITS (M=9.20, SE=1.26). A main effect of Product on ad-libitum smoking was also found, $F(3, 78.53)=5.82$, $p=.001$, see Figure 1b. Specifically, the consumption of NC (M=11.49, SE=.94) decreased the number of self-administered puffs relative to PI (M=14.59, SE= .96; $p<.001$). No interaction between Product and Smoking Status was identified ($p=.547$).

Since the PRT began at variable times for each participant (i.e. when they decided to smoke), we conducted a supplementary analysis including Time Lapse as a covariate in the model. None of the findings differed between analyses including Time Lapse as a covariate and those reported previously.

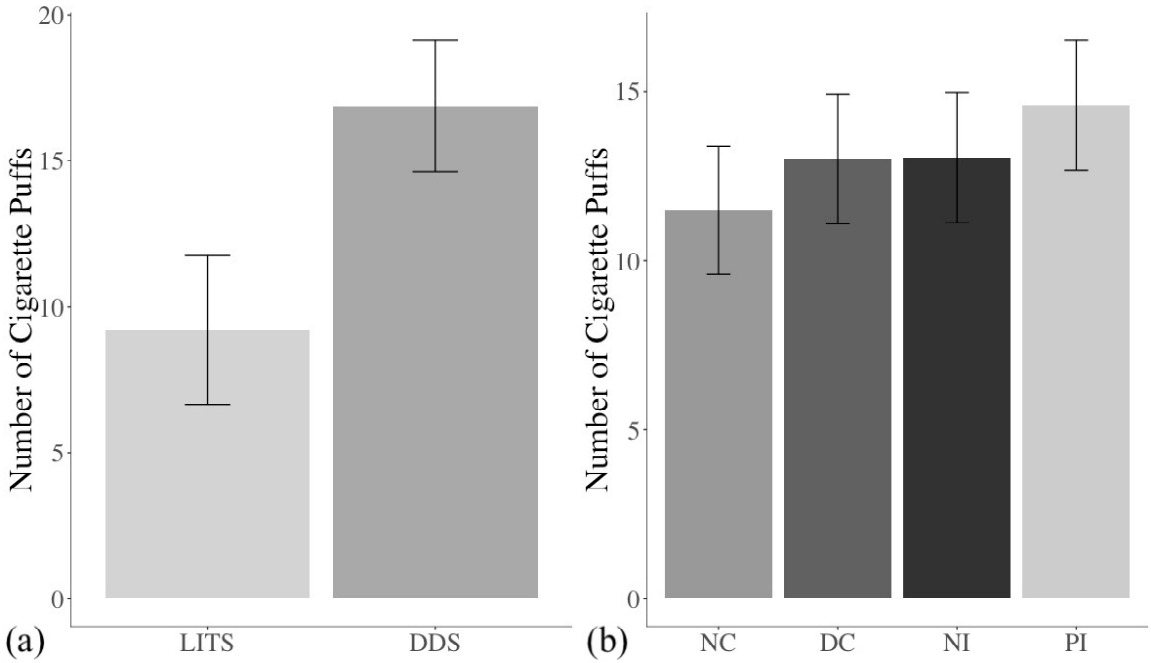

Figure 1. Estimated marginal means and 95% Confidence Intervals for number of cigarette puffs earned on the PR task. (a) Daily Dependent Smokers (DDS) self-administered significantly more cigarette puffs relative to Light and Intermittent Smokers (LITS) (p<.001). (b) Pre-administration of nicotine cigarettes (NC) significantly reduced the number of cigarette puffs earned relative to placebo inhaler (PI) (p<.001).

3.3.3 Heart Rate

A main effect of Time was observed for average heart rate, $F(2, 228.21)=12.08$, $p<.001$, with significantly higher average heart rates at baseline (T1; M=76.83, SE=1.58) and immediately following product administration (T2; M=77.82, SE=1.58) compared to after the 60 minute absorption period (M=74.13, SE=1.58; $p=.002$, $p<.001$ respectively). Additionally, a main effect of Product was observed, $F(3, 84.52)=10.25$, $p<.001$, with higher average heart rates in the NC (M=80.91, SE=1.75) condition compared to NI (M=74.50, SE=1.76), PI (M=73.70, SE=1.75), and DC (M=75.93, SE=1.75; $p<.001$, $p<.001$, $p=.004$ respectively). Lastly, there was a Product by Time interaction, $F(6, 228.48)=7.21$, $p<.001$, see Figure 2. All significant differences were found immediately succeeding product self-administration (T2), with higher average heart rates following the consumption of NC (M=86.64, SE=1.96) compared to NI (M=75.17, SE=1.98), PI (M=71.55, SE=1.97), and DC (M=77.91, SE=1.97; all $p<.001$), as well as following DC relative to PI ($p=.006$). No other interactions or main effects of Product were found (all $p>.065$).

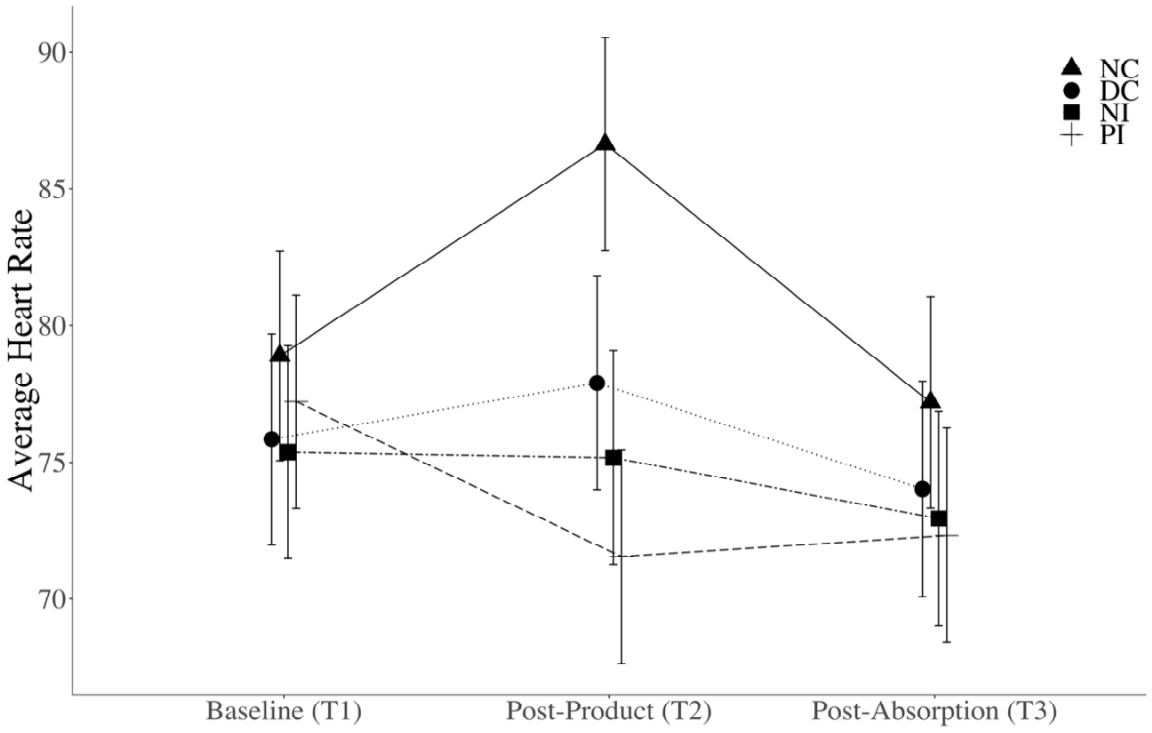

Figure 2. Estimated marginal means and 95% Confidence Intervals for average heart rate by Product and Time. All significant effects were found following product administration (T2). Administration of nicotine cigarettes (NC) significantly increased average heart rate relative to denicotinized cigarettes (DC), nicotine inhaler (NI), and placebo inhaler (PI) (p<.001). DC increased average heart rate relative to PI (p=.006).

3.3.4 Cigarette Withdrawal

A significant main effect of Time was observed for cigarette withdrawal, $F(2, 235.91)=6.70$, $p=.001$, with higher withdrawal scores at baseline (T1; M=.61, SE=.07) and after the 60-minute absorption period (T3; M=.57, SE=.07) compared to immediately following product administration (T2; M=.49, SE=.07; $p=.001$, $p<.037$ respectively). A main effect of Smoking Status was found, $F(1, 38.14)=4.34$, $p=.044$, such that DDS experienced more withdrawal symptoms overall relative to LITS, however the FDR for this finding was >5% (adjusted $p=.103$).

Lastly, a Time by Smoking Status interaction was observed for cigarette withdrawal, $F(2, 235.91)=7.10$, $p=.001$, see Figure 3. Specifically, DDS had significantly higher withdrawal scores at baseline (T1; M=.83, SD=.09) compared to LITS (M=.39, SE=.11, $p=.004$). LITS withdrawal scores did not vary significantly over time (all $p\geq.627$), whereas DDS experienced significantly less cigarette withdrawal following product administration (T2; M=.57, SD=.09) relative to baseline (T1; M=.83, SD=.09, $p<.001$) and following the absorption period (T3; M=.70, SD=.09, $p=.025$). DDS experienced the most withdrawal symptoms at baseline compared to all other time points assessed (all $p\leq.015$). No other interactions or main effects of Product were observed (all $p\geq.07$).

Since LITS experienced a steady, low level of cigarette withdrawal throughout the study, and DDS experienced withdrawal symptoms that fluctuated significantly over time, we conducted exploratory post-hoc analyses on the impact of Product among DDS (without LITS). A Product by Time interaction was observed for cigarette withdrawal among DDS, $F(6, 138.10)=2.28$, $p=.039$, with significantly lower withdrawal scores

immediately following the consumption of NC (T2; M=.42, SE=.13) relative to PI (M=.72, SE=.13, p=.043). However, the FDR for this finding slightly exceeded the 5% threshold (adjusted p=.058).

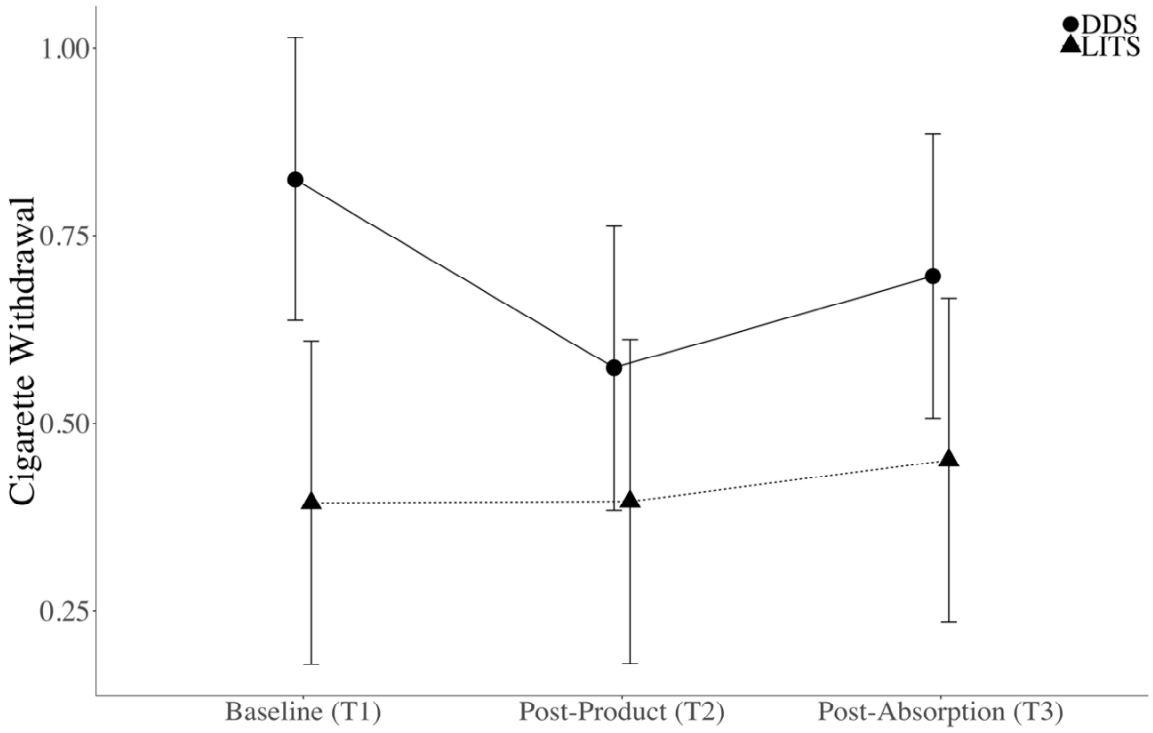

Figure 3. Estimated marginal means and 95% Confidence Intervals for cigarette withdrawal scores by Smoking Status and Time. Daily Dependent Smokers (DDS) reported significantly higher withdrawal scores at baseline (T1) relative to Light and Intermittent Smokers (LITS) (p=.004). DDS reported significantly lower levels of withdrawal following product administration (T2) relative to baseline (T1) and following the absorption period (T3). DDS also reported higher withdrawal scores at baseline relative to post-product absorption (T3; all $p \leq .025$).

3.3.5 Cigarette Craving

A main effect of Time was observed for craving, $F(2, 231.15)=31.48$, $p<.001$, with higher craving scores at baseline (T1; M=1.40, SE=.12) compared to after product administration (T2; M=.93, SE=.12) and following the absorption period (T3; M=1.20, SE=.12; $p<.001$, $p=.002$ respectively). Additionally, craving scores after product administration (T2) were significantly lower than scores following the absorption period (T3; $p<.001$). A main effect of Smoking Status was also observed for craving, $F(1, 39.394)=16.38$, $p<.001$, such that DDS reported higher overall craving (M=1.63; SE=.15) compared to LITS (M=0.73; SE=0.17, $p<.001$). Moreover, a main effect of Product was observed for craving, $F(3, 85.16)=11.24$, $p<.001$, such that craving scores were significantly lower in the NC condition (M=.95; SE=.13) compared to NI (M=1.25; SE=.13; $p<.021$) and PI (M=1.48; SE=.13; $p<.001$), in addition to lower craving in the DC condition (M=1.04; SE=.13) compared to PI ($p<.001$).

A significant Product by Time interaction for craving was also identified, $F(6, 231.32)=8.89$, $p<.001$, see Figure 4. Relative to baseline (T1), lower craving scores were observed following the consumption (T2) of NC (M=.49, SE=.14, $p<.001$), DC (M=.64, SE=.15, $p<.001$), and NI (M=1.09, SE=.15, $p=.038$). In the NC and DC conditions, craving scores increased from T2 to T3 (post-absorption; $p=.001$, $p=.002$, respectively), however craving at T3 remained significantly lower than baseline (T1; $p<.001$, $p=.025$, respectively). There was no change in craving scores following T2 in the NI condition (all $p\geq.454$). Moreover, lower craving scores were observed following consumption (T2) of NC and DC relative to NI ($p<.001$, $p=.01$ respectively) and PI (M=1.50, SE=.15; both $p<.001$). After the 60-minute absorption period (T3), craving scores remained

significantly lower in the NC (M=.91, SE=.14) and DC conditions (M=1.07, SE=.15) relative to PI (M=1.56, SE=.15; $p<.001$, $p=.004$ respectively).

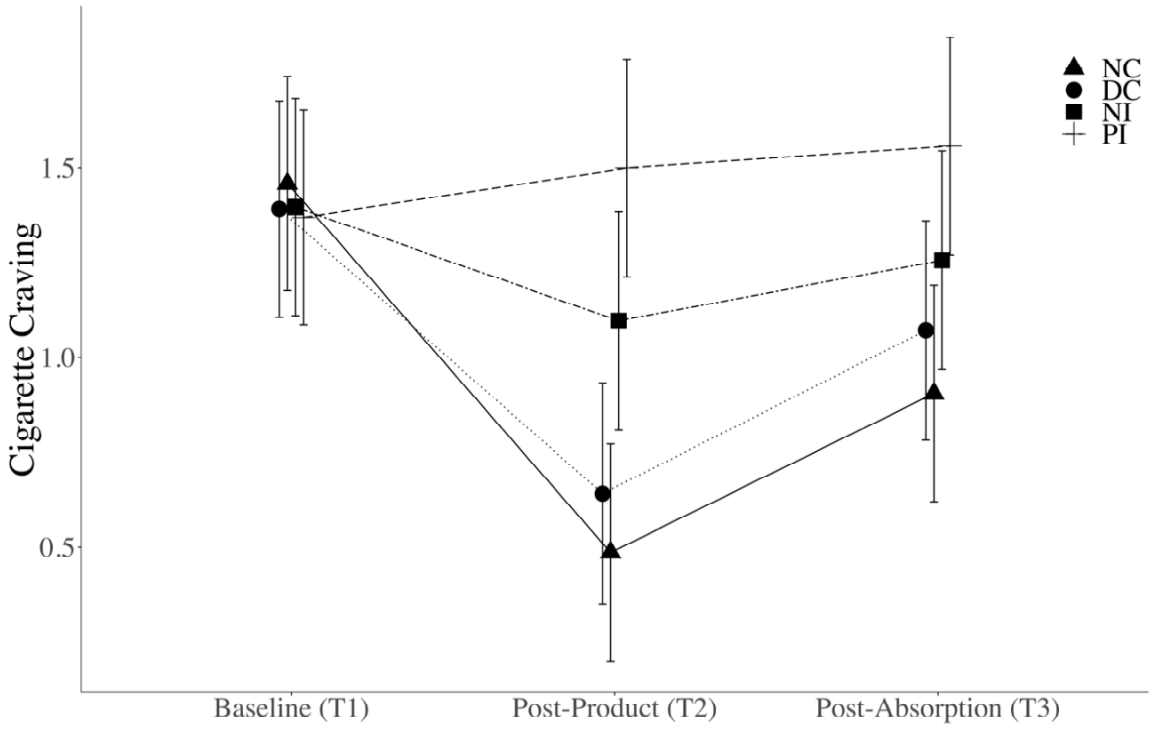

Figure 4. Estimated marginal means and 95% Confidence Intervals for cigarette craving scores by Product and Time. Following product administration (T2), nicotine cigarettes (NC) and denicotinized cigarettes (DC) significantly decreased craving relative to nicotine inhaler (NI) and placebo inhaler (PI) ($p \leq .01$). Following absorption (T3), craving scores were significantly lower in NC and DC conditions relative to PI ($p \leq .004$). Craving decreased from baseline (T1), following the administration (T2) of NC, DC, and NI ($p \leq .038$), and increased from T2 to T3 post-NC and DC consumption ($p \leq .002$). Craving was significantly higher at baseline (T1) relative to T3 in the NC and DC conditions ($p \leq .025$).

Lastly, a Smoking Status by Time interaction was observed for craving, $F(2, 231.15)=4.92$, $p=.008$, see Figure 5. Compared to LITS, DDS reported significantly higher craving scores at baseline (T1), following product administration (T2), and at the end of the absorption period (T3). Detailed statistics are reported in Table 3. LITS craving was significantly lower following product administration (T2) relative to baseline (T1; $p=.005$), however did not change significantly between T2 and T3 ($p=.645$). In contrast, DDS experienced significantly less craving immediately following product administration (T2), relative to baseline (T1), and following the absorption period (T3; all $p<.001$). DDS craving levels at baseline (T1) were also significantly higher than those following product absorption (T3; $p<.001$). No other interactions were observed (all $p\geq.39$).

Table 3

Estimated marginal means, standard errors, and p-values for craving ratings by Time and Smoking Status

Variable	M (SE)	*p*
T1 (Baseline)		
LITS	.85 (.18)	<.001
DDS	1.96 (.15)	
T2 (Post-product administration)		
LITS	.57 (.18)	.003
DDS	1.30 (.15)	
T3 (Post-absorption period)		
LITS	.76 (.18)	<.001
DDS	1.64 (.15)	

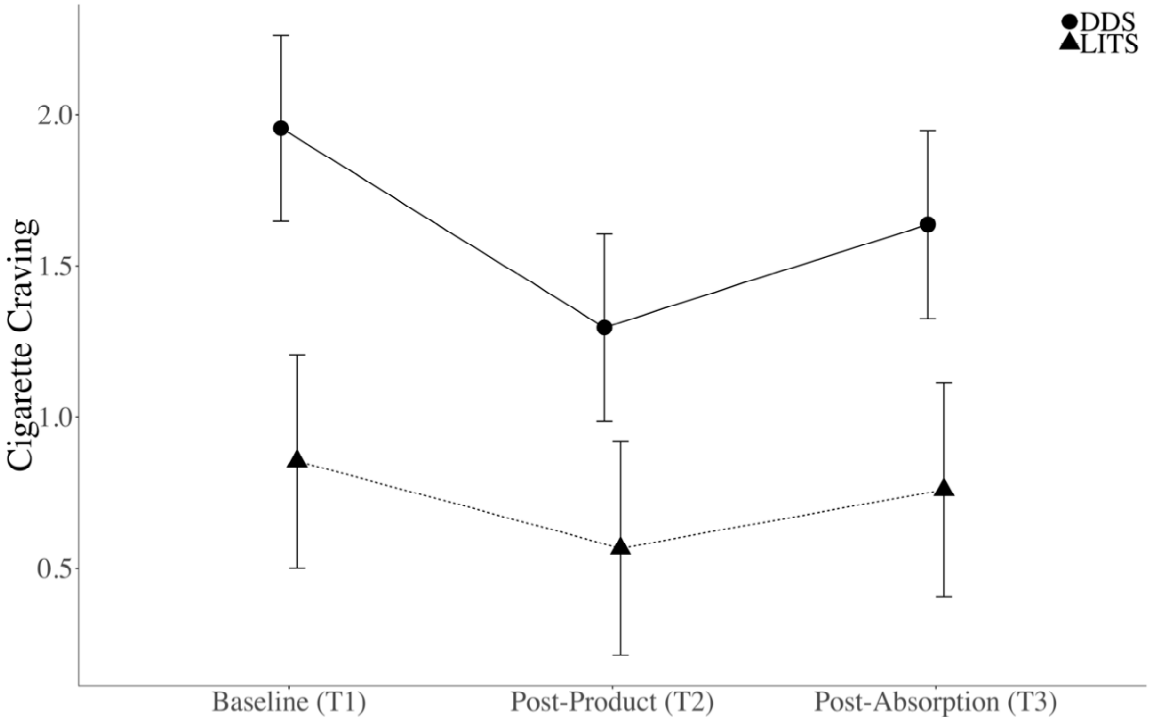

Figure 5. Estimated marginal means and 95% Confidence Intervals for cigarette craving scores by Smoking Status and Time. Relative to Light and Intermittent Smokers (LITS), Daily Dependent Smokers (DDS) reported significantly higher cigarette craving scores at baseline (T1), following product administration (T2), and following the absorption period (T3) ($p \leq .003$). LITS craving was significantly lower following product administration (T2) relative to baseline (T1; $p = .005$), while DDS craving was significantly lower following product administration (T2) relative to baseline (T1) and following the absorption period (T3). DDS also experienced higher craving at baseline (T1) compared to following the absorption period (T3; all $p < .001$).

CHAPTER 4. DISCUSSION

4.1 Overview of Study Aims and Methodology

The purpose of the present work was to examine how nicotine and non-nicotine factors collectively and independently impacted cigarette craving and withdrawal, smoking lapse, and subsequent smoking behaviour among LITS and DDS. In order to achieve this aim, a sample of non-treatment seeking LITS and DDS participated in four experimental laboratory sessions where they received a series of products (NC, DC, NI, PI) in randomized, double-blind order following overnight abstinence. Each product manipulated nicotine and tobacco content allowing for the investigation of nicotine alone (NI), nicotine in the context of a tobacco cigarette (NC), and a tobacco cigarette without nicotine (DC), relative to placebo (PI) (Barrett, 2010). In addition to completing subjective assessments of craving and withdrawal throughout each session, participants engaged in a modified smoking lapse task (McKee, 2009; McKee et al., 2012) modeling key features of lapse behaviour, including the extent to which they could delay smoking, and the quantity of subsequent cigarette self-administration. To date, this task has only been used among DDS; therefore, we modified the paradigm in attempt to enhance its' sensitivity to detecting any potential effects among LITS.

4.2 Overview of Main Findings

In addition to highlighting differences between LITS and DDS, the present results demonstrate that non-nicotine factors make important contributions to the reinforcing properties motivating cigarette smoking in all smokers. Nicotine was also found to influence the rewarding value of smoking, but only in the context of other non-nicotine factors. Findings also emphasize the impact of salient smoking cues on the ability to

delay smoking over and above the effect of pharmacological factors for both LITS and DDS. Taken together, the present results suggest that an interaction of nicotine and non-nicotine factors are implicated in modulating cigarette craving, withdrawal, and smoking behaviour among all smokers.

Consistent with previous investigations, LITS in our study varied from DDS on a number of key demographic characteristics (e.g. Coggins et al., 2009; Reyes-Guzman et al., 2017; Shiffman, 2009). For example, in addition to having lower dependence scores and smoking fewer cpd relative to DDS, LITS tended to be younger, started using tobacco later in life, and reported being a smoker for a shorter amount of time. While LITS reported an absence of traditional dependence (FTCD=0), both DDS and LITS had a comparable amount of unsuccessful lifetime quit attempts, suggesting that other factors may be motivating their continued smoking.

In line with the idea that LITS are not motivated by cigarette dependence, we hypothesized that LITS would report less abstinence-induced cigarette craving and withdrawal compared to DDS. Smoking status was initially found to impact overall withdrawal scores, however FDR analyses revealed that this effect may have been (>5%) a false positive. Upon further investigation, DDS only experienced a significantly higher degree of withdrawal symptoms compared to LITS following overnight abstinence (i.e. at baseline). We discovered that LITS reported consistently low levels of withdrawal symptoms throughout the study, whereas withdrawal symptoms among DDS followed a U-shaped curve, with the lowest level of symptoms reported immediately following product administration (i.e. T2). These laboratory findings extend previous research from

naturalistic studies showing a lack of withdrawal symptoms among LITS following extended periods of abstinence (Shiffman et al., 2015, 1995).

With regards to cigarette craving, DDS reported significantly higher craving ratings overall and at each time point throughout the study. In contrast to withdrawal symptoms, both DDS and LITS craving scores followed a similar U-shaped curve, with more intense craving fluctuations among DDS. While LITS experienced consistently low levels of withdrawal, their craving levels tended to be more variable over time. This is in contrast to craving and withdrawal levels among DDS which tended to follow similar, fluctuating trends. The observed patterns of craving and withdrawal are consistent with the idea that LITS experience phasic cravings, fluctuating in the presence of certain situational stimuli, but do not likely experience background cravings driven by withdrawal-related mechanisms (Shiffman et al., 2014a). In the context of the present study, both LITS and DDS may have experienced phasic increases in craving because of a known smoking opportunity (Carter & Tiffany, 2001; Schlagintweit, Greer, Good, & Barrett, 2015), however it is also possible that pharmacological manipulation played a role in modulating cigarette cravings.

We were interested in examining the extent to which nicotine and non-nicotine pharmacological factors influenced craving and withdrawal among LITS and DDS. Interestingly, none of the products reliably decreased cigarette withdrawal among any of the participants, rather, it appears as though the administration of products *in general* resulted in an immediate decrease in withdrawal symptoms. While this was identified as a significant main effect of Time (i.e. across all smokers), visual inspection of withdrawal scores among DDS and LITS (Figure 3) indicate that this decrease following product

administration is likely driven by DDS and weakened by LITS. To further investigate this possibility, exploratory post-hoc analyses with DDS alone found that the consumption of NC (relative to PI) resulted in an immediate decrease in withdrawal symptoms. Overall, these findings were partially in line with our initial hypothesis that nicotine-containing products would result in an alleviation of withdrawal symptoms among DDS. In fact, nicotine with and without tobacco has been shown to play a key role in decreasing withdrawal-related symptoms and craving among DDS (Darredeau & Barrett, 2010b; Darredeau et al., 2013; Schlagintweit & Barrett, 2016; Shiffman et al., 2006). While it is possible that the dose of nicotine in the inhaler was insufficient to attenuate withdrawal symptoms, we used a strict dosing regimen to maximize nicotine exposure (Barrett, 2010; Schneider et al., 2001). Another explanation is that our sample of non-treatment seeking moderate-to-heavily dependent smokers (i.e. DDS) were simply less responsive to nicotine in the context of an inhaler as NRTs tend to be most effective among treatment-motivated, heavily dependent smokers (Gourlay et al., 1995).

To assess the impact of pharmacological manipulation on cigarette craving, we first examined each individual product over time. Our findings indicated that the administration of any of the pharmacologically active products (NC, DC, NI) decreased subjective cigarette craving immediately post-consumption. Upon further investigation, cigarette products (NC, DC) were significantly better at decreasing craving among all smokers relative to the inhalers (NI, PI). However, after the absorption period, the cigarettes were only associated with decreased craving relative to PI (not NI). This is likely attributable to the shorter half-life of nicotine and non-nicotine constituents in tobacco smoke relative to nicotine in inhalers (Schneider et al., 2001). Nevertheless, this

60-minute absorption period was required in attempt to achieve similar nicotine concentrations (from NI and NC) at the beginning of the behavioural tasks. Overall, our findings suggest that non-nicotine factors are necessary to curb cigarette craving in all smokers. In addition to contributing to the wealth of research supporting the role of non-nicotine factors in modulating cigarette craving among DDS (Barrett, 2010; Faulkner et al., 2018; Rose & Behm, 2004a), these findings also provide insight into the mechanisms motivating smoking among LITS. Notably, this does not rule out the possibility that LITS smoke for the reinforcing properties of nicotine (Russell, 1971), rather it is likely that they smoke for the reinforcing effects of nicotine in the context of other non-nicotine factors (i.e. sensorimotor characteristics of smoking, non-nicotine constituents). This is further supported by evidence that nicotine alone (in the context of NRT) was less effective at decreasing craving among LITS in our study and in previous investigations (McGrath et al., 2015).

We were also interested in examining the extent to which LITS and DDS were able to delay smoking in the presence of proximal smoking cues following different pharmacological manipulations. First, we found that LITS delayed smoking for a significantly longer period of time than DDS. While this may have been a false positive (FDR>5%), this finding is supported by a previous investigation wherein LITS waited longer before smoking relative to DDS (Shiffman et al., 2013). We also found that none of the products had an impact on participants' ability to delay smoking. This is in line with the hypothesis that pharmacological factors would not be sufficient to prevent smoking lapse among all smokers in the presence of smoking stimuli (cigarettes, lighter, ashtray). Indeed, LITS are more likely to smoke when cigarettes are readily available

(Shiffman et al., 2014a), and when they are in the presence of certain stimuli or environments (i.e. stimulus control; Ferguson, Shiffman, Dunbar, & Schüz, 2016; Shiffman et al., 2014b). While DDS are more likely to smoke for withdrawal-avoidance (Benowitz, 2010; Shiffman & Paty, 2006), they are also sensitive to smoking-associated cues (Schlagintweit & Barrett, 2016; Shiffman et al., 2006), suggesting that smoking cues may facilitate relapse among all smokers despite the use of pharmacological interventions. This idea is also supported by the two-factor model of smoking (Shiffman et al., 2015), where DDS lapse in the presence of smoking cues even when withdrawal symptoms are fully satiated (Shiffman et al., 2006).

Also consistent with our hypothesis, LITS self-administered fewer cigarette puffs relative to DDS. This is in line with previous findings that link dependence severity and a higher number of cpd with more cigarette consumption (Roche et al., 2014; Shiffman et al., 2013). Additionally, NC was reliably associated with decreased cigarette self-administration (relative to PI). This replicates findings from Barrett (2010) and lends support to our prediction that a combination of nicotine and non-nicotine factors are required to influence cigarette consumption among all smokers.

Next, to test whether pharmacologically active doses of nicotine were administered, heart rate was assessed throughout the study. We found that heart rate was significantly elevated following the consumption of cigarettes relative to the inactive placebo, suggesting a pharmacologically active dose of nicotine in the NC was administered (Benowitz, 1986). Surprisingly however, the administration of NI did not significantly influence heart rate. It is possible that this reflects the rewarding properties associated cigarette smoking relative to NRT consumption as participants consistently

rated cigarettes more pleasurable than the inhalers (i.e. liking) in the present investigation.

Overall, participants in our study were relatively accurate at distinguishing pharmacologically active products from the inactive inhaler (PI). Specifically, they rated all products significantly higher than PI in terms of nicotine content, strength, and harshness, with NC often rated the highest overall. While all smokers rated DC and NI comparable in nicotine content, they rated NI as significantly more harsh that DC, highlighting the harshness associated with nicotine that may be attenuated by tar (Rose et al., 1999). Overall, participants were relatively accurate at identifying tar in cigarettes, however DDS tended to rate NI higher in tar relative to LITS, despite the complete absence of tar found in inhalers. It is possible that LITS are more aware of the constituents within cigarettes as they have been shown to pay more attention to health information in general (Reyes-Guzman et al., 2017). Lastly, LITS tended to rate the inhalers higher in flavour relative to DDS, supporting findings that olfactory and gustatory (i.e. taste) function are often impaired in regular smokers (Vennemann, Hummel, & Berger, 2008).

Consistent with past research, the tobacco-containing products (NC, DC) were rated significantly higher than the inhalers in terms of liking, with participants having overall preference for NC. Notably, this pattern of liking mirrors our findings related to cigarette craving such that NC and DC decreased cravings relative to NI and PI. This would suggest that nicotine alone (i.e. NI) is not acutely pleasurable, but rather nicotine in the context of tobacco, or even tobacco without nicotine, possesses acute reinforcing properties. Indeed, the non-nicotine constituents of tobacco, the sensorimotor components

associated with smoking (i.e. smells, tastes, throat sensations), and the act of smoking itself all appear to be essential to smoking satisfaction (Rose, 2006; Rose & Levin, 1991).

4.3 Implications

Overall, an improved understanding of the nicotine and non-nicotine factors associated with smoking lapse behaviour among LITS and DDS have important implications for research exploring pathways associated with substance use and dependence. While naturalistic investigations have identified distinct patterns and motives for smoking among LITS and DDS, there is a lack of knowledge with regards to the basic mechanisms facilitating continued cigarette smoking among LITS. Additionally, previous research using laboratory-based smoking lapse paradigms have failed to include LITS, limiting the applicability of their findings to DDS. The present study was the first, to our knowledge, examining the extent to which cigarette craving, withdrawal, and smoking lapse behaviour could be attenuated or facilitated by nicotine and non-nicotine among LITS and DDS. Overall, findings suggest that while LITS and DDS are unique in their characteristics and experiences of craving and withdrawal, both nicotine and non-nicotine factors play important roles in motivating continued smoking. These factors should therefore be considered when developing pharmacological and behavioural interventions for smoking cessation and piloted among a diverse range of smokers.

4.4 Limitations & Future Directions

Results from the present study should be considered in light of the following limitations. First, we had a high drop-out rate (~30%) in our study, particularly among females, that resulted in a smaller sample size than originally intended. As such, it is

possible that we may have been underpowered to detect more complex three-way interaction effects across Smoking Status, Product, and Time. Nevertheless, our sample size is comparable to that of a previous investigation using similar methodology (e.g. Barrett, 2010), suggesting we were likely sufficiently powered to detect main effects two-way interactions. Moreover, since the attrition in our study was mostly specific to females, we were unable to examine potential sex differences. These are important considering that females tend to experience more withdrawal-related symptoms following acute abstinence (Leventhal et al., 2007), and are often more sensitive to non-nicotine components of smoking (e.g. DC, olfactory cues Barrett, 2010; Faulkner et al., 2018). This is a considerable gap in research examining LITS as many studies also fail to consider sex differences (Fernando et al., 2006; Shiffman & Terhorst, 2017). Future laboratory investigations should therefore explore to what extent sex differences occur among LITS with regards to smoking motivation and pharmacological responsivity.

Additionally, the DC used in our study contained trace amount of nicotine (0.05mg). While the nicotine yield of the NC was more than 26 times higher than that of DC, cigarettes with nicotine yields as low as 0.05mg can produce a low degree of nicotinic acetylcholine receptor occupancy (Faulkner et al., 2018). Thus, it is possible that nicotine had a small influence in the similar effects produced by NC and DC, however it is most likely that other non-nicotine factors played a more significant role. Finally, our sample consisted of healthy non-treatment seeking smokers, which is not necessarily representative of all substance using populations. For example, DDS are more likely than LITS to present with comorbid psychiatric conditions and engage in polysubstance use (Reyes-Guzman et al., 2017). Including participants without medical

conditions was necessary to ensure that no other factors were confounding the results, a common practice in mechanistic studies. Treatment-motivated smokers tend to respond differently to pharmacological manipulations, particularly NRTs (Schlagintweit, Campbell, & Barrett, 2017). While the present study was a necessary first step to identify the mechanisms underlying smoking lapse behaviour among LITS relative to DDS, it will be important to examine these processes in treatment-motivated groups.

4.5 Conclusions

In conclusion, LITS and DDS differ with regards to their demographic characteristics, experiences of craving and withdrawal, and smoking behaviour. While LITS show a relative absence of traditional cigarette dependence (i.e. withdrawal) and smoke less than DDS, they experience phasic cravings and may not differ in their ability to delay smoking in the presence of smoking stimuli. Additionally, both nicotine and non-nicotine factors seem to be important for curbing craving and smoking behaviour among all smokers. Overall, the results from the present study provide insight into the possible mechanisms facilitating continued cigarette smoking in a diverse sample of non-treatment seeking LITS and DDS.

REFERENCES

Al-Delaimy, W. K., Pierce, J. P., Messer, K., White, M. M., Trinidad, D. R., & Gilpin, E. A. (2007). The California Tobacco Control Program's effect on adult smokers: (2) Daily cigarette consumption levels. *Tobacco Control*, *16*(2), 91–95. https://doi.org/10.1136/tc.2006.017061

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

Barrett, S. P. (2010). The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers: *Behavioural Pharmacology*, *21*(2), 144–152. https://doi.org/10.1097/FBP.0b013e328337be68

Benowitz, N. L. (1986). Clinical Pharmacology of Nicotine. *Annual Review of Medicine*, *37*(1), 21–32. https://doi.org/10.1146/annurev.me.37.020186.000321

Benowitz, Neal L. (2010). Nicotine Addiction. *The New England Journal of Medicine*, *362*(24), 2295–2303. https://doi.org/10.1056/NEJMra0809890

Benowitz, Neal 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

Bickel, W. K., & Kelly, T. H. (1988). The Relationship of Stimulus Control to the Treatment of Substance Abuse. *National Institute on Drug Abuse Research Monograph Series.*, *84*, 122–140.

Bond, A., & Lader, M. (1974). The use of analogue scales in rating subjective feelings. *British Journal of Medical Psychology*, *47*, 211–218.

Breland, A. B., Evans, S. E., Buchhalter, A. R., & Eissenberg, T. (2002). Acute effects of Advance: a potential reduced exposure product for smokers. *Tobacco Control*, *11*(4), 376–378. https://doi.org/10.1136/tc.11.4.376

Buchhalter, A. R., Acosta, M. C., Evans, S. E., Breland, A. B., & Eissenberg, T. (2005). Tobacco abstinence symptom suppression: The role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. *Addiction*, *100*(4), 550–559. https://doi.org/10.1111/j.1360-0443.2005.01030.x

Carter, B. L., & Tiffany, S. T. (2001). The cue-availability paradigm: The effects of cigarette availability on cue reactivity in smokers. *Experimental and Clinical Psychopharmacology*, *9*(2), 183–190. https://doi.org/10.1037/1064-1297.9.2.183

Centers for Disease Control and Prevention [CDC]. (2011). Vital signs: Current cigarette smoking among adults aged ≥18 years--United States, 2005-2010. *MMWR. Morbidity and Mortality Weekly Report*, *60*(35), 1207–1212.

Coggins, C. R. E., Murrelle, E. L., Carchman, R. A., & Heidbreder, C. (2009). Light and intermittent cigarette smokers: A review (1989–2009). *Psychopharmacology*, *207*(3), 343–363. https://doi.org/10.1007/s00213-009-1675-4

Darredeau, C., & Barrett, S. P. (2010a). The role of nicotine content information in smokers' subjective responses to nicotine and placebo inhalers. *Human Psychopharmacology: Clinical and Experimental*, *25*, 577–581. https://doi.org/10.1002/hup

Darredeau, C., & Barrett, S. P. (2010b). The role of nicotine content information in smokers' subjective responses to nicotine and placebo inhalers. *Human Psychopharmacology: Clinical and Experimental*, *25*(7–8), 577–581. https://doi.org/10.1002/hup.1159

Darredeau, C., Stewart, S. H., & Barrett, S. P. (2013). The effects of nicotine content information on subjective and behavioural responses to nicotine-containing and denicotinized cigarettes: *Behavioural Pharmacology*, *24*(4), 291–297. https://doi.org/10.1097/FBP.0b013e3283635fd9

DiFranza, J. R., Savageau, J. A., Fletcher, K., O'Loughlin, J., Pbert, L., Ockene, J. K., … Wellman, R. J. (2007). Symptoms of Tobacco Dependence After Brief Intermittent Use: The Development and Assessment of Nicotine Dependence in Youth–2 Study. *Archives of Pediatrics & Adolescent Medicine*, *161*(7), 704–710. https://doi.org/10.1001/archpedi.161.7.704

DiFranza, J. R., Savageau, J. A., Rigotti, N. A., Fletcher, K., Ockene, J. K., McNeill, A. D., … Wood, C. (2002). Development of symptoms of tobacco dependence in youths: 30 month follow up data from the DANDY study. *Tobacco Control*, *11*(3), 228–235. https://doi.org/10.1136/tc.11.3.228

Donny, E. C., Denlinger, R. L., Tidey, J. W., Koopmeiners, J. S., Benowitz, N. L., Vandrey, R. G., … Hatsukami, D. K. (2015). Randomized Trial of Reduced-Nicotine Standards for Cigarettes. *New England Journal of Medicine*, *373*(14), 1340–1349. https://doi.org/10.1056/NEJMsa1502403

Fagerström, K. (2012). Determinants of Tobacco Use and Renaming the FTND to the Fagerström Test for Cigarette Dependence. *Nicotine & Tobacco Research*, *14*(1), 75–78. https://doi.org/10.1093/ntr/ntr137

Faulkner, P., Petersen, N., Ghahremani, D. G., Cox, C. M., Tyndale, R. F., Hellemann, G. S., & London, E. D. (2018). Sex differences in tobacco withdrawal and responses to smoking reduced-nicotine cigarettes in young smokers. *Psychopharmacology*, *235*(1), 193–202. https://doi.org/10.1007/s00213-017-4755-x

Feng, C., Wang, H., Lu, N., Chen, T., He, H., Lu, Y., & Tu, X. M. (2014). Log-transformation and its implications for data analysis. *Shanghai Archives of Psychiatry*, *26*(2), 105–109. https://doi.org/10.3969/j.issn.1002-0829.2014.02.009

Ferguson, S. G., Shiffman, S., Dunbar, M., & Schüz, N. (2016). Higher Stimulus Control is Associated with Less Cigarette Intake in Daily Smokers. *Psychology of Addictive Behaviors : Journal of the Society of Psychologists in Addictive Behaviors*, *30*(2), 229–237. https://doi.org/10.1037/adb0000149

Fernando, W. W., Wellman, R. J., & DiFranza, J. R. (2006). The relationship between level of cigarette consumption and latency to the onset of retrospectively reported withdrawal symptoms. *Psychopharmacology*, *188*(3), 335–342. https://doi.org/10.1007/s00213-006-0497-x

Ginzel, K. H. (1975). The importance of sensory nerve endings as sites of drug action. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *288*(1), 29–56. https://doi.org/10.1007/BF00501812

Gloria, R., Angelos, L., Schaefer, H. S., Davis, J. M., Majeskie, M., Richmond, B. S., … Baker, T. B. (2009). An fMRI investigation of the impact of withdrawal on regional brain activity during nicotine anticipation. *Psychophysiology*, *46*(4), 681–693. https://doi.org/10.1111/j.1469-8986.2009.00823.x

Gourlay, S. G., Forbes, A., Marriner, T., Pethica, D., & McNeil, J. J. (1995). Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. *BMJ : British Medical Journal*, *311*(7001), 363–366.

Hajek, P., West, R., & Wilson, J. (1995). Regular smokers, lifetime very light smokers, and reduced smokers: Comparison of psychosocial and smoking characteristics in women. *Health Psychology*, *14*(3), 195–201. https://doi.org/10.1037/0278-6133.14.3.195

Hughes, J. R., & Hatsukami, D. (1986). Signs and Symptoms of Tobacco Withdrawal. *Archives of General Psychiatry*, *43*(3), 289. https://doi.org/10.1001/archpsyc.1986.01800030107013

Hughes, J. R., & Hatsukami, D. (1998). Errors in using tobacco withdrawal scale. *Tobacco Control*, *7*(1), 92–93.

Hughes, J. R., Keely, J., & Naud, S. (2004). Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction*, *99*(1), 29–38. https://doi.org/10.1111/j.1360-0443.2004.00540.x

Hughes, J. R., Keely, J. P., Niaura, R. S., Ossip-Klein, D. J., Richmond, R. L., & Swan, G. E. (2003). Measures of abstinence in clinical trials: Issues and recommendations. *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco*, *5*(1), 13–25.

Husten, C. G. (2009). How should we define light or intermittent smoking? Does it matter? *Nicotine & Tobacco Research*, *11*(2), 111–121. https://doi.org/10.1093/ntr/ntp010

Jamal, A., Homa, D. M., O'Connor, E., Babb, S. D., Caraballo, R. S., Singh, T., … King, B. A. (2015). Current cigarette smoking among adults - United States, 2005-2014. *MMWR. Morbidity and Mortality Weekly Report*, *64*(44), 1233–1240. https://doi.org/10.15585/mmwr.mm6444a2

Juliano, L. M., & Brandon, T. H. (1998). Reactivity to instructed smoking availability and environmental cues: Evidence with urge and reaction time. *Experimental and Clinical Psychopharmacology*, *6*(1), 45–53. https://doi.org/10.1037/1064-1297.6.1.45

Leeman, R. F., O'Malley, S. S., White, M. A., & McKee, S. A. (2010). Nicotine and Food Deprivation Decrease the Ability to Resist Smoking. *Psychopharmacology*, *212*(1), 25–32. https://doi.org/10.1007/s00213-010-1902-z

Leventhal, A. M., Boyd, S., Moolchan, E. T., Waters, A. J., Lerman, C., & Pickworth, W. B. (2007). Gender Differences in Acute Tobacco Withdrawal: Effects on Subjective, Cognitive, and Physiological Measures. *Experimental and Clinical Psychopharmacology*, *15*(1), 21–36. https://doi.org/10.1037/1064-1297.15.1.21

Marlatt, G. A., Curry, S., & Gordon, J. R. (1988). A longitudinal analysis of unaided smoking cessation. *Journal of Consulting and Clinical Psychology*, *56*(5), 715–720. https://doi.org/10.1037/0022-006X.56.5.715

McClernon, F. J., Westman, E. C., & Rose, J. E. (2004). The effects of controlled deep breathing on smoking withdrawal symptoms in dependent smokers. *Addictive Behaviors*, *29*(4), 765–772. https://doi.org/10.1016/j.addbeh.2004.02.005

McGrath, D. S., Peloquin, M. P., Ferdinand, J. C., & Barrett, S. P. (2015). Acute effects of nicotine on alcohol cue-reactivity in nondependent and dependent smokers. *Experimental and Clinical Psychopharmacology*, *23*(1), 29–36. https://doi.org/10.1037/a0038606

McKee, S. A. (2009). Developing human laboratory models of smoking lapse behavior for medication screening. *Addiction Biology*, *14*(1), 99–107. https://doi.org/10.1111/j.1369-1600.2008.00135.x

McKee, S. A., Weinberger, A. H., Shi, J., Tetrault, J., & Coppola, S. (2012). Developing and Validating a Human Laboratory Model to Screen Medications for Smoking Cessation. *Nicotine & Tobacco Research*, *14*(11), 1362–1371. https://doi.org/10.1093/ntr/nts090

Niaura, R., Sayette, M., Shiffman, S., Glover, E. D., Nides, M., Shelanski, M., … Sorrentino, J. (2005). Comparative efficacy of rapid-release nicotine gum versus nicotine polacrilex gum in relieving smoking cue-provoked craving. *Addiction*, *100*(11), 1720–1730. https://doi.org/10.1111/j.1360-0443.2005.01218.x

Norregaard, J., Tonnesen, P., & Petersen, L. (1993). Predictors and Reasons for Relapse in Smoking Cessation with Nicotine and Placebo Patches. *Preventive Medicine*, *22*(2), 261–271. https://doi.org/10.1006/pmed.1993.1021

Pang, R. D., & Leventhal, A. M. (2013). Sex Differences in Negative Affect and Lapse Behavior During Acute Tobacco Abstinence: A Laboratory Study. *Experimental and Clinical Psychopharmacology*, *21*(4), 269–276. https://doi.org/10.1037/a0033429

Perkins, K. A., Gerlach, D., Vender, J., Meeker, J., Hutchison, S., & Grobe, J. (2001). Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli. *Nicotine & Tobacco Research*, *3*(2), 141–150. https://doi.org/10.1080/14622200110043059

Picard, F., Sadaghiani, S., Leroy, C., Courvoisier, D. S., Maroy, R., & Bottlaender, M. (2013). High density of nicotinic receptors in the cingulo-insular network. *NeuroImage*, *79*, 42–51. https://doi.org/10.1016/j.neuroimage.2013.04.074

Picciotto, M. R., Addy, N. A., Mineur, Y. S., & Brunzell, D. H. (2008). It is not "either/or": Activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors related to nicotine addiction and mood. *Progress in Neurobiology*, *84*(4), 329–342. https://doi.org/10.1016/j.pneurobio.2007.12.005

Reyes-Guzman, C. M., Pfeiffer, R. M., Lubin, J., Freedman, N. D., Cleary, S. D., Levine, P. H., & Caporaso, N. E. (2017). Determinants of Light and Intermittent Smoking in the U.S.: Results from Three Pooled National Health Surveys. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, *26*(2), 228–239. https://doi.org/10.1158/1055-9965.EPI-16-0028

Roche, D. J. O., Bujarski, S., Moallem, N. R., Guzman, I., Shapiro, J. R., & Ray, L. A. (2014). Predictors of smoking lapse in a human laboratory paradigm. *Psychopharmacology*, *231*(14), 2889–2897. https://doi.org/10.1007/s00213-014-3465-x

Rose, J., & Behm, F. (2004a). Effects of low nicotine content cigarettes on smoke intake. *Nicotine & Tobacco Research*, *6*(2), 309–319. https://doi.org/10.1080/14622200410001676378

Rose, J., & Behm, F. (2004b). Extinguishing the rewarding value of smoke cues: Pharmacological and behavioral treatments. *Nicotine & Tobacco Research*, *6*(3), 523–532. https://doi.org/10.1080/14622200410001696501

Rose, J. E. (2006). Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology*, *184*(3), 274–285. https://doi.org/10.1007/s00213-005-0250-x

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

Rose, J. E., Tashkin, D. P., Ertle, A., Zinser, M. C., & Lafer, R. (1985). Sensory blockade of smoking satisfaction. *Pharmacology Biochemistry and Behavior*, *23*(2), 289–293. https://doi.org/10.1016/0091-3057(85)90572-6

Rose, J. E., Turner, J. E., Murugesan, T., Behm, F. M., & Laugesen, M. (2010). Pulmonary delivery of nicotine pyruvate: Sensory and pharmacokinetic characteristics. *Experimental and Clinical Psychopharmacology*, *18*(5), 385–394. https://doi.org/10.1037/a0020834

Rose, J. E., Westman, E. C., Behm, F. M., Johnson, M. P., & Goldberg, J. S. (1999). Blockade of Smoking Satisfaction Using the Peripheral Nicotinic Antagonist Trimethaphan. *Pharmacology Biochemistry and Behavior*, *62*(1), 165–172. https://doi.org/10.1016/S0091-3057(98)00153-1

Russell, M. A. (1971). Cigarette smoking: Natural history of a dependence disorder. *The British Journal of Medical Psychology*, *44*(1), 1–16.

Schiller, J. S., Lucas, J. W., & Peregoy, J. A. (2012). Summary health statistics for u.s. Adults: National health interview survey, 2011. *Vital and Health Statistics. Series 10, Data from the National Health Survey*, (256), 1–218.

Schlagintweit, H. E., & Barrett, S. P. (2016). Does acute tobacco smoking prevent cue-induced craving? *Journal of Psychopharmacology*, *30*(5), 468–473. https://doi.org/10.1177/0269881116639288

Schlagintweit, H. E., Campbell, N. K., & Barrett, S. P. (2017). Quit Intentions Moderate Subjective and Physiological Responses to Acute Nicotine Replacement Therapy Administration in Dependent Smokers. *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco*, *19*(8), 922–929. https://doi.org/10.1093/ntr/ntw307

Schlagintweit, H. E., Greer, H., Good, K. P., & Barrett, S. P. (2015). The impact of anticipated and unanticipated smoking opportunities on cigarette smoking and nicotine lozenge responses. *Drug and Alcohol Dependence*, *147*, 97–102. https://doi.org/10.1016/j.drugalcdep.2014.12.012

Schlagintweit, H. E., Perry, R. N., Darredeau, C., & Barrett, S. P. (2019). Non-pharmacological Considerations in Human Research of Nicotine and Tobacco Effects: A Review. *Nicotine & Tobacco Research*, ntz064. https://doi.org/10.1093/ntr/ntz064

Schneider, N. G., Olmstead, R. E., Franzon, M. A., & Lunell, E. (2001). The Nicotine Inhaler. *Clinical Pharmacokinetics*, *40*(9), 661–684. https://doi.org/10.2165/00003088-200140090-00003

Shiffman, S. (2009). Light and intermittent smokers: Background and perspective. *Nicotine & Tobacco Research*, *11*(2), 122–125. https://doi.org/10.1093/ntr/ntn020

Shiffman, S., Dunbar, M. S., & Benowitz, N. L. (2014). A Comparison of Nicotine Biomarkers and Smoking Patterns in Daily and Non-daily Smokers. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, *23*(7), 1264–1272. https://doi.org/10.1158/1055-9965.EPI-13-1014

Shiffman, S., Dunbar, M. S., & Ferguson, S. G. (2015). Stimulus control in intermittent and daily smokers. *Psychology of Addictive Behaviors*, *29*(4), 847–855. https://doi.org/10.1037/adb0000052

Shiffman, S., Dunbar, M. S., Kirchner, T. R., Li, X., Tindle, H. A., Anderson, S. J., … Ferguson, S. G. (2013). Cue Reactivity in Non-Daily Smokers: Effects on Craving and Smoking Behavior. *Psychopharmacology*, *226*(2), 321–333. https://doi.org/10.1007/s00213-012-2909-4

Shiffman, S., Dunbar, M. S., Li, X., Scholl, S. M., Tindle, H. A., Anderson, S. J., & Ferguson, S. G. (2014a). Craving in Intermittent and Daily Smokers During Ad Libitum Smoking. *Nicotine & Tobacco Research*, *16*(8), 1063–1069. https://doi.org/10.1093/ntr/ntu023

Shiffman, S., Dunbar, M. S., Li, X., Scholl, S. M., Tindle, H. A., Anderson, S. J., & Ferguson, S. G. (2014b). Smoking Patterns and Stimulus Control in Intermittent and Daily Smokers. *PLoS ONE*, *9*(3), e89911. https://doi.org/10.1371/journal.pone.0089911

Shiffman, S., Dunbar, M. S., Scholl, S. M., & Tindle, H. A. (2012). Smoking motives of daily and non-daily smokers: A profile analysis. *Drug and Alcohol Dependence*, *126*(3), 362–368. https://doi.org/10.1016/j.drugalcdep.2012.05.037

Shiffman, S., Ferguson, S. G., Gwaltney, C. J., Balabanis, M. H., & Shadel, W. G. (2006). Reduction of abstinence-induced withdrawal and craving using high-dose nicotine replacement therapy. *Psychopharmacology*, *184*(3), 637–644. https://doi.org/10.1007/s00213-005-0184-3

Shiffman, S., Kurland, B. F., Scholl, S. M., & Mao, J. M. (2018). Nondaily Smokers' Changes in Cigarette Consumption With Very Low-Nicotine-Content Cigarettes: A Randomized Double-blind Clinical Trial. *JAMA Psychiatry*, *75*(10), 995. https://doi.org/10.1001/jamapsychiatry.2018.1831

Shiffman, S., & Paty, J. (2006). Smoking patterns and dependence: Contrasting chippers and heavy smokers. *Journal of Abnormal Psychology*, *115*(3), 509–523. https://doi.org/10.1037/0021-843X.115.3.509

Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. A., & Hickcox, M. (1996). First lapses to smoking: Within-subjects analysis of real-time reports. *Journal of Consulting and Clinical Psychology*, *64*(2), 366–379.

Shiffman, S., Scholl, S. M., Mao, J., Ferguson, S. G., Hedeker, D., Primack, B., & Tindle, H. A. (2019). Using Nicotine Gum to Assist Nondaily Smokers in Quitting: A Randomized Clinical Trial. *Nicotine & Tobacco Research*, ntz090. https://doi.org/10.1093/ntr/ntz090

Shiffman, S., & Terhorst, L. (2017). Intermittent and daily smokers' subjective responses to smoking. *Psychopharmacology*, *234*(19), 2911–2917. https://doi.org/10.1007/s00213-017-4682-x

Shiffman, S., Dunbar, M. S., Tindle, H. A., & Ferguson, S. G. (2015). Non-daily Smokers' Experience of Craving on Days They Do Not Smoke. *Journal of Abnormal Psychology*, *124*(3), 648–659. https://doi.org/10.1037/abn0000063

Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. D., & Elash, C. (1995). Nicotine withdrawal in chippers and regular smokers: Subjective and cognitive effects. *Health Psychology*, *14*(4), 301–309. https://doi.org/10.1037/0278-6133.14.4.301

Shiffman, S., Paty, J. A., Kassel, J. D., Gnys, M., & Zettler-Segal, M. (1994). Smoking behavior and smoking history of tobacco chippers. *Experimental and Clinical Psychopharmacology*, *2*(2), 126–142. https://doi.org/10.1037/1064-1297.2.2.126

Stead, L. F., Perera, R., Bullen, C., Mant, D., Hartmann-Boyce, J., Cahill, K., & Lancaster, T. (2012). Nicotine replacement therapy for smoking cessation. *The Cochrane Database of Systematic Reviews*, *11*, CD000146. https://doi.org/10.1002/14651858.CD000146.pub4

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

Sweitzer, M. M., Denlinger, R. L., & Donny, E. C. (2013). Dependence and Withdrawal-Induced Craving Predict Abstinence in an Incentive-Based Model of Smoking Relapse. *Nicotine & Tobacco Research*, *15*(1), 36–43. https://doi.org/10.1093/ntr/nts080

Thrul, J., Bühler, A., & Ferguson, S. G. (2014). Situational and mood factors associated with smoking in young adult light and heavy smokers. *Drug and Alcohol Review*, *33*(4), 420–427. https://doi.org/10.1111/dar.12164

Tindle, H. A., & Shiffman, S. (2011). Smoking Cessation Behavior Among Intermittent Smokers Versus Daily Smokers. *American Journal of Public Health*, *101*(7), e1–e3. https://doi.org/10.2105/AJPH.2011.300186

Vennemann, M. M., Hummel, T., & Berger, K. (2008). The association between smoking and smell and taste impairment in the general population. *Journal of Neurology*, *255*(8), 1121–1126. https://doi.org/10.1007/s00415-008-0807-9

Wertz, J. M., & Sayette, M. A. (2001). A review of the effects of perceived drug use opportunity on self-reported urge. *Experimental and Clinical Psychopharmacology*, *9*(1), 3–13. https://doi.org/10.1037/1064-1297.9.1.3

Willner, P., Hardman, S., & Eaton, G. (1995). Subjective and behavioural evaluation of cigarette cravings. *Psychopharmacology*, *118*(2), 171–177. https://doi.org/10.1007/BF02245836

World Health Organization. (2015). *WHO global report on trends in prevalence of tobacco smoking, 2015.* Retrieved from http://apps.who.int/iris/bitstream/10665/156262/1/9789241564922_eng.pdf

Zhu, S.-H., Sun, J., Hawkins, S., Pierce, J., & Cummins, S. (2003). A population study of low-rate smokers: Quitting history and instability over time. *Health Psychology*, *22*(3), 245–252.

Appendix A

Table 4

Mixed model test statistics for Smoking self-administration, Average heart rate, and Cigarette withdrawal models excluding influential multivariate outlier cases

Effect	Test statistic		
	df	*F*	*p*
Smoking self-administration: Number of cigarette puffs			
Product	3, 76.83	4.89	.004
Smoking Status	1, 36.04	21.30	<.001
Product*Smoking Status	3, 76.83	.61	.613
Average heart rate			
Time	2, 223.98	20.46	<.001
Smoking Status	1, 38.12	.359	.552
Product	3, 84.56	8.69	<.001
Time*Product	6, 224.37	14.26	<.001
Product*Smoking Status	3, 84.56	.099	.960
Time*Smoking Status	2, 223.98	2.43	.090
Time*Product*Smoking Status	6, 224.37	.770	.594
Cigarette withdrawal			
Time	2, 222.27	8.07	<.001
Smoking Status	1, 38.13	4.27	.046[1]
Product	3, 77.08	.98	.405
Time*Product	6, 222.55	2.03	.063
Product*Smoking Status	3, 77.08	1.01	.394
Time*Smoking Status	2, 222.27	6.21	.002
Time*Product*Smoking Status	6, 222.55	1.54	.165

Note. Mixed model analyses only excluding the influential outlier cases identified during data screening using the same covariate structure as reported in the main Results section.
[1]FDR adjusted *p*-value = .107.