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Animal research has consistently demonstrated increased pain in the context of nicotine deprivation, and there is cross-sectional evidence that tobacco smokers may experience greater pain following periods of smoking abstinence. This study aimed to examine current pain intensity as a function of nicotine deprivation among 137 daily tobacco smokers who did not endorse chronic pain and were recruited to participate in a primary study of the effects of smoking abstinence on experimental pain reactivity. Participants were randomized to either deprivation (12–24 hr abstinence) or continued ad lib smoking conditions. Compliance with the manipulation was biochemically verified via expired carbon monoxide (CO). Current pain intensity was assessed at baseline (Session 1) and following the deprivation manipulation (Session 2) using a single item that asked participants to indicate their current level of pain on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine). At baseline, the majority of participants (51.1%) reported no pain ($M = 1.75$). As hypothesized, participants randomized to nicotine deprivation (vs. continued smoking) reported greater current pain intensity following the manipulation. Among smokers who reported no pain at baseline, those who abstained from smoking were nearly 3.5 times more likely to endorse pain at Session 2. These results suggest that daily tobacco smokers may experience greater pain during the first 12–24 hr of smoking abstinence. Future research should examine the role of pain in nicotine withdrawal, and whether tailored interventions may be needed to account for nicotine deprivation-induced amplification of pain.

Public Health Significance
Nicotine deprivation (vs. continued smoking) increased pain reporting among cigarette smokers recruited from the general population. This study provides initial evidence that smokers may experience greater pain during the early stages of smoking abstinence.

Keywords: pain, tobacco, smoking, nicotine deprivation, abstinence

Tobacco smoking and pain are both highly prevalent and co-occurring conditions, which together result in nearly $800 billion in annual health care expenditures and lost productivity (Gaskin & Richard, 2012; U.S. Department of Health & Human Services, 2014; Xu, Bishop, Kennedy, Simpson, & Pechacek, 2015). Current smokers are more likely to experience pain, relative to nonsmokers (Volkman et al., 2015), and cigarette smoking has been identified as a unique risk factor in the onset and progression of several painful conditions (Aho & Heliovaara, 2004; Shiri, Karppinen, Leino-Arjas, Solovieva, & Viikari-Juntura, 2010). Pain has been shown to motivate smoking urge and behavior (Ditre & Brandon, 2008; Ditre, Heckman, Butts, & Brandon, 2010; Kosiba, Zale, & Ditre, 2018), and greater pain has been positively associated with daily cigarette consumption (Andersson, Ejlertsson, & Leden, 1998; Bakhshaie et al., 2016; Pirouzi et al., 2011). Bidirectional relations between pain and smoking have been posited to interact in the manner of a positive feedback loop, resulting in greater pain and the maintenance of

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There has been no prior dissemination of the ideas appearing in this article. These are secondary data are from a primary study that tested the effects of nicotine deprivation on experimental pain reactivity. These analyses examine the effects of nicotine deprivation on current pain reporting, in the absence of experimental pain induction.

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tobacco dependence (Ditre, Brandon, Zale, & Meagher, 2011; Zale, Maisto, & Ditre, 2016).

There is also reason to suspect that pain may increase during periods of smoking abstinence. For example, animal models have consistently demonstrated increased experimental pain reactivity following nicotine deprivation using hot plate, tail flick, and plantar stimulation assays (e.g., Grabus et al., 2005; Jackson, McIntosh, Brunzell, Sanjakdar, & Damaj, 2009). Human laboratory studies have shown that nicotine-deprived smokers are more sensitive to experimental pain induction than both nondeprived smokers (Ditre, Zale, LaRowe, Kosiba, & De Vita, in press) and nonsmokers (Baiamonte, Stickley, & Ford, 2016; Perkins et al., 1994). There is also some evidence that greater nicotinic acetylcholine receptor (nAChR) availability during periods of smoking abstinence may be positively associated with greater experimental pain reactivity (Cosgrove et al., 2009, 2010).

Although laboratory pain models offer advantages with regard to internal validity (e.g., standardized application of painful stimuli), a major limitation of these models is that they do not allow for naturalistic assessment of pain. To more fully understand the effects of smoking abstinence on pain, a critical next step is to assess changes in deprivation-induced pain intensity in the absence of laboratory stimuli (Bennett, 2012; Woolf & Mannion, 1999). Given that pain is a potent motivator of smoking behavior (e.g., Ditre & Brandon, 2008), increased pain intensity in the context of nicotine deprivation would likely make it even harder to quit smoking, thus undermining the goals of tobacco cessation interventions. However, no previous work has examined pain reporting following experimental manipulation of nicotine deprivation.

The goal of these analyses was to test the effects of a nicotine deprivation manipulation on current pain intensity among a sample of daily tobacco smokers who do not endorse chronic pain, and participated in a primary study of the effects of nicotine deprivation on experimental pain reactivity (Ditre et al., in press). We hypothesized that smokers randomized to nicotine deprivation (vs. continued ad lib smoking) would report greater current pain intensity following the manipulation. Given that nicotine has acute analgesic properties (Ditre, Heckman, Zale, Kosiba, & Maisto, 2016), we also hypothesized that, among smokers who did not report pain at baseline, nicotine-deprived smokers (vs. continued smokers) would be more likely to endorse the presence of pain following the deprivation manipulation (in part, due to the discontinuation of nicotine-induced analgesia). Finally, we predicted that greater current pain intensity following the manipulation would be positively associated with several indices of nicotine deprivation (i.e., exhaled CO, nicotine withdrawal severity, urge to smoke).

Method

Participant Recruitment

These are secondary analyses of data collected for a two-session study testing the effects of nicotine deprivation on experimental pain reactivity (Ditre et al., in press). The current study utilized data obtained from the baseline assessment and following the deprivation manipulation (but prior to experimental pain induction). Participants were recruited from the local community via newspaper and Internet advertisements, and screened by phone for the following inclusion criteria: (a) 18–65 years of age; (b) currently smoking ≥15 cigarettes per day (selected to ensure dependence on nicotine; Donny, Griffin, Shiffman, & Sayette, 2008); and (c) ability to speak and read English. Respondents were excluded if they endorsed (a) a current attempt to reduce or quit smoking; (b) current chronic pain; or (c) current use of prescription pain medications. Eligible respondents were scheduled for a baseline visit, and all participants were instructed not to use any over-the-counter pain medication (e.g., acetaminophen or NSAIDs such as aspirin/ibuprofen) for 24 hr prior to the experimental session.

Procedure

Permission to conduct research was obtained from the University's Institutional Review Board. Participants were asked to attend two study sessions. The timing of study sessions was not standardized. At the baseline session (Session 1), participants provided informed consent and biochemical verification of smoking status via exhaled carbon monoxide (CO ≥8ppm). Participants were randomized to continued (ad libitum) smoking ($n = 63$) or nicotine deprivation (12–24 hrs smoking abstinence; $n = 74$) conditions. Although experimenters were not blinded to condition, all measures were completed via computer-based self-report without the experimenter present. Upon arrival to the experimental session (Session 2), compliance with smoking instructions was verified via self-report and exhaled carbon monoxide (continued smoking ≥8ppm; deprivation <8ppm or a 50% reduction from baseline; Benowitz et al., 2002; Evans, Sutton, Oliver, & Drobes, 2015; Piper & Curtin, 2006), and current pain intensity was assessed. Manipulation checks confirmed that participants randomized to nicotine deprivation (vs. continued smoking) evinced lower exhaled CO ($p < .001$), and scored higher on measures of nicotine withdrawal ($p < .05$) and urge to smoke ($p < .001$). Participants were compensated $100 for attending both study sessions.

Measures

Biochemical verification of smoking status. Expired CO was measured at both study visits using a CoVita ToxCO CO monitor. Expired CO is measured in parts per million (ppm), and provides an indirect, noninvasive measure of blood Carboxyhemoglobin (Bittoun, 2008) that is most sensitive to recent smoking (e.g., within 24 hr; Bittoun, 2008; Marrone, Paulpillai, Evans, Singleton, & Heishman, 2010).

Tobacco use and dependence. Historical and current tobacco use (e.g., number of cigarettes smoked per day) were assessed via self-report at the baseline session. Tobacco dependence was assessed using the widely used, reliable and valid Heaviness of Smoking Index (HSI; Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989). The HSI is comprised of two items (i.e., "How soon after you wake up do you smoke your first cigarette?" and "How many cigarettes per day do you smoke?"; Heatherton et al., 1989), and yields a total score that ranges from 0 to 6, with higher scores representing greater levels of tobacco dependence.

Current pain intensity. A numerical rating scale (NRS) was used to assess current pain intensity. The NRS is commonly used in both clinical and research settings, and it has been shown to be more responsive to changes in pain intensity when compared to similar measures of current pain (e.g., the visual analogue scale;

Ferreira-Valente, Pais-Ribeiro, & Jensen, 2011). Participants responded to a single item (i.e., "Please rate your pain by selecting the one number that tells how much pain you have right now."), using a scale that ranged from 0 (no pain) to 10 (pain as bad as you can imagine). Current pain intensity was assessed at baseline and following the nicotine deprivation manipulation.

Nicotine withdrawal symptoms. The Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986) was used to assess the severity of nine prototypical nicotine withdrawal symptoms (i.e., anger/irritability, anxiety, depressed mood, craving, difficulty concentrating, increased appetite, sleep problems, restlessness, impatience) following the nicotine deprivation manipulation. Participants rated each item on a seven-point Likert scale from 0 (*none*) to 6 (*severe*) based on their experience over the past 24 hr. Responses were summed to generate the total score, with higher scores representing greater withdrawal severity. Internal consistency in the current sample was good ($\alpha = .88$).

Urge to smoke. The Brief Questionnaire of Smoking Urges (QSU-B; Cox, Tiffany, & Christen, 2001) includes 10 items (e.g., "I have an urge for a cigarette") that are rated on a seven-point Likert-type scale ranging from 1 (*strongly disagree*) to 7 (*strongly agree*). Items are summed to yield a total score (range 10–70), with higher scores indicating greater urge to smoke. The QSU-B has demonstrated good reliability and internal consistency (Cox et al., 2001; West & Ussher, 2010), and we observed evidence of excellent internal consistency in the current sample (QSU-B total score $\alpha = .93$).

Anxiety symptoms. The Generalized Anxiety Disorder-7 (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006) is a seven item measure of generalized anxiety symptomatology based on the diagnostic criteria described in the *DSM–IV* (APA, 1994), and was selected for its utility as a broad-based index of anxiety and worry. The GAD-7 asks participants to indicate how often they have been bothered by various problems (e.g., "Feeling nervous, anxious, or on edge") over the past two weeks. Each item is rated on a four-point Likert scale ranging from 0 (not at all) to 3 (nearly every day), and a total score is generated by summing all items. The GAD-7 has evinced good criterion, construct, factorial, and procedural validity, and has been shown to be a reliable measure of anxiety in the general population (Lowe et al., 2008; Spitzer et al., 2006). Internal consistency in the current sample was excellent ($\alpha = .92$).

Depression symptoms. The Center for Epidemiological Studies-Depression scale (CES-D; Radloff, 1977), a 20 item measure that uses a four-point Likert scale ranging from 0 (*rarely or none of the time*) to 3 (*most or all of the time*), was used to assess how often the participant has experienced various psychological and physiological symptoms of depression over the past week. Total scores are calculated by summing all items. The CES-D has evinced good sensitivity and specificity among community samples (Lewinsohn, Seeley, Roberts, & Allen, 1997). Internal consistency in the current sample was good ($\alpha = .82$).

Alcohol and cannabis use. The Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) is a 10 item instrument used to assess the risk for alcohol abuse. The Cannabis Use Disorders Identification Test—Revised (CUDIT-R) is an eight-item questionnaire that assesses problematic cannabis use within the past 6 months. The AUDIT and CUDIT-R were both administered at baseline.

Data Analytic Plan

All analyses were conducted using SPSS Statistics 21 (IBM Corp, 2012). Effects of the deprivation manipulation on current pain were tested using analysis of covariance (ANCOVA), controlling for baseline pain intensity. Researchers have recommended using ANCOVA (with pretest score included as a covariate) for testing prepost outcomes (e.g., Dimitrov & Rumrill, 2003), in part because ANCOVA has been shown to yield similar information in a more parsimonious manner than repeated measures ANOVA and gain score analyses (Huck & McLean, 1975). Additional covariates (i.e., gender, age, race, anxiety, and depression) were identified a priori based on known associations with pain reactivity (e.g., McMahon, Koltzenburg, Tracey, & Turk, 2013). Among participants who reported no pain at baseline, we then tested the effects of the deprivation manipulation on the likelihood of reporting pain at Session 2 using logistic regression (also controlling for gender, age, race, anxiety, and depression). Consistent with previous research, NRS scores were dichotomized to reflect the presence (NRS >0) or absence (NRS $= 0$) of pain (e.g., Pinto, McIntyre, Nogueira-Silva, Almeida, & Araújo-Soares, 2012). Finally, bivariate correlations between current pain intensity and several indices of nicotine deprivation/withdrawal (i.e., exhaled CO, nicotine withdrawal severity, urge to smoke) were examined among the total sample.

Results

Descriptive Overview of Sample Characteristics

Participants included 137 current daily tobacco smokers (continued smoking = 63, nicotine deprivation = 74; 43.8% female; $M_{age} = 40.24$, $SD = 12.42$), who reported smoking 22 cigarettes per day ($M = 22.34$, $SD = 13.30$) for an average of 23 years ($M = 23.18$, $SD = 12.18$). The mean HSI score was 3.91 ($SD = 1.26$), indicating a moderate level of nicotine dependence (Chaiton, Cohen, McDonald, & Bondy, 2007). About 40% of the sample ($n = 55$) identified as black or African American. The majority of the sample (60.6%) reported their highest level of education as high school graduate or less, and about 41% of the sample ($n = 56$) reported incomes of less than $10,000.00 per year. On average, participants reported mild pain at baseline ($M = 1.75$, $SD = 2.38$). At baseline, pain intensity was positively associated with nicotine withdrawal severity, $r = .26$, $p < .01$. No significant correlations were observed between pain intensity and either exhaled CO or urge to smoke at baseline ($ps > .05$). No differences in any of the baseline characteristics were observed between conditions (all $ps > .05$), and participants randomized to nicotine deprivation were no more likely to endorse pain at baseline, compared to those randomized to continued smoking ($p = .54$). See Table 1 for additional sample characteristics.

Table 1
Baseline Sociodemographic, Smoking, and Pain Characteristics by Condition

Variable	Continued smoking (n = 63) n (%)	Nicotine deprivation (n = 74) n (%)	Total sample (n = 137) n (%)
Gender			
Male	38 (60.3%)	39 (52.7%)	77 (56.2%)
Ethnicity			
Hispanic/Latino	3 (4.8%)	3 (4.1%)	6 (4.4%)
Race			
White	34 (54.0%)	42 (56.8%)	76 (55.5%)
Black or African American	27 (42.9%)	28 (37.8%)	55 (40.1%)
American Indian/Alaska Native	2 (3.2%)	4 (5.4%)	6 (4.4%)
Marital Status			
Single	40 (63.5%)	41 (55.4%)	81 (59.1%)
Married	9 (14.3%)	14 (18.9%)	23 (16.8%)
Divorced/Separated/Widowed	14 (22.2%)	19 (25.7%)	33 (24.1%)
Education			
0–11 Years	17 (27.0%)	15 (20.3%)	32 (23.4%)
12 Years	23 (36.5%)	28 (37.8%)	51 (37.2%)
12–15 Years	17 (26.9%)	24 (32.5%)	41 (29.9%)
≥16 Years	6 (9.5%)	7 (9.6%)	13 (9.4%)
Household income			
<10,000$	30 (47.6%)	26 (35.1%)	56 (40.9%)
10,000$–29,999$	20 (31.7%)	25 (33.8%)	45 (32.8%)
30,000$–49,999$	7 (11.1%)	10 (13.5%)	17 (12.4%)
≥50,000$	6 (9.5%)	13 (17.7%)	19 (13.9%)
	M (SD)	M (SD)	M (SD)
Age	40.86 (12.75)	39.72 (12.19)	40.24 (12.42)
Cigarettes per day	20.24 (11.71)	24.14 (15.55)	22.34 (13.30)
Years of Regular/Daily smoking	22.86 (11.71)	23.45 (12.64)	23.17 (12.18)
Tobacco dependence[1]	3.84 (1.13)	3.97 (1.35)	3.91 (1.26)
Baseline pain intensity[2]	1.37 (1.98)	2.08 (2.65)	1.75 (2.38)
Anxiety symptoms[3]	6.81 (5.56)	7.23 (5.56)	7.04 (5.55)
Depressive symptoms[4]	16.44 (9.54)	18.95 (11.69)	17.80 (10.79)
AUDIT[5]	8.36 (1.94)	10.67 (2.25)	6.02 (7.55)
CUDIT-R[6]	9.93 (1.85)	7.91 (1.26)	8.71 (6.23)

[1] Heaviness of Smoking Index. [2] Numerical Rating Scale. [3] Generalized Anxiety Disorder-7 items. [4] Center for Epidemiological Studies—Depression. [5] Alcohol Use Disorders Identification Test. [6] Cannabis Use Disorder Identification Test—Revised. No group differences were observed on any sociodemographic, smoking, or pain characteristics (all ps > .08).

Effects of the Nicotine Deprivation Manipulation on Current Pain Intensity

As hypothesized, ANCOVA revealed that smokers in the nicotine deprivation group reported greater current pain intensity following the deprivation manipulation (M = 1.78, SE = 0.35), relative to those in the continued smoking group (M = 0.73, SE = 0.38; $F[1, 126] = 7.93$, $p < .01$, $\eta_p^2 = .06$). This effect was evident above and beyond the variance accounted for by baseline pain intensity and covariates (see Table 2 and Figure 1). Logistic regression further revealed that, among smokers who reported no pain at baseline, those who were randomized to deprivation were nearly 3.5 times more likely to report pain at the second study session (vs. those randomized to continued smoking; OR = 3.41, $p < .05$; see Table 3). Although there are known gender differences in pain reporting (e.g., Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009), we did not observe an interactive effect of deprivation and gender in either the ANCOVA or logistic regression model.

Associations Between Current Pain Intensity and Indices of Nicotine Deprivation

We observed a negative correlation between current pain intensity and exhaled CO, $r = -.20$, $p = .02$, indicating that lower levels of exhaled CO were associated with higher current pain intensity ratings following the deprivation manipulation. Further, current pain intensity ratings were positively associated with self-reported urge to smoke, $r = .21$, $p = .01$. We did not observe a significant association between current pain intensity and nicotine withdrawal severity, $r = .08$, $p = .38$.

Discussion

This is the first study to examine the effects of nicotine deprivation on current pain intensity. As hypothesized, daily cigarette smokers randomized to nicotine deprivation reported greater current pain intensity relative to smokers randomized to continued smoking. Among smokers who reported no pain at baseline, nicotine-deprived smokers were nearly 3.5 times more likely to

Table 2
ANCOVA: Deprivation Manipulation on Current Pain Intensity

Variable	*df*	*MS*	*F*	η^2	*p*
Gender	1	2.747	.628	.005	.430
Age	1	3.855	.881	.007	.350
Race	2	15.562	3.558	.053	.031
Anxiety[1]	1	.474	.108	.001	.742
Depression[2]	1	7.337	1.677	.013	.198
Baseline Pain Intensity[3]	1	72.859	16.658	.117	<.001
Deprivation Condition	1	34.701	7.934	.059	.006
Error	126	4.374			

Note. Gender: 0 = Female, 1 = Male; Deprivation Condition: 0 = Continued smoking, 1 = Nicotine deprivation.
[1] Generalized Anxiety Disorder—7 item. [2] Center for Epidemiological Studies-Depression scale. [3] Numerical Rating Scale.

Table 3
Logistic Regression: Odds of Pain Following the Deprivation Manipulation

Variable	*B*	*SE*	Odds Ratio	*p*
Gender	.841	.590	2.318	.154
Age	−.025	.023	.975	.268
Race	−.211	.350	.810	.547
Anxiety[1]	−.186	.092	.831	.043*
Depression[2]	.031	.040	1.031	.443
Deprivation Condition	1.226	.614	3.409	.046*
Constant	.337	1.697	1.401	.842

Note. Gender: 0 = Female, 1 = Male; Deprivation Condition: 0 = Continued smoking, 1 = Nicotine deprivation.
[1] Generalized Anxiety Disorder—7 item. [2] Center for Epidemiological Studies-Depression scale. * $p < .05$.

report the presence of pain following the nicotine deprivation manipulation, relative to participants who were randomized to continue smoking ad lib. Taken together, these results suggest that smokers may experience increased pain during the early stages of smoking abstinence.

Nicotine deprivation has been linked to greater experimental pain reactivity (Ditre et al., in press; Grabus et al., 2005), and the current findings extend this work by demonstrating that deprived smokers may also experience greater current pain intensity (vs. continued smokers), even in the absence of a laboratory pain stimulus. This finding may be consistent with an opponent process model of addiction (e.g., Koob & Le Moal, 2008; Solomon, 1980), which proposes that the initial acute effects of a substance is counteracted by the withdrawal effects of that drug. Indeed, greater pain during nicotine deprivation may be conceptualized as an opponent process of acute nicotine analgesia (Ditre et al., 2016).

The current study also examined associations between current pain intensity and other indices of nicotine deprivation/withdrawal following the manipulation. As expected, higher current pain intensity ratings were associated with lower exhaled CO. Exhaled CO is an indirect measure of blood carboxyhemoglobin that is most sensitive to recent smoking (e.g., within 24 hr; Bittoun, 2008; Marrone et al., 2010), and the current results are the first to suggest that exhaled CO may be incrementally related to current pain reporting. We also observed a positive correlation between current pain intensity and current urge to smoke following the deprivation manipulation. This finding is consistent with previous work demonstrating that pain can be a potent motivator of smoking (Ditre & Brandon, 2008; Ditre et al., 2010; Kosiba et al., 2018). Although we did not observe a significant association between current pain intensity and our measure of nicotine withdrawal, we did observe positive associations between current pain intensity and several other indices of nicotine deprivation/withdrawal (i.e., exhaled CO and urge to smoke), thus supporting the notion that pain warrants investigation as a symptom or correlate of the nicotine withdrawal syndrome.

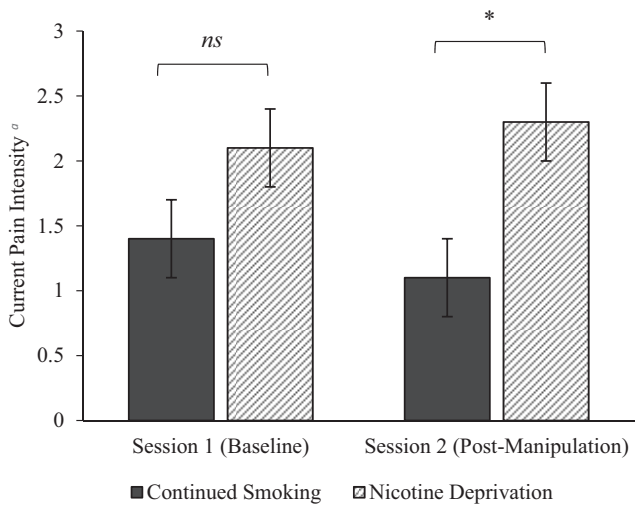

Figure 1. Unadjusted mean pain intensity ratings (with standard errors) as a function of experimental condition and study session. [a] *Numerical Rating Scale (NRS)*; ns = not significant ($p > .05$); * $p < .01$.

Strengths of the current study include experimental manipulation of nicotine deprivation, and biochemical verification of compliance with smoking instructions. In addition, we used valid and reliable assessments of pain, smoking urge, and nicotine withdrawal, and we were able to statistically control for individual difference factors that are known to influence pain reporting (i.e., gender, age, race, anxiety/depression symptoms; Wall, Melzack, & Bonica, 1994). Although this study marks a crucial first step in understanding the effect of nicotine deprivation on pain intensity, it remains unclear whether these results reflect a nicotine withdrawal effect or an offset effect of nicotine (e.g., Hughes, 2007). Indeed, nicotine has analgesic properties (Ditre et al., 2016) that are likely mediated by activation of both $\alpha4\beta2$ nicotinic acetylcholine receptors and the endogenous opioid system (Damaj et al., 2007; Marubio et al., 1999), and it is possible that the observed results could be explained by the discontinuation of nicotine administration. Alternatively, increased pain intensity may represent a nicotine withdrawal effect, and future research should employ a longer period of follow-up to determine whether increased pain intensity subsides after longer durations of abstinence or concomitant with other indices of withdrawal.

Smokers were excluded from the current study if they were prescribed pain medications or endorsed chronic pain, and the

extent to which these findings extend to individuals with clinical pain remains unclear. Although participants reported mild pain on average at baseline, the source of this acute pain was not assessed. Therefore, future studies should incorporate more thorough assessments of baseline pain (e.g., type, location, duration), and should assess the effects of smoking abstinence on current pain intensity among smokers who experience persistent pain. Future research would also benefit from assessing the source of pain onset/exacerbation (i.e., musculoskeletal vs. neuropathic) in the context of smoking abstinence, investigating the role of pain-related cognitive processes (i.e., pain-related anxiety, pain catastrophizing) during smoking abstinence (e.g., LaRowe, Langdon, Zvolensky, Zale, & Ditre, 2017), and examining the effects of pain medication use on deprivation-pain relations. Further, the inclusion of additional experimental groups (e.g., 2 hr deprivation, 48 hr deprivation) may help to clarify the time course of deprivation-induced changes in pain. Additionally, past-24 hr use of over-the-counter pain medications was not biochemically verified and use of substances beyond alcohol and cannabis (e.g., caffeine, nonprescription opioid pain medications) was not assessed in the current study. Future work should incorporate a more thorough assessment of substance use (e.g., urine toxicology screening), and determine whether the use of substances (particularly those with documented antinociceptive properties) moderates the effects of nicotine deprivation on pain reporting. Furthermore, given the high rates of co-occurrence among pain, smoking, and anxiety disorders (e.g., Zale et al., 2016), future studies may benefit from testing the role of anxiety-relevant factors (e.g., pain-related anxiety, anxiety sensitivity) in the effects of nicotine deprivation on pain severity. Finally, future work may benefit from standardizing the timing of study sessions, given that some evidence indicates that pain ratings may vary based on time of day (e.g., Aviram, Shochat, & Pud, 2015).

Clinical implications of this work include the possibility that increased pain following periods of smoking abstinence may precipitate relapse to smoking (e.g., Allen, Bade, Hatsukami, & Center, 2008). Given that nicotine administration confers acute pain-inhibitory effects (Ditre et al., 2016), smoking in response to deprivation-induced increases in pain may negatively reinforce smoking behavior and contribute to the maintenance of tobacco dependence (e.g., Eissenberg, 2004). Thus, deprivation-induced pain exacerbation may undermine cessation treatments, and tailored interventions may benefit from accounting for amplification of pain during the early stages of quitting. For example, given evidence that nicotine can produce acute analgesia (Ditre et al., 2016), high dose nicotine replacement therapy may help to reduce deprivation-induced increases in pain. Results of this study suggest clinical utility in the assessment of current pain among daily tobacco smokers, including those who do not endorse clinical or persistent pain.

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