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Pack-Years of Tobacco Cigarette Smoking as a Predictor of Spontaneous Pain Reporting and Experimental Pain Reactivity

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Abstract

The pack-years formula is a widely used estimate of lifetime tobacco smoking exposure, and greater pack-years have been associated with greater risk of chronic pain development and poorer pain-related outcomes among smokers with chronic pain. The pathophysiology underlying these associations is poorly understood. Regular tobacco smoking exposure may dysregulate homeostatic pain processes, producing an allostatic state of pain facilitation. Maladaptive pain mechanisms, such as central and peripheral sensitization, are chronic pain risk factors. Yet, no published research has involved a determination of the relation between lifetime-smoking exposure and dysregulated pain processing. The current study used hierarchical linear regression analyses to test pack-years of tobacco smoking as a predictor of (1) spontaneous pain reporting (current pain severity, pain frequency in the last 180 days) among a sample of 228 daily smokers without chronic pain, and (2) experimental capsaicin-induced pain reactivity (pain intensity, area of flare, mechanical pain sensitivity, and area of mechanical hyperalgesia) among 101 daily smokers without chronic pain. Gender and alcohol-related factors (consumption and dependence) were explored as statistical moderators. As hypothesized, results indicated that pack-years smoking was positively and significantly associated with spontaneous current pain severity, past 180-day pain frequency, experimental pain intensity, mechanical pain sensitivity ratings, and area of mechanical hyperalgesia. Pack-years smoking was not significantly associated with neurogenic flare. Moderation analyses produced null results. These findings implicate central sensitization, but not peripheral sensitization, as a potentially relevant factor that may underlie the association between chronic tobacco smoking and increased risk for persistent pain development.

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by

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Pack-Years of Tobacco Cigarette Smoking as a Predictor of Pain Reporting and Reactivity

Tobacco dependence and pain are both highly prevalent and co-occurring conditions, with a combined annual economic burden in excess of $800 billion in the United States alone (CDC, 2014; Gaskin & Richard, 2012; IOM, 2011; Tsang et al., 2008). Pain is a multidimensional, subjective experience that consists of sensory-physiological, motivational-affective, and cognitive-evaluative components (McMahon, Koltzenburg, Tracey, & Turk, 2013). Smoking prevalence among individuals with co-occurring pain (e.g., 42-68%; Michna et al., 2004; Zvolensky, McMillan, Gonzalez, & Asmundson, 2009) may be greater than twice the rate observed in the general population (e.g., 15%; Jamal et al., 2016). Thus, interrelations between pain and tobacco cigarette smoking are of increasing interest to researchers and clinicians.

Bidirectional models have posited that these conditions interact reciprocally, resulting in greater pain and the maintenance of tobacco dependence (Ditre, Brandon, Zale, & Meagher, 2011; Zale, Maisto, & Ditre, 2016). Although nicotine has been shown to reduce pain in the short-term (e.g., Ditre, Heckman, Zale, Kosiba, & Maisto, 2016), long-term smoking has been implicated in the onset and progression of several chronically painful conditions (Shiri & Falah-Hassani, 2016; Shiri, Karppinen, Leino-Arjas, Solovieva, & Viikari-Juntura, 2010; Sugiyama et al., 2010). Despite these known associations, research has yet to specify how regular tobacco use can engender pathological pain states.

A recently proposed allostatic load model of addiction and pain may account for how chronic substance use can lead to pain development (Egli, Koob, & Edwards, 2012). Allostatic load models attempt to describe homeostatic dysregulation that results in persistent aberrant states, and have been used to account for phenomena observed in disorders related to addiction, stress, and emotion (Koob & Le Moal, 2001). In particular, the allostatic load model specific to

addiction and pain (see Figure 1) posits that repeated opponent process cycles of substance-induced analgesia and withdrawal-induced hyperalgesia may dysregulate overlapping neural substrates to produce an imbalanced state of pain facilitation (Egli et al., 2012; Koob & Le Moal, 1997; Koob & Le Moal, 2001). From this perspective, it could be hypothesized that chronic smoking (along with commensurate tobacco use/disuse cycles) dysregulates homeostatic pain mechanisms (i.e., endogenous pain facilitation/inhibition) to engender an allostatic state that over-facilitates nociception. Consistent with this perspective, experimental research has reliably demonstrated acute pain-inhibitory effects of nicotine *administration* (Ditre et al., 2016; Jackson & Damaj, 2013), and pain-facilitating effects of acute nicotine *deprivation* (Damaj, Kao, & Martin, 2003; Ditre, Zale, Kosiba, De Vita, & LaRowe, 2017; Grabus et al., 2005; Jackson, McIntosh, Brunzell, Sanjakdar, & Damaj, 2009). Yet, no published research has examined the relation between lifetime-smoking exposure and dysregulated pain processing.

The associations between chronic smoking and pain reporting have been studied for nearly three decades (e.g., Deyo & Bass, 1989), with more recent research implicating pack-years smoking as a unique risk factor in the development of persistent pain (Shiri & Falah-Hassani, 2016; Shiri et al., 2010; Sugiyama et al., 2010). The pack-years formula is a widely used estimate of lifetime smoking exposure that is calculated by multiplying the number of cigarette packs smoked per day by the number of years smoking (Bernaards, Twisk, Snel, Van Mechelen, & Kemper, 2001). Greater pack-years have been associated with increased pain intensity, frequency, and duration among smokers seeking treatment for chronic pain (Scott, Goldberg, Mayo, Stock, & Poitras, 1999). Epidemiological studies have indicated that the risk for developing persistent pain increases as a function of greater pack-years (Deyo & Bass, 1989; Dubé et al., 2015; Mikkonen et al., 2008; Pisinger et al., 2011; Scott et al., 1999; Sugiyama et al.,

2010). These data are consistent with the notion that lifetime smoking exposure may dysregulate pain processes, and promote the transition from acute to chronic pain (i.e., pain that extends beyond the expected period of healing; Turk & Okifuji, 2001). However, these findings do not address the pathophysiology underlying the transition to chronic pain in smokers. No research has been reported that tests the associations between pack-years smoking and either *current spontaneous pain reporting* or *experimental pain reactivity* among smokers without chronic pain.

Addressing this research gap would have important clinical implications. To inform intervention design, researchers have emphasized the importance of identifying dysregulated pain processes that increase the risk for persistent pain development (McGreevy, Bottros, & Raja, 2011). Abnormal patterns of pain processing vary across clinical syndromes. This variability reflects differing underlying mechanisms that may yield insights about the pathophysiology, diagnosis, and treatment of clinical conditions (Lautenbacher & Fillingim, 2004). Despite empirical evidence suggesting that smoking causes pain (e.g., Shiri et al., 2010), the pathophysiological mechanisms underlying this relation are poorly understood. Once identified, clinical researchers could examine the extent to which these neuroplastic mechanisms can be modified using behavioral and pharmacological interventions (McGreevy et al., 2011). Although additional research is needed to address these empirical gaps, current spontaneous pain reporting and experimental pain reactivity represent two complementary pain assessment methods that could inform our understanding of how chronic tobacco exposure may influence pain development.

Current spontaneous pain reporting can be readily assessed by asking smokers to rate the severity of pain they are experiencing right now (e.g., using numerical rating scales of current pain intensity), and to indicate the frequency with which they experience pain (e.g., number of

days with pain). Although greater current pain reporting can reflect dysregulated pain processing, it does not provide information regarding pathophysiological mechanisms of action (Arendt-Nielsen & Lautenbacher, 2004). Measuring psychophysiological reactivity to experimental pain induction, on the other hand, can yield insights into underlying mechanisms using a variety of laboratory methods (Arendt-Nielsen & Yarnitsky, 2009), including the current gold-standard approach of quantitative sensory testing (QST).

The term quantitative sensory testing represents the evaluation of perceptual responses to the systematic application of quantifiable sensory stimuli (Boivie, 2003; Cruz-Almeida & Fillingim, 2014; Hansson, Backonja, & Bouhassira, 2007; Olesen, van Goor, Bouwense, Wilder-Smith, & Drewes, 2012). Unlike self-reported pain ratings, QST employs highly standardized psychophysiological protocols to assess nervous system processes that underlie the experience of pain. QST evaluates both central and peripheral nervous system mechanisms using laboratory models that mimic painful conditions without causing lasting tissue damage (Edens & Gil, 1995). The capsaicin QST model induces prolonged nociception that approximates spontaneous burning pain associated with neuropathic and inflammatory clinical pain states (Arendt-Nielsen & Andersen, 2005; Benarroch & Low, 1991; Hsieh & Lin, 1999; Parkhouse & Le Quesne, 1988). In addition to experimental pain intensity ratings, this approach permits tests of neurogenic flare and mechanical hyperalgesia, which reflect peripheral and central sensitization, respectively (LaMotte, Lundberg, & Torebjork, 1992; Simone & Ochoa, 1991; Torebjork, Lundberg, & LaMotte, 1992). Given that peripheral and central sensitization are considered maladaptive neuroplastic mechanisms in the transition from acute to persistent pain (McGreevy et al., 2011), it is important to examine these processes among smokers who have not yet developed chronic pain.

Experimental pain intensity ratings provide a general measure of pain reactivity that involves peripheral conduction via afferent pain neurons (Schaible, 2006), and nociceptive processing in the central nervous system (Coghill, Sang, Maisog, & Iadarola, 1999). *Neurogenic flare* is considered a measure of peripheral sensitization (Klede, Handwerker, & Schmelz, 2003), in that it reflects visible neuropeptide-induced vasodilation caused by peripheral C-fiber activation (Brain & Grant, 2004; Geber et al., 2007; Holzer, 1998; Schmelz, 2009). Mechanical hyperalgesia is considered a measure of central sensitization (Klede et al., 2003) in that it reflects enhanced excitability of spinal dorsal horn neurons (Treede, Handwerker, Baumgärtner, Meyer, & Magerl, 2004), and the release of several pain-related neurotransmitters (i.e., glutamate, substance P, CGRP, somatostatin, and nitric oxide) at the central level (Sandkühler, 2009; Serra, Campero, & Ochoa, 1998; Ziegler, Magerl, Meyer, & Treede, 1999).

An important next step in this line of research is to assess the extent to which pack-years smoking may be associated with increased current spontaneous pain reporting and experimental pain reactivity among smokers who have not yet developed chronic pain. Therefore, the current study had two primary aims. Aim 1 was to test pack-years of tobacco cigarette smoking as a predictor of spontaneous current pain severity and past 180-day pain frequency among daily smokers without chronic pain. Specifically, it was hypothesized that greater pack-years would predict greater current pain severity and greater frequency of pain during the last 180 days. Aim 2 was to test whether pack-years smoking would predict experimental pain reactivity outcomes (i.e., pain intensity, neurogenic flare, and mechanical hyperalgesia) among a sample of daily cigarette smokers who do not have chronic pain. For the second aim, it was hypothesized that greater pack-years would predict greater experimental pain intensity ratings, larger area of neurogenic flare, greater mechanical pain sensitivity, and larger area of mechanical hyperalgesia.

As an exploratory aim, the current study also examined gender and alcohol-related factors as potential moderators of the relations hypothesized in Aims 1 and 2. Smokers are more likely to be male (CDC, 2015), and there is evidence that females are more sensitive to experimentally induced pain (Granot et al., 2008; Racine et al., 2010; Wise, Price, Myers, Heft, & Robinson, 2002). Furthermore, researchers have hypothesized that chronic episodes of alcohol intoxication and withdrawal may produce an allostatic pain state, and alcohol dependence has been associated with greater allostatic load and dysregulated pain processing (Egli et al., 2012). The allostatic load generated from co-occurring alcohol and tobacco use may be greater than the dysregulation caused by either drug alone. Accordingly, the effects hypothesized in Aims 1 and 2 may be more evident among smokers who reported greater quantities and frequencies of alcohol consumption, as well as those who endorsed greater levels of alcohol dependence.

Method

Participants

Participants were recruited from the community to participate in a larger, two-session experimental study that tested the effects of nicotine deprivation using a capsaicin pain model (Ditre et al., 2017). Respondents were screened by phone for the following inclusion criteria: (1) between 18-65 years of age; (2) currently smoking ≥ 15 cigarettes per day; and (3) ability to speak and read English. Respondents were excluded if they endorsed: (1) a current attempt to reduce or quit smoking; (2) current chronic pain; (3) current use of prescription pain medications; or (4) pepper allergy (contraindicated for capsaicin pain induction). Participants attended a baseline assessment and were subsequently randomized to one of three experimental conditions: continued smoking (N = 66), minimal 2-hour deprivation (N = 35), or extended 12-24 hour deprivation (N = 127).

The parent study included a minimal deprivation group to ensure that continued smokers were not experiencing acute analgesic effects of nicotine. As expected, the primary study revealed no differences between the continued smoking and minimal deprivation groups on measures of cigarette craving, nicotine withdrawal, or current pain intensity prior to the experimental pain induction (Ditre et al., 2017). Findings from the parent study indicated that extended nicotine-deprivation significantly increased all measures of pain reactivity (Ditre et al., 2017). These observed effects would likely confound analyses aiming to examine associations between pack-years smoking and pain reactivity among daily smokers. That is, a deprivation-induced increase in pain reactivity represents an altered state that is likely different from how a participant might typically present under usual conditions. Given that current spontaneous pain reporting was assessed at the baseline session of the larger study (i.e., prior to randomization to deprivation condition), Aim 1 analyses included the entire sample (N = 228). To examine pain reactivity as a function of lifetime smoking exposure, Aim 2 analyses excluded participants who were randomly assigned to the extended nicotine deprivation condition to avoid the confounds described above. Thus, Aim 2 analyses included N = 101 participants who were randomized to either continued smoking (n = 66) or minimal deprivation conditions (n = 35).

Measures

Baseline assessment.

Demographic questionnaire. Participants reported demographic information, including age, gender, race, ethnicity, education, employment status, and annual income.

Smoking questionnaire. A smoking questionnaire assessed smoking history and current smoking status. *Pack-years smoking* was determined using two items where participants were asked, “For how many years, altogether, have you been a regular/daily smoker?” and “Since you

started regular/daily smoking, what is the average number of cigarettes you smoke per day?" Consistent with previous research, pack-years was computed as: $\left(\frac{\text{cigarettes per day}}{20}\right) \times$ years smoking (Deyo & Bass, 1989; Dubé et al., 2015; Mikkonen et al., 2008; Pisinger et al., 2011; Scott et al., 1999; Sugiyama et al., 2010). In previous research, the pack-years calculation has demonstrated high test-retest reliability (*ICC* = .76; Brigham et al., 2009), and moderate to good relative validity when compared to prospective tobacco use estimates (κ = 0.79; Bernaards et al., 2001)

***Alcohol Consumption*.** The Alcohol Use Disorder Identification Test (AUDIT; Babor, Higgins-Biddle, Saunders, & Monteiro, 2001; Saunders, Aasland, Babor, De la Fuente, & Grant, 1993) is a 10-item instrument that assesses current (defined in this study as the last 12 months) risk for alcohol abuse. The AUDIT has been shown to be a reliable and valid screening measure for possible hazardous or harmful alcohol consumption in adults. Items on this measure are summed to produce an overall score, with a total of 8 or more suggesting hazardous use and possible alcohol dependence. Furthermore, the AUDIT assesses three sub-domains of alcohol consumption, alcohol-related consequences, and symptoms of alcohol dependence, respectively (Reinert & Allen, 2002). Due to the aforementioned associations between alcohol-related factors, allostatic load, and dysregulated pain processing reported in the literature (Egli et al., 2012), we were primarily interested in testing the constructs of alcohol consumption (items 1-3) and dependence (items 8-10) as potential moderators of the effects hypothesized in Aims 1 and 2. Given our theoretical basis, we suspected that any detected alcohol-related interactions would most likely pertain to the consumption subscale, as it is comprised of items that assess quantity and frequency of alcohol use (Babor et al., 2001).

Aim 1 pain reporting outcomes.

Current spontaneous pain severity and frequency of pain. A single item from the Graded Chronic Pain Scale (*GCPS*; Von Korff, 2011) assessed current pain severity. Participants responded to the question "How would you rate your pain RIGHT NOW?" using a numerical rating scale that ranged from 0 (no pain) to 10 (pain as bad as it could be). Pain frequency in the last 180 days was assessed with another item that asked, "On how many days in the last 180 days (6 months) have you had pain?" (Von Korff, 2011).

Aim 2 experimental pain reactivity outcomes.

***Experimental pain intensity*.** Capsaicin-induced pain intensity was assessed using a visual analogue scale (VAS) that ranged from 0 (no pain) to 10 (pain as bad as you can imagine). The VAS has shown strong reliability and internal consistency in previous research (Price, Bush, Long, & Harkins, 1994). Participants provided ratings at five-minute intervals throughout the capsaicin application period. Consistent with the data analytic approach in the primary study, total pain ratings were obtained by calculating the area under the VAS curves (AUC) for each participant using the trapezoidal method (Matthews, Altman, Campbell, & Royston, 1990). The AUC calculation provides a summary measure that integrates serial pain assessments over the duration of the capsaicin procedure (Lee, Lee, Wu, Lee, & Chen, 2005). Thus, the AUC consists of information from all available data points, whereas less optimal measures, such as peak pain intensity, are quantified using only a portion of the data and may be less valid representations of sequential pain ratings.

***Neurogenic flare*.** Neurogenic flare was quantified as the area of visible skin inflammation (i.e., redness extending beyond the capsaicin application site; Helme & McKernan, 1985). Consistent with previous work, the flare boundary was traced onto transparent acetate and scanned to generate an area value in pixels (Helme & McKernan, 1985). The pixels were subsequently converted into squared centimeters (cm2) for analysis.

Mechanical hyperalgesia. Mechanical hyperalgesia (i.e., increased sensitivity to mechanical stimulation) was assessed using a 6.65 von Frey hair (Bell-Krotoski & Tomancik, 1987; Bell-Krotoski, Fess, Figarola, & Hiltz, 1995). A standardized 300 grams of force was applied at points separated by 1 centimeter (cm) along 8 linear paths radiating from the center of the application site to form 8 concentric von Frey rings (Modir & Wallace, 2010). Participants rated pain intensity at each point using a numerical rating scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine). Two distinct measures of mechanical hyperalgesia were quantified. First, *pain sensitivity* to mechanical stimulation was estimated by calculating the AUC for each von Frey ring. Second, the *area* of mechanical hyperalgesia was computed by entering the boundaries of hyperalgesia (defined as the last 50% reduction in pain ratings along each von Frey path) into an established vector algorithm (Gottrup et al., 2004; Werner, Petersen, Rowbotham, & Dahl, 2013).

Procedure

Participants were recruited to participate in the parent study using internet and newspaper advertisements (Ditre et al., 2017). Eligible daily tobacco smokers attended a baseline assessment session, where they provided informed consent, verified smoking status via exhaled carbon monoxide ($CO \geq 8ppm$), completed measures of smoking history, spontaneous current pain reporting (Aim 1 outcomes), and other relevant variables (e.g., sociodemographic info). Participants were then randomized to 1 of the 3 experimental conditions, scheduled for an experimental session, and compensated $20. At the experimental session, participants completed pre-application measures, underwent a capsaicin QST pain reactivity assessment (Aim 2 outcomes), and completed post-application measures. Participants were then debriefed and compensated $80. Procedural details are shown in Figure 2.

Experimental pain induction. Experimental pain was induced using capsaicin, a vanilloid receptor agonist derived from chili peppers (Arendt-Nielsen & Andersen, 2005). A 10% capsaicin solution was applied to the non-dominant volar forearm via a 1.5cm x 1.5cm gauze pad (Baron et al., 1999). Capsaicin pain peaks in approximately 15-20 minutes (Geber et al., 2007; Petersen, Jones, Segredo, Dahl, & Rowbotham, 2001), and the substance was removed after 30 minutes.

Data Analytic Strategy

All statistical analyses were conducted using SPSS, version 21 (IBM, Armonk, New York). A series of bivariate correlations were performed to test zero-order associations among pack-years smoking, pain outcomes, sociodemographic factors, and AUDIT scores. Variables that were significantly associated with either the independent or dependent variables were considered for inclusion in subsequent analyses, as either covariates or potential moderators (Pocock, Assmann, Enos, & Kasten, 2002). Distributional assumptions were considered, and transformations (e.g., logarithmic, square root) were applied when indicated to improve data normality (Howell, 2012).

The data-analytic strategy was hierarchical linear regression, and the enter method was used at each step. The enter method inputs all independent variables (predictors) simultaneously into the model. Enter is standard method of variable entry, unless theory sufficiently supports a different method. The extent to which the pack-years variable contributed to the prediction of the dependent variable was evaluated. The *t* test was used to determine the significance of each predictor, whereas change in *R* squared (ΔR^2) and squared semi-partial correlations (sr^2) were used to assess the relative contribution of pack-years smoking to the observed variance in pain outcomes.

For Aim 1, separate hierarchical regression models were constructed to test each pain reporting outcome (current spontaneous pain severity, pain frequency in the last 180 days) among the entire sample (N = 228). Sociodemographic covariates were entered in the first step, and pack-years smoking was entered in the last step. For Aim 2 analyses, separate models tested each pain reactivity outcome (experimental pain intensity, area of flare, area of mechanical pain sensitivity ratings, and area of secondary hyperalgesia) among the non-deprived participants (N = 101). Sociodemographic covariates were entered in the first step, and the second step included procedural factors that may have influenced pain reactivity outcomes (i.e., time since last cigarette, room temperature). Pack-years smoking was entered into the final step of the models.

For the exploratory aims, gender and alcohol use (i.e., AUDIT consumption and dependence subscale scores) were tested as moderators of the associations between pack-years smoking and pain outcomes in both of the study samples. A significance level of $p < .05$ was used to determine if interaction terms were significant in the regression model. Moderation was tested using the PROCESS Macro for SPSS (Hayes, 2013).

Results

Aim 1: Pack-Years Smoking and Spontaneous Pain Reporting

Participant characteristics. In Aim 1, participants included 228 current daily tobacco smokers (42.1% female; M_{age} = 41.5, SD = 12.4), who reported smoking approximately 21 cigarettes per day (SD = 11) for an average of 24.4 years (SD = 12.3). The number of pack-years smoking for the sample ranged from 1.4 to 165, and had an average of 27.0 (SD = 23.2). The sample was predominately Caucasian (57.5%), and most participants had at least a high school education (76.8%). On average, participants reported experiencing pain on 44.2 days in the past

6 months. The sample yielded an average AUDIT score of 6.5 (*SD* = 7.7). Additional sociodemographic, pain, smoking, and drinking data are presented in Table 1.

Bivariate correlations. The pack-years variable was log transformed to achieve a greater approximation of its distribution to normality before correlations and regressions were calculated. Pack-years smoking was positively correlated with current spontaneous pain severity ($r = .22$, $p < .01$), pain frequency in the last 180 days ($r = .18$, $p < .01$), and age ($r = .69$, $p < .001$). Pain severity was also correlated with alcohol dependence ($r = .18$, $p < .01$), whereas pain frequency was correlated with alcohol consumption ($r = .23$, $p < .01$). Given known associations between age, smoking exposure, and pain (e.g., Scott, 1999), all Aim 1 analyses were designed to control for age. Additional bivariate analyses are presented in Table 2.

Pack-years smoking and current spontaneous pain severity. As seen in Table 3, results of the hierarchical regression analysis revealed that age did not account for a significant portion of the variance in current spontaneous pain severity ratings (Step 1: p = .62). However, as hypothesized, a positive and significant association between pack-years smoking and current pain severity was observed (Step 2: $\beta = .30$, $p < .01$). Examination of the ΔR^2 statistic at Step 2 revealed that pack-years accounted for approximately 5% of the unique variance in pain severity ratings.

Pack-years smoking and frequency of pain in the last 180 days. Similar to the finding observed for current spontaneous pain severity, the results of separate hierarchical regression analyses indicated that pack-years smoking was positively and significantly associated with the frequency of pain in the last 180 days (Step 2: $\beta = .30$, $p < .01$), even after controlling for age (Table 4). As indicated by the ΔR^2 value at Step 2, pack-years accounted for approximately 2% of the unique variance in reported pain frequency.

Aim 2: Pack-Years Smoking and Experimental Pain Reactivity

Participant characteristics. In the Aim 2 sample, participants included 101 daily tobacco smokers, who reported smoking an average of 20.5 cigarettes per day (*SD* = 12.9) for approximately 24.8 years (*SD* = 12.4). The number of pack-years smoking for the sample in Aim 2 ranged from 1.4 to 112.5, and averaged 26.9 (*SD* = 21.1). The sample was predominately male (59.4%) and Caucasian (50.5%). The sample yielded an average AUDIT score of 6.0 (*SD* = 6.7). Additional sociodemographic, smoking, and drinking data are presented in Table 5.

Bivariate correlations. Before calculating correlations and regressions, square root transformations were applied to positively skewed area measurements of flare and mechanical hyperalgesia to improve normality. Log transformations were used to improve normality of mechanical pain sensitivity ratings for each of the von Frey rings. As presented in Table 6, pack-years of tobacco cigarette smoking was positively correlated with age ($r = .75$, $p < .001$) and mechanical pain ratings at the outermost (8^{th}) von Frey ring ($r = .20$, $p < .05$). Age was also negatively associated with area of flare ($r = -.30$, $p < .01$) and mechanical pain ratings at the innermost (1^{st}) von Frey ring ($r = -.21$, $p < .05$). Race was positively associated with area of flare ($r = .48$, $p < .001$), and negatively associated with mechanical pain ratings at the outermost von Frey ring ($r = -.31$, $p < .01$) and time since last cigarette ($r = -.20$, $p < .05$). Gender was negatively correlated with mechanical pain ratings at the innermost (1^{st}) von Frey ring. AUDIT consumption scores were negatively correlated with area of mechanical hyperalgesia ($r = -.27$, $p < .01$). Again, based on these observations, and known associations between age, smoking exposure, and pain (e.g., Scott, 1999), all Aim 2 analyses were designed to control for the influence of age. Furthermore, previous research has demonstrated that African Americans tend to show less hyperalgesia and neurogenic flare in response to the application of topical capsaicin,

especially in comparison to Caucasian participants (Wang et al., 2010). Given that the current sample has a similar proportion of White and Non-White participants (47.5% African American), as well as the observed associations between race, flare, and mechanical pain sensitivity, race was entered as a covariate in all Aim 2 analyses.

Experimental pain intensity ratings. As seen in Table 8, results of hierarchical regression analysis revealed that neither age nor race accounted for a significant portion of the variance in experimental pain intensity ratings at Step 1 ($p = .52$). Experimental factors added in Step 2 (i.e., time since last cigarette and room temperature) did not account for a significant portion of the variance in pain intensity ratings either ($p = .57$). At Step 3 however, as hypothesized, the analyses revealed a positive and significant association between pack-years smoking and experimental pain intensity ratings ($\beta = .51$, $p < .01$). Examination of the ΔR^2 statistic at Step 3 showed that pack-years smoking accounted for approximately 11% of the unique variance in pain intensity ratings.

Neurogenic flare. As shown in Table 9, hierarchical regression analyses revealed that both age and race accounted for a significant portion of variance in area of flare measurements at Step 1 ($p = .00$). Whereas age ($p = .00$), race ($p = .00$), and room temperature ($p = .02$) accounted for a significant portion of variance in flare measurements at Step 2, time since last cigarette did not ($p = .88$). At Step 3 however, no association was observed between pack-years smoking and area of flare ($p = .38$).

Mechanical pain sensitivity. As demonstrated in Table 10, Step 1 of the hierarchical regression model revealed that neither age nor race accounted for a significant portion of variance in the mechanical hyperalgesia area measurements ($p = .32$). Whereas age ($p = .57$), race ($p = .12$), and time since last cigarette ($p = .39$) were not significant at Step 2, room

temperature accounted for a significant portion of variance in mechanical hyperalgesia area measurements (p = .04). As hypothesized, Step 3 analyses revealed a positive and significant association between pack-years smoking and area of mechanical hyperalgesia, even after controlling for these relevant factors (Step 3: β = .30, p < .05). Examining the ΔR^2 statistic at Step 3 revealed that pack-years of tobacco smoking accounted for approximately 4% of the unique variance in mechanical hyperalgesia area measurements. Also as hypothesized, separate hierarchical models revealed that pack-years smoking was positively and significantly associated with ratings of mechanical pain sensitivity at seven of the von Frey rings (*p's* < .05), even after controlling for age, race, time since last cigarette, and room temperature. For these associations, the proportion of variance accounted for by pack-years smoking ranged from 4 - 8%. Table 7 presents the results at Step 3 for mechanical pain sensitivity ratings at each von Frey ring.

Exploratory Moderation Analyses

Separate exploratory regression models were used to test gender and AUDIT subscale scores (i.e., consumption and dependence) as moderators of the association of pack-years smoking with outcomes in Aim 1 and 2. Analyses revealed no moderation effects of gender on any of the associations tested in either sample (*p's* > .05). Similarly, neither of the AUDIT subscale scores was a significant moderator of the observed associations of pack-years on spontaneous pain reporting and experimental pain reactivity (*p's* > .05). Coefficients for the exploratory moderation analyses are presented in Table 11.

Discussion

The current study is the first to investigate pack-years, an index of lifetime tobacco smoking exposure, as a predictor of spontaneous pain reporting (i.e., current pain severity and frequency) and experimental pain reactivity (i.e., pain intensity, neurogenic flare, and mechanical

hyperalgesia) among smokers without chronic pain. As hypothesized, pack-years smoking was observed to be positively and significantly associated with greater current spontaneous pain severity and frequency of pain in the past 180 days. These findings highlight the relevance of smoking and pain relations, even among those without chronic pain. Also as hypothesized, greater pack-years smoking was associated with greater capsaicin-induced pain intensity, heightened mechanical pain sensitivity, and larger areas of mechanical hyperalgesia. As such, this study provides evidence for an exposure-response relation between lifetime tobacco smoking exposure and dysregulated pain processes, primarily at the central level. Pack-years was not found to be significantly associated with neurogenic flare measurements, which provide an index of peripheral sensitization. Taken together, these data implicate central sensitization, but not peripheral sensitization, as a relevant factor to consider in the relation between chronic tobacco smoking and increased risk for persistent pain development.

Nicotinic acetylcholine receptors (nAChRs) are widespread throughout the central nervous system, especially in regions associated with pain transmission, such as the spinal dorsal horn, locus coeruleus, and thalamus (Shi et al., 2010). Activation of these receptors results in the release of endogenous opioids and norepinephrine, which can reduce facilitatory pain pathways and enhance inhibitory pain pathways, resulting in reduced transmission of nociceptive input. That is, nicotine can confer analgesia by acting on nAChRs in the brain and spinal cord (Shi et al., 2010). An allostatic load model of substance use and pain (e.g., Egli, Koob, & Edwards, 2012) would posit that repeated opponent process cycles of nicotine-induced analgesia and withdrawal-induced hyperalgesia would dysregulate these central mechanisms to engender a persistent imbalance that favors pain facilitation. Consistently, the current results provide evidence for enhanced facilitation of pain transmission at the central level as a function of

smoking chronicity. Associations between peripheral pain mechanisms and tobacco use are less understood due to a disproportionate focus on central processes in the extant literature. Although analyses for an index of peripheral processes (neurogenic flare) produced null findings in the current study, additional research would be needed before concluding that effects were exclusively central in nature.

The results implicating the importance of central sensitization may be viewed in the context of other clinically relevant research findings. In this regard, there are data that suggest that central sensitization, a chronic pain-risk factor, can be modified using pharmacological and behavioral strategies. Pharmacological research has shown that NMDA antagonists (e.g., Ketamine) inhibit central sensitization (McGreevy et al., 2011). Additionally, a brief Cognitive Behavioral intervention for pain has been shown to significantly reduce secondary hyperalgesia (i.e., central sensitization) in healthy human subjects undergoing an experimental pain task (Salomons, Moayedi, Erpelding, & Davis, 2014). Although additional clinical research is needed, reducing central sensitization in chronic tobacco smokers may mitigate the risk of persistent pain development following an acute injury. Behavioral interventions that promote smoking cessation may also affect dysregulated pain processing in smokers.

Despite stated concerns about difficulties smokers may have with short-term abstinence, researchers have proposed that recovery from the effects of chronic nicotine exposure may improve pain pathophysiology in the long-term (Shi et al., 2010). Though more research is needed, clinical attempts to treat the pathophysiological effects of chronic smoking on pain may potentially be enhanced in the context of prolonged smoking abstinence. If chronic smoking engenders an allostatic state of pain facilitation, then removing this potential cause may improve additional efforts to reduce maladaptive sensitization. Nonetheless, tobacco cessation alone may

not be enough to mitigate the effects of chronic smoking, which have been shown to produce persistent alterations in nervous system functioning that can endure long after cessation (Perkins et al., 2001). Combining smoking cessation interventions with targeted treatments for pain may have the benefit of improving outcomes for both (Ditre et al., 2011; Zale et al., 2016). Integrated treatments, such as Cognitive Behavioral Therapy protocols for pain and smoking cessation (Zale et al., 2016), and tailored nicotine replacement therapies that confer analgesic effects in smokers with pain (Ditre et al., 2016), have been proposed. Additionally, psychoeducation about smoking-health interactions has been shown to increase motivation to quit smoking (e.g., McCaul et al., 2006; Zvolensky, Lejuez, Kahler, & Brown, 2003). Guidelines for brief motivational substance-use interventions emphasize education about interactions between substance use and health-related conditions (SAMHSA, 2012).

Although smokers with co-occurring pain may benefit from these types of tailored interventions (Ditre et al., 2011; Zale et al., 2014), the current study also has implications for smokers who have not yet developed pain. Providers may deliver brief psychoeducational interventions that inform patients about the interrelations between smoking and pain, including how smoking exposure is associated with increased pain sensitivity, dysregulated pain processing, and greater risk for chronic pain development. Further study of the pathophysiological mechanisms underlying the association between tobacco smoking and pain development could ultimately inform clinical research that aims to break the causal chain.

None of the reported main effects were found to be moderated by gender or alcohol-related variables. Null findings may be attributable to several factors. Moderation analyses may have had limited statistical power, particularly in the reduced Aim 2 sample (N = 101). The sizes of the main effects detected in this study were relatively small, and the regression models

explained a modest proportion of variance in the tested outcomes. Moderation effect sizes may be even smaller, which could have further reduced power to detect interactions (Collins et al., 2009). In addition, despite known sex/gender differences on certain measures of experimental pain reactivity (e.g., threshold and tolerance), most research has shown no such differences on measures of pain intensity, even when using varying models of experimental pain (Racine et al., 2012). In exploratory analyses, alcohol consumption and dependence were tested as moderators, because it was thought that allostatic load might have been greater among those with a history of heavy drinking and chronic tobacco smoking (Egli et al., 2012). Although the first three items of the AUDIT measure quantity and frequency of recent (defined as past year in this study) alcohol consumption, they do not quantify lifetime alcohol exposure. Future research may benefit from using instruments that specifically measure alcohol use patterns over the lifetime (e.g., Concordia Lifetime Drinking Questionnaire; Chaikelson, Arbuckle, Lapidus, & Gold, 1994).

Although not tested in this study, ethnic/racial differences may be a potential moderating factor that should be considered in future research. Ethnic/racial disparities in smoking-related factors have been reported in the literature (Sakuma et al. 2016; Caraballo, Yee, Gfroerer, & Mirza, 2008). Responses to experimentally induced pain have also been found to differ as a function of ethnicity/race (Rahim-Williams et al. 2012; Wang et al. 2010). Thus, future investigations would benefit from examining interaction effects between ethnicity/race, tobacco smoking exposure, and pain reactivity.

The current study had several notable strengths. The recruitment of a relatively large community sample of daily tobacco smokers was beneficial, for both external validity and statistical power in the primary aims. By examining these associations in a sample without chronic pain, hypotheses about the transition to persistent pain in smokers may be advanced.

Employing sophisticated QST methods permitted various mechanistic insights that likely have implications for the study, prevention, diagnosis, and treatment of pain in tobacco smokers.

Several limitations of the current study should also be considered in interpreting its findings. First, the retrospective pack-years calculation may be susceptible to recall errors (Bernaards et al., 2001; Brigham et al., 2009). The equation can generate a similar outcome for individuals with disparate smoking histories. For example, someone who smoked 10 cigarettes a day for 10 years would have the same number of pack-years as someone who smoked 20 cigarettes for 5 years (i.e., 5 pack-years). It also does not account for quit attempts, periods of abstinence during the lifetime, or other forms of tobacco use (e.g., cigar smoking). Furthermore, any index of lifetime substance use will also be strongly associated with age, given that older adults will have had more time to expose themselves to substances compared to younger individuals. Despite these limitations, the pack-years calculation remains a commonly used method for estimating lifetime smoking exposure, which cannot be quantified by other tobacco use variables alone (e.g., cigarettes per day; Bernaards et al., 2001; Brigham et al., 2009). Second, the sample consisted primarily of daily tobacco smokers who reported smoking at least 15 cigarettes per day. Although the relations under study may be more evident among daily tobacco smokers, future research should also examine these processes among lighter and intermittent smokers to enhance external validity. Former smokers should also be examined to determine the extent to which indicators of allostatic load have persisted or alleviated post-cessation. Third, this was a cross-sectional, observational study, and therefore it is not possible to make inferences about the dynamics of relations among variables. Future research may benefit from the application of prospective designs that assess pain reactivity closer to the onset of smoking to examine pathophysiological changes over time. Fourth, experimental pain models,

such as the capsaicin paradigm used in this study, are merely analogs of clinical pain. Standardized pain induced in a laboratory differs from pain occurring in other contexts (e.g., clinical setting), which may limit the generalizability of outcomes associated with these models (Edens and Gil, 1995). Nonetheless, clinical pain often covaries with numerous confounding factors (e.g., depression), whereas experimental pain induction reduces threats to internal validity while providing useful measures of pain nervous system functioning (Olesen et al., 2012; Kumar Reddy et al. 2012). Fifth, although these data may provide insight into mechanisms of endogenous pain facilitation (i.e., peripheral and central sensitization) that have been implicated in the development of persistent pain, future research may also examine the effect of lifetime smoking exposure on endogenous pain inhibition (e.g., conditioned pain modulation) among smokers. Finally, many factors relevant to the study aims were not included in analyses because they were not measured in the parent study. For example, the parent study did not collect secondary traces of neurogenic flare, and analyses of inter-rater reliability for this outcome could not be conducted. Additionally, although alcohol use was assessed as a component of the AUDIT, use of additional substances was not measured. Future research should include a comprehensive assessment of current and past substance use, given that other drugs have been posited to affect allostatic load (e.g., Egli et al., 2012; Elman & Borsook, 2016).

In conclusion, the current study provides preliminary evidence of dysregulated pain processing as a function of lifetime smoking exposure. Results suggest that central sensitization may be a possible mechanism underlying associations between tobacco smoking exposure and pain. Despite smoking being identified as a causal agent in chronic pain development, poor pathophysiological understanding of this association remains a critical barrier to successful pain prevention and treatment for this population (Shi et al. 2010). Indeed, the precise explication of

mechanisms underlying these associations will require extensive research. Given the results of the current study, future research that examines smoking-pain pathophysiology is warranted. Identifying dysregulated pain processes in regular smokers would allow clinical researchers to examine the extent to which these neuroplastic mechanisms can be modified using various interventions.

Table 1

Aim 1 Sample Sociodemographic and Smoking Characteristics

Participant Characteristics (*N* = 228)	*N*	%
Gender		
Female	96	42.1
Income		
<30K	169	74.1
30-50K	27	11.9
>50K	32	14.0
Education		
Did not graduate high school	53	23.2
High school or part college	134	58.7
Technical school/Associates	27	12.0
Four-year college or more	14	6.1
Marital Status		
Single	138	60.5
Married	36	15.8
Divorced/Other	54	23.7
Ethnicity		
Hispanic/Latino	9	3.9
Not Hispanic/Latino	219	96.1
Race		
Caucasian	131	57.5
Black/African American	89	39.0
Other	8	3.5
	M	*SD*
Age	41.5	12.4
Pack-Years Smoking [1]	27.0	23.2
Average Cigarettes Per Day	21.1	11.0
Years of Regular Smoking	24.4	12.3
AUDIT Total [2]	6.5	7.7
Consumption	3.2	3.2
Dependence	1.3	2.8
Problematic Use	2.0	3.3

Note. [1] Pack-Years = $\frac{cigarettes\ per\ day}{20} \times years\ smoking$; [2] Alcohol Use Disorders Identification Test.

Table 2

Bivariate Pearson Correlations Between Primary Variables of Interest

Variable	*r*						
	1	2	3	4	5	6	7
1. Pack-Years Smoking	-	.22**	.18**	.69***	.03	-.05	-.01
2. Pain Severity		-	.53***	.10	.09	.05	.18**
3. Pain Frequency			-	.10	.08	.23**	.10
4. Age				-	-.05	-.04	-.02
5. Gender					-	.19**	.16*
6. AUDIT Consumption [1]						-	.50***
7. AUDIT Dependence							-

Note. $N = 228$. [1] Alcohol Use Disorders Identification Test.

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

Table 3

Hierarchical Regression Model with Spontaneous Current Pain Severity Entered as the Criterion Variable

		ΔR^2	*β*	*t*	sr^2	*p*
Step 1		.01				.14
	Age		.10	1.48	.01	.62
Step 2		.05				.00**
	Age		-.12	-1.21	.01	.23
	Pack-Years Smoking		.30	3.34	.05	.00**

Note. N = 228. ΔR^2= change in R^2; *β* = standardized beta weights; sr^2 = squared semi-partial correlations;
*p < .05, ** p < .01, *** p < .001

Table 4

Hierarchical Regression Model with Past 180-Day Pain Frequency Entered as the Criterion Variable

		ΔR^2	*β*	*t*	sr^2	*p*
Step 1		.01				.14
	Age		.10	1.53	.01	.13
Step 2		.02				.00**
	Age		-.04	-.47	.00	.64
	Pack-Years Smoking		.21	2.30	.02	.02*

Note. N = 228. ΔR^2= change in R^2; *β* = standardized beta weights; sr^2 = squared semi-partial correlations;
*p < .05, ** p < .01, *** p < .001

Table 5

Aim 2 Sample Sociodemographic and Smoking Characteristics

Participant Characteristics (*N* = 101)	*N*	%
Gender		
Female	41	40.6
Income		
<30K	81	80.2
30-50K	10	9.8
>50K	10	10.0
Education		
Did not graduate high school	26	25.7
High school or part college	59	58.4
Technical school/Associates	9	8.9
Four-year college or more	7	7.0
Marital Status		
Single	65	64.4
Married	13	12.9
Divorced/Other	23	22.7
Ethnicity		
Hispanic/Latino	5	5
Not Hispanic/Latino	96	95
Race		
Caucasian	51	50.5
Black/African American	47	46.5
Other	3	3.0
	M	*SD*
Age	42.5	12.9
Pack-Years Smoking [1]	26.9	21.1
Average Cigarettes Per Day	20.5	10.3
Years of Regular Smoking	24.8	12.4
AUDIT Total [2]	6.0	6.7
Consumption	3.0	2.9
Dependence	1.2	2.4
Problematic Use	1.9	2.8

Note. [1] Pack-Years = $\frac{cigarettes\ per\ day}{20} \times years\ smoking$; [2] Alcohol Use Disorders Identification Test.

Table 6

Bivariate Pearson Correlations Between Primary Variables of Interest

Variable	*r*												
	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Pack-Years Smoking	-	.13	-.12	.05	.20*	-.01	.75***	.10	.12	.09	-.13	-.16	.08
2. AUC Pain Intensity		-	.24*	.46***	.29**	.58***	-.11	-.03	-.05	.05	-.08	-.16	.13
3. Area of Flare			-	.02	-.17	.12	-.30**	.48***	-.03	-.13	.30**	-.04	-.13
4. Mechanical Hyperalgesia Area				-	.73***	.82***	-.06	-.14	-.09	.10	.18	-.27**	.14
5. von Frey Ring 8 (outermost)					-	.51***	.15	-.31**	-.04	.10	.14	-.11	.20*
6. von Frey Ring 1 (innermost)						-	-.21*	-.05	-.20*	.07	.21*	-.19	.13
7. Age							-	-.05	.10	.18	-.13	-.06	.07
8. Race								-	.11	-.20*	.18	-.05	-.13
9. Gender [1]									-	.02	-.03	.25*	.14
10. Time Since Last Cigarette										-	-.05	.09	.00
11. Room Temperature (°F)											-	-.08	-.18
12. AUDIT Consumption [2]												-	.39***
13. AUDIT Dependence													-

Note. $N = 101$. [1] Gender: 0 = female, 1 = male; [2] Alcohol Use Disorders Identification Test.
*$p < .05$, ** $p < .01$, *** $p < .001$

Table 7

Hierarchical Regressions of Experimental Pain Reactivity Outcomes on Pack-Years Smoking

	ΔR^2	β	*t*	sr^2	*p*
AUC Pain Intensity	.11	.51	3.47	.11	.00**
Area of Flare	.01	.11	0.88	.01	.38
Area of Mechanical Hyperalgesia	.04	.30	2.03	.04	.04*
von Frey Ring 1	.08	.43	2.98	.08	.00**
von Frey Ring 2	.07	.40	2.78	.07	.00**
von Frey Ring 3	.07	.40	2.77	.07	.00**
von Frey Ring 4	.06	.37	2.56	.06	.01*
von Frey Ring 5	.05	.34	2.33	.05	.02*
von Frey Ring 6	.02	.24	1.64	.02	.10
von Frey Ring 7	.04	.30	2.10	.04	.04*
von Frey Ring 8	.05	.33	2.35	.05	.02*

Note. N = 101. These data reflect only Step 3 of the individual hierarchical regressions of Aim 2 experimental pain reactivity outcomes on pack-years smoking. Thus, all analyses presented have been adjusted for age, race, time since last cigarette, and room temperature; ΔR^2= change in R^2; β = standardized beta weights; sr^2 = squared semi-partial correlations.

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

Table 8

Hierarchical Regression Model with Experimental Pain Intensity Entered as the Criterion Variable

		ΔR^2	β	t	sr^2	p
Step 1		.01				.52
	Age		-.11	-1.10	.01	.28
	Race		-.04	-0.38	.00	.71
Step 2		.01				.57
	Age		-.13	-1.28	.01	.21
	Race		-.01	-0.10	.00	.93
	Time Since Last Cig.		.07	0.63	.00	.53
	Room Temp (°F)		-.09	-0.86	.00	.39
Step 3		.11				.00**
	Age		-.52	-3.49	.11	.00**
	Race		-.08	0.80	.00	.42
	Time Since Last Cig.		.08	0.79	.00	.43
	Room Temp (°F)		-.06	-0.06	.00	.57
	Pack-Years		.51	3.47	.11	.00**

Note. N = 101. ΔR^2= change in R^2; β = standardized beta weights; sr^2 = squared semi-partial correlations.

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

Table 9

Hierarchical Regression Model with Area of Flare Entered as the Criterion Variable

		ΔR^2	β	t	sr^2	p
Step 1		.30				.00***
	Age		-.27	-3.23	.07	.00**
	Race		.46	-5.49	.21	.00***
Step 2		.04				.08
	Age		-.25	-2.97	.06	.00**
	Race		.43	5.04	.17	.00***
	Time Since Last Cig.		.01	0.15	.00	.88
	Room Temp (°F)		.19	2.29	.04	.02*
Step 3		.01				.38
	Age		-.34	-2.62	.05	.01*
	Race		.42	4.75	.16	.00***
	Time Since Last Cig.		.02	0.18	.00	.86
	Room Temp (°F)		.20	2.36	.04	.02*
	Pack-Years		.11	0.88	.01	.38

Note. N = 101. ΔR^2= change in R^2; β = standardized beta weights; sr^2 = squared semi-partial correlations.

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

Table 10

Hierarchical Regression Model with Area of Mechanical Hyperalgesia Entered as the Criterion Variable

		ΔR^2	*β*	*t*	sr^2	*p*
Step 1		.02				.32
	Age		-.07	-0.67	.00	.50
	Race		-.14	-1.40	.02	.16
Step 2		.05				.09
	Age		-.06	-0.58	.00	.57
	Race		-.16	-1.56	.02	.12
	Time Since Last Cig.		.09	0.86	.01	.39
	Room Temp (°F)		.21	2.07	.04	.04*
Step 3		.04				.04*
	Age		-.29	-1.85	.03	.06
	Race		-.20	-1.91	.04	.05
	Time Since Last Cig.		.10	0.94	.01	.35
	Room Temp (°F)		.23	2.28	.05	.03*
	Pack-Years		.30	2.03	.04	.04*

Note. $N = 101$. ΔR^2= change in R^2; *β* = standardized beta weights; sr^2 = squared semi-partial correlations.

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

Table 11

Results from the Last Steps of Exploratory Moderation Regressions

	Gender		AUDIT: Consumption Score		AUDIT: Dependence Score	
Criterion Variables	*b*	*t*	*b*	*t*	*b*	*t*
Spontaneous Pain Reporting (Aim 1; *N* = 228)						
Current Pain Severity	0.20	0.26	-0.03	-0.36	0.02	0.13
Past 180-Day Pain Frequency	-3.61	-0.20	-0.89	-0.30	-1.52	-0.41
Experimental Pain Reactivity (Aim 2; *N* = 101)						
AUC Pain Intensity	-2.17	-0.64	1.70	0.37	1.40	0.11
Area of Flare	1.19	1.27	0.03	0.23	0.32	1.30
Mechanical Hyperalgesia Area	0.19	0.09	0.21	0.78	-0.60	-0.79
Von Frey Ring 8 (Outermost)	-0.12	-0.57	0.00	-0.16	-0.09	-1.17
Von Frey Ring 1 (Innermost)	-0.05	-0.14	0.03	0.86	-0.01	-0.06

Note. [1] Alcohol Use Disorder Identification Test. No significant interaction effects were identified.

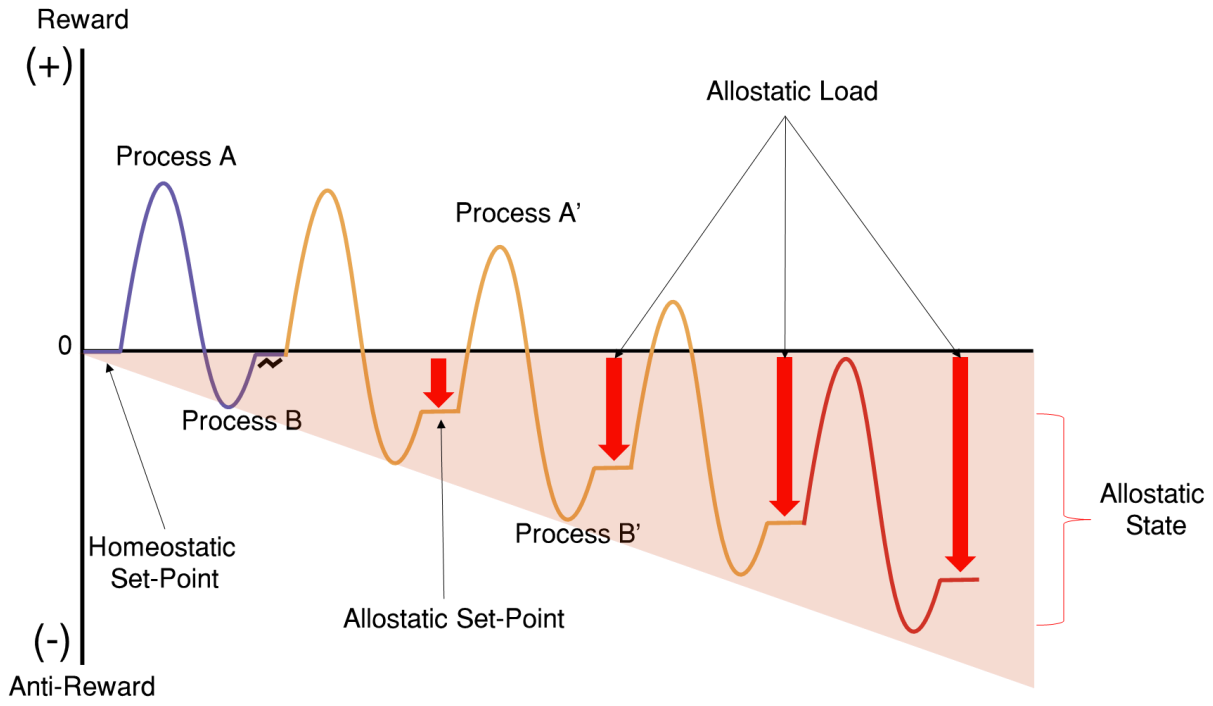

Figure 1. Illustration depicting the allostatic-load model of addiction proposed G. F. Koob and Le Moal (2001), an extension of the opponent-process model of motivation in addiction proposed by Solomon and Corbit (1974). Initial drug use produces hedonic effects (Process A); subsequent disuse leads to withdrawal-induced opponent effects (Process B), before returning to set-point at baseline. Chronic use/disuse cycles result in diminished hedonic effects (Process A') and amplified opponent effects (Process B') due to the suppression of the set-point by allostatic load. Eventually, chronic substance use leads to an enduring pathophysiological state. Allostatic load suppresses the set-point far below baseline, such that drug use serves to mitigate opponent effects instead of producing hedonic effects. This allostatic state reflects a chronic deviation of the homeostatic system from its normal function.

Baseline Session	Smoking Manipulation	Experimental Session	
Informed Consent CO Verification Baseline Measures Randomization	12-24 hour Extended Deprivation 2 hour Minimal Deprivation Continued Smoking	Capsaicin Pain Induction	Post-Application Measures

Figure 2. Experimental procedure in the parent study (Ditre et al., under review).

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