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Sex Differences in Negative Affect and Lapse Behavior During Acute Tobacco Abstinence: A Laboratory Study

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Abstract

Heightened negative affect during acute tobacco abstinence in women relative to men could be an important factor underlying sex differences in smoking motivation. However, little controlled experimental work addresses this hypothesis. The current study investigated sex differences in withdrawal-related negative affect, time to start smoking on a lab analogue smoking lapse task, and the interrelation between sex, withdrawal-related negative affect, and smoking lapse behavior. Following a baseline session, current smokers (women: $n = 68$, men: $n = 131$) attended two counterbalanced lab sessions (16 hours smoking abstinence and ad libitum smoking) during which they completed self-report measures of mood and withdrawal symptoms followed by a laboratory analogue smoking lapse task. In this task participants are monetarily rewarded for delaying smoking. Performance on this task serves as an analogue model of smoking lapse behavior by measuring smoker's capability to resist temptation to smoke under conditions where abstinence is advantageous. Females showed greater abstinence induced increases in composite negative affect as well as several particular negative affect states (i.e., POMS Anger, Anxiety, Depression, and Confusion, $ps < .05$) but no differences in abstinence induced changes in other forms of affect or craving. Females also exhibited marginally greater abstinence induced decreases in their willingness to delay smoking for money ($p = .10$), which was mediated by abstinence induced increases in anger ($p < .05$). These results suggest that differential sensitivity to abstinence induced negative affect, particularly anger, could underlie sex specific smoking patterns. Negative affect during tobacco abstinence may be an important factor for understanding and treating nicotine addiction in women.

Keywords

sex differences; negative affect; nicotine withdrawal; abstinence; smoking

Findings from several clinical trials suggest that females successfully quit smoking less often than males (Borrelli, Papandonatos, Spring, Hitsman, & Niaura, 2004; Borrelli, Spring, Niaura, Hitsman, & Papandonatos, 2001; Burgess et al., 2009; Cepeda-Benito, Reynoso, & Erath, 2004; Hyland et al., 2004; Japuntich et al., 2011; Wetter et al., 1999b). However, whether these effects are present at population level is not clear (Jarvis, Cohen, Delnevo, & Giovino, 2012). Regardless, it is important to study sex specific factors that underlie smoking behavior.

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Withdrawal severity during abstinence has been linked to increased risk of smoking lapse (al'Absi, Hatsukami, Davis, & Wittmers, 2004; Allen, Bade, Hatsukami, & Center, 2008; Nakajima & al'Absi, 2012; Patterson, Kerrin, Wileyto, & Lerman, 2008; Piper et al., 2011; Swan, Ward, & Jack, 1996), presumably because withdrawal may provoke negative reinforcement processes whereby individuals are motivated to resume smoking to offset aversive withdrawal effects. Hence, the severity and typology of withdrawal symptoms from smoking are an important potential contributing factor to sex differences in smoking behavior. Withdrawal symptoms that emerge during the first day of smoking abstinence are important to study because a significant number of individuals lapse on their planned quit date or avoid making a quit attempt altogether perhaps due to anticipation of withdrawal (Japuntich et al., 2011). In addition, acute abstinence effects are relevant to the withdrawal experiences of smokers not attempting to quit that may ultimately maintain daily smoking behavior (e.g., symptoms experienced before the first cigarette of the day).

Although numerous studies address the sex-withdrawal relationship, findings have been mixed. Some studies show that women experience greater tobacco withdrawal on some or all measures (al'Absi, Amunrud, & Wittmers, 2002; al'Absi et al., 2004; Field & Duka, 2004; Leventhal et al., 2007; Pergadia et al., 2010; Pomerleau, Tate, Lumley, & Pomerleau, 1994; Strong, Kahler, Ramsey, Abrantes, & Brown, 2004; Waters et al., 2004; Wetter et al., 1999a; Xu et al., 2008). Other studies, however, do not find an effect of sex on withdrawal (Evans, Blank, Sams, Weaver, & Eissenberg, 2006; Hughes, Gust, Skoog, Keenan, & Fenwick, 1991; Svikis, Hatsukami, Hughes, Carroll, & Pickens, 1986). Prior studies have employed a range of different study designs, sample sizes, and measures, which may explain some of the mixed evidence. Indeed, research that does not take into account baseline levels of withdrawal symptoms during nonabstinent states (Gunn, 1986), use retrospective designs (Pomerleau et al., 1994), or employ small sample sizes have limitations that might obscure sex differences in tobacco withdrawal.

To our knowledge, only one controlled laboratory study utilized sample sizes large enough to detect a moderate-sized sex difference in withdrawal has been published. This study found that females experienced greater abstinence induced increases on measures specific to subjective negative affect but no differences on other subjective symptoms, physiological measures nor cognitive performance (Leventhal et al., 2007). Because this study took an exploratory approach examining sex differences across a myriad of relevant subjective, cognitive and physiological outcomes, it is important to replicate sex differences in abstinence induced changes in negative affect using an a priori hypothesis. Leventhal et al., 2007 found suggestive evidence that abstinence induced changes in negative affect mediated sex differences on self-report retrospective measures of typical time to first cigarette of the day. Specifically, women (vs. men) experienced greater abstinence induced increases in negative affect, which in turn predicted smoking earlier in the day. This is an important finding because latency to first cigarette of the day: (a) is an important marker of nicotine dependence and ability to quit smoking (Baker et al., 2007); (b) may reflect diminished ability to resist the temptation to smoke as a result of motivation; and (c) could model the processes that occur when individuals lapse back to smoking on the first day of a quit attempt. Thus, it could suggest that withdrawal-related negative affect could mediate sex specific smoking patterns. However, retrospective self-reports of latency to first cigarette are vulnerable to recall errors and biases, which can limit the validity of such measures. Hence, it is necessary to extend these findings to an objective behavioral measure that is not susceptible to these errors and biases.

To address these gaps, we examined sex differences in overnight tobacco abstinence effects on subjective negative affect and an objective behavioral economic measure of lapse behavior based upon one's ability to delay smoking to earn a monetary reward. Given prior

results, we hypothesized that women would report greater abstinence provoked exacerbations in negative affect but not other subjective affect indices and exhibit greater abstinence induced increases in lapse behavior (i.e., diminished ability to delay smoking for money). We further hypothesized sex differences in abstinence induced lapse behavior would be mediated by greater abstinence induced increases in negative affect. The present study extends past research by (a) employing a sizable sample (male $n = 131$; female $n = 68$) within the context of a well-controlled counterbalanced within-participant experimentally induced tobacco abstinence design; (b) testing an a priori hypothesis focused on negative affect outcomes; and (c) including a controlled objective measure (i.e., a behavioral analogue smoking lapse task) that assesses relative reward value of initiating smoking when delaying smoking is monetarily reinforced (McKee, 2009). Delineating sex specific processes in lapse behavior could provide a guide for sex specific treatments through suggesting that minimizing particular negative affective withdrawal effects may be particularly important in treating nicotine addiction in women.

Method

Participants

Participants, 297 nontreatment seeking smokers, were recruited from the Los Angeles area via advertisements announcing the opportunity to take part in a study of individual differences in tobacco withdrawal effects. Inclusion criteria required participants to be 18 years of age or older, a regular smoker for at least the past 2 years (≥ 10 cigs/day), and fluent in English. Exclusion criteria included: (a) current *DSM-IV* non-nicotine substance dependence; (b) current *DSM-IV* mood disorder or psychotic symptoms; (c) breath carbon monoxide (CO) levels <10 ppm at intake to prevent admission of individuals overreporting their smoking in order to participate; (d) use of noncigarette forms of tobacco or nicotine products; (e) current use of psychiatric or psychoactive medications; (e) currently pregnant; and (f) planning to quit or substantially cut down their smoking in the next 30 days. Participants were compensated approximately \$200 for completing the study. Seventy-four participants were deemed ineligible, 22 participants dropped out prior to completing all study sessions, and two participants twice failed to meet abstinence criteria during abstinent session (see below). This left a final sample of 199 smokers (women = 68, male = 131). The 2:1 sex ratio is consistent with Los Angeles County estimates of smoking prevalence 19% to 10% males to females ("Cigarette Smoking in Los Angeles County: Local Data to Inform Tobacco Policy," 2010). Of our female participants, self-report assessments indicated that 34 were menstruating and not on hormonal birth control, eight females indicated birth control (three tubal ligations, two IUDs, three hormonal birth control), and 26 indicated no menstruation in the past year. The University of Southern California Internal Review Board approved the protocol.

Procedure

Following a preliminary telephone eligibility screening, participants attended a baseline session involving informed consent, breath CO analysis, psychiatric interview, and baseline questionnaire measures. Participants found eligible at the baseline session subsequently attended two counterbalanced experimental sessions starting at noon: abstinent (16 hours of smoking abstinence) and nonabstinent (ad libitum smoking). Experimental sessions were scheduled a minimum of 24 hours apart. Time between the experimental sessions ranged from 2–33 days ($mean = 11.5$ days, $SD = 6.4$). At the start of both sessions, participants completed a breath alcohol analysis and CO assessment. Participants with a positive breath alcohol analysis (i.e., BrAC > 0.00 g/dl) were rescheduled for a different day. Following published recommendations indicating a CO cutoff of 10 ppm or greater for recent smoking and prior laboratory tobacco withdrawal research (Leventhal, Waters, Moolchan, Heishman,

& Pickworth, 2010), participants with a CO reading > 9 ppm at their abstinent session were considered non-abstinent and scheduled for a second attempt to complete the abstinent session ($n = 11$). Participants failing to maintain abstinence at their second attempt were excluded from further participation ($n = 2$). To control for any abstinence that may have occurred prior to arriving for the nonabstinent session, participants smoked a cigarette of their preferred brand at the beginning of that session.

On the experimental days, participants arrived at the laboratory at noon. In the nonabstinent session only, participants started the session by smoking a cigarette followed by breath analysis for alcohol and CO levels (12:00–12:10). The abstinent session started with breath analysis for alcohol and CO levels (12:00–12:10). Following the breath analysis procedures, participants completed measures of nicotine withdrawal (Minnesota Withdrawal Scale, MNWS), affect (Profile of Mood States, POMS), and craving (The Brief Questionnaire of Smoking Urges, QSU; 12:10–12:30), and computer cognitive tasks assessing attention to smoking stimuli (12:30–13:00). Following the self-report measures and cognitive tasks, participants underwent a smoking lapse analogue task (described below) consisting of the delay period (13:00–13:50), self-administration period (13:50–14:50), and rest period (ending 2 h and 50 minutes after the start of the delay period).

Baseline Session Measures

The Structured Clinical Interview for *DSM-IV* Non-Patient Edition (First, Spitzer, Gibbon, & Williams, 2002) was used to assess mood disorders, psychosis, and substance use disorder for eligibility purposes. The Center for Epidemiologic Studies Depression Scale (CES-D; Shafer, 2006) assessed baseline depressive symptomatology. An author constructed questionnaire assessed demographic, including height and weight, which were used to compute body mass index (BMI), and smoking characteristics (e.g., cigs/day, age of smoking onset, etc.). The Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) was administered as a measure of nicotine dependence severity.

Experimental Sessions Measures

The following questionnaires show sufficient sensitivity to tobacco abstinence effects and adequate psychometric properties (Hughes, 2007; Leventhal, 2010) and were administered once at each experimental session.

The Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986)—The 11-item MNWS variant used in the study assesses withdrawal symptoms experienced “so far today” on 6-point Likert scales and yields a composite index based on mean response per item.

The Brief Questionnaire of Smoking Urges (QSU; Cox, Tiffany, & Christen, 2001)—The QSU measured smoking urges experienced “right now.” Items were rated on 6-point Likert scales and yields a composite index based on mean response per item.

The Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971)—The current study used a 72-item version of the POMS, which provided eight scales—five negative affect scales (Anger, Anxiety, Confusion, Depression, and Fatigue) and three positive affect scales (Elation, Friendliness, and Vigor). We also report composite scores for negative affect (NA, mean of all negative affect scales) and positive affect (PA, mean of all positive affect scores). Participants rated affect adjectives on a 5-point Likert scale based on how they were feeling “right now” and each subscale is computed based on mean response per item.

Laboratory Analogue Smoking Lapse Task—Responses on this task appear to be modulated by tobacco abstinence (Leeman, O'Malley, White, & McKee, 2010). During this task, participants received a tray containing eight cigarettes, a lighter, and an ashtray. At the outset of the delay period, participants were instructed they could commence smoking at any point over the next 50 minutes, but they would earn \$0.20 for each 5 minutes they delay smoking (monetary value based on prior piloting among smokers from the same population). Thus, participants could earn a maximum of \$2 for delaying smoking. The delay period ended when the participant indicated they wanted to smoke or at the end of 50 minutes for participants choosing not to smoke. Following the delay period, participants began the self-administration period. During this period, participants could smoke as much or little as they wanted for 60 minutes. They were instructed they would not have another opportunity to smoke again until 16:00. Participants were told they had a \$1.60 credit and for each cigarette lit would cost \$0.20. Following the self-administration period, participants started the rest period until 16:00 during which they were not allowed to smoke. To avoid disrupting natural smoking processes or draw attention to craving, we did not collect self-report measures throughout the delay and self-administration periods.

Data Analysis

Preliminary analysis involved reporting sample descriptive statistics by sex and carrying out single-sample *t* tests for each abstinence induced change score in the overall sample to examine whether abstinence effects depart from zero. For the primary analysis, linear regression models tested associations between sex and abstinence induced changes in outcome indexes. In each regression model, the corresponding nonabstinent outcome measure was included as predictor to control for nonabstinent ratings. Because nicotine dependence (FTND) contributes to withdrawal symptom expression and may vary by sex, we also controlled for this variable in regression models. To control for multiple comparisons for the effects of sex on regressions predicting abstinence induced changes, we report corrected significance values using a Bonferroni-Holm correction in addition to uncorrected significance levels. We also reported the main effect of abstinence scores on each outcome stratified by sex to further describe any sex differences in abstinence induced change scores. Sex differences in abstinence induced change scores reaching at least a trend level ($p < .10$) for particular subjective measures and delay on the relapse analogue task were examined for mediational analyses to explore whether the effects of sex on abstinence induced changes in delay were mediated by abstinence induced changes in subjective withdrawal symptoms. Mediational paths were analyzed by computing the product of the coefficients from two regression models: (a) one examining relation between the predictor (sex) and the mediator (abstinence induced changes in subjective withdrawal symptoms) controlling for FTND and nonabstinent scores; and (b) one examining the relation between the mediator (abstinence induced changes in subjective withdrawal symptoms) and the outcome (abstinence induced changes in delay on the lapse analogue task). The product of the coefficients served as the indicator of the strength of the indirect effect, for which significance was determined using the PRODCLIN approach involving estimating asymmetric confidence intervals (CIs) around the mediational effect (MacKinnon, Fritz, Williams, & Lockwood, 2007).

The primary analyses focused on our hypothesized outcomes indicative of negative affect (POMS Anger, Anxiety, Confusion, Depression, Fatigue, and NA Composite) and lapse behavior (minutes of delay on the laboratory analogue smoking lapse task). We also explored sex effects on the individual POMS negative affect scales of Anger, Anxiety, Confusion, Depression, Fatigue, and NA Composite. Secondary analyses examined additional outcomes of interest, including composite withdrawal symptom (MNWS),

positive affect (POMS Elation, Friendliness, Vigor, and PA Composite), and craving (QSU) to examine the specificity of effect to negative affect.

Results

Preliminary Analyses

There were no significant sex differences in sociodemographic and smoking characteristics or depression levels of the sample (see Table 1). In terms of the primary outcomes, within the full sample abstinence significantly increased the POMS NA Composite and four negative affect scales (i.e., POMS Anger, Anxiety, Depression, and Confusion; $ps < .05$), but there was no significant effect on fatigue ($p = .77$). Additionally, abstinence decreased amount of time participants were willing to delay smoking for money on the smoking lapse task and number of cigarettes smoked ($p < .0001$). Examination of secondary outcomes illustrated significant abstinence effects in composite withdrawal symptoms (MNWS; $p < .0001$), positive affect (POMS Friendliness, Elation, Vigor, and PA Composite; $ps < .0001$), and craving (QSU; $p < .0001$).

Primary Analyses

After controlling for nonabstinent scores and nicotine dependence severity, females reported more severe abstinence induced increases on four negative affect scales (i.e., POMS Anger, Anxiety, Depression, and Confusion) and the NA Composite ($ps < .05$; Table 2). There were no sex differences in fatigue. Additionally, females exhibited marginally greater abstinence induced decreases in their willingness to delay smoking for money on the lapse analogue task ($p = .10$), but there were no sex differences in abstinence induced change in total amount of cigarettes smoked ($p > .05$, Table 2). After applying a Bonferroni-Holm correction for multiple corrections, sex differences in abstinence induced changes in Anxiety and NA Composite scores remained significant.

Subjective withdrawal symptoms showing at least a marginally significant effect of sex were tested in mediational analyses (see Table 3). Results showed that Anger, β [95% CI] = .032 [.003–.075], demonstrated a significant mediational effect. Here, women reported greater abstinence induced increases in anger than men, which in turn predicted greater abstinence induced reductions in willingness to delay initiating smoking. Other subjective withdrawal symptoms did not significantly mediate sex differences in delay (see Table 3).

Secondary Analyses

There was a nonsignificant trend for sex differences in abstinence induced changes in composite withdrawal symptoms (MNWS; $p = .06$; Table 2), with women showing more severe increases in withdrawal. There were no sex differences in abstinence induced changes in positive affect or craving (QSU, POMS Friendliness, Elation, Vigor, or Positive Affect Composite, $p > .05$; Table 2).

Discussion

In line with our hypothesis, women compared with men experienced greater abstinence-provoked exacerbation in several negative affect states (Anger, Anxiety, Depression, and Confusion), and composite NA. After applying a correction for type-I error, sex differences in abstinence induced changes in Composite NA and Anxiety remained significant, suggesting that the other effects should be treated with caution. We did not find sex differences in one negative affect state (i.e., Fatigue), however, a prior study found no sex differences in abstinence effects on a similar measure tapping drowsiness (Leventhal et al., 2007), suggesting the sex differences in abstinence effects may be restricted to other

negative affective states. Secondary analyses showed specificity in the withdrawal profile exhibited by women, as sex did not modulate sensitivity to abstinence effects on positive affect nor on smoking urges. Though there was suggestive evidence that women reported greater abstinence induced increases on a composite measure of withdrawal symptoms, this may be driven by the negative affect symptoms amalgamated into this index.

In this study, we used a behavioral economic task (McKee, 2009) to objectively measure whether sex differences in abstinence induced increases in negative affect ultimately influences smoking lapse-like behavior. The use of this task as a proximal outcome modeling lapse behavior could clarify the role of negative affect influence on early relapse risk in women. There was suggestive evidence at the trend level that women exhibited more abstinence induced lapse-like behavior on this task (i.e., less able to delay smoking for monetary reward), a relation mediated by higher abstinence induced increases in anger. However, we found that sex did not moderate the effect of abstinence on willingness to purchase cigarettes during the self-administration period. These findings suggest that women may be more sensitive than men to abstinence effects on the motivation to initiate smoking but perhaps not so for the motivation to continue after being given the opportunity to smoke. These results may be relevant to understanding sex differences in risk of initial lapse versus lapse-to-relapse processes in women during smoking cessation (Japuntich, Piper, Leventhal, Bolt, & Baker, 2011).

Overall, these results are consistent with previous work suggesting that females report greater increases in negative affect resulting from tobacco abstinence (Leventhal et al., 2007; Pergadia et al., 2010; Xu et al., 2008), are more likely to resume smoking to relieve distress from withdrawal (Gunn, 1986), and smoke more (Perkins, Giedgowd, Karelitz, Conklin, & Lerman, 2012) and sooner (Weinberger & McKee, 2012) following an experimental negative mood induction. The fact that anger in particular mediated this effect is interesting as a previous report showed smokers reporting larger increases in anger following a quit attempt were more likely to relapse (Allen, Allen, Lunos, & Pomerleau, 2010; Patterson et al., 2008; Rose & Behm, 2013). Thus, sex differences in abstinence induced negative affect, particularly increases in anger, could underlie sex differences in ability to maintain abstinence during cessation attempts by altering the relative value of reinitiating smoking versus continuing to abstain from smoking. Perhaps the incorporation of behavioral interventions aimed toward anger management and reduction—an approach that is currently being applied to treat other addictions (for example, alcohol dependence; Walitzer, Deffenbacher, Slawiak, & Stasiewicz, 2011)—may perhaps augment smoking cessation success in women.

Collectively, these findings could be of clinical relevance because evidence suggesting that: (a) individuals experiencing larger increases in negative affect during abstinence in a cessation attempt are less likely to successfully to maintain abstinence (Allen et al., 2010; Piper et al., 2011); and (b) women lapse sooner during a quit attempt than men (Japuntich et al., 2011). Hence, women may be more likely to maintain smoking behavior following brief periods of abstinence (e.g., overnight, temporary restrictions due to work) or lapse earlier during a quit attempt in order to suppress withdrawal distress.

The results of this study need to be interpreted within the context of its limitations. For one this study did not control for menstrual cycle in premenopausal women. Although we collected data on birth control status and last menstrual cycle, we did not collect data about regularity of menstrual cycle; thus, we are unable to even retrospectively control for this factor. Currently, the literature regarding menstrual cycle effects on withdrawal remains mixed with some studies suggesting greater withdrawal in the luteal versus the follicular phase of the menstrual cycle (Allen, Hatsukami, Christianson, & Brown, 2000; Perkins et

al., 2000), but not all studies find an effect of menstrual phase on withdrawal symptoms (Masson & Gilbert, 1999). If menstrual cycle does contribute to the effect of withdrawal or craving, controlling for these factors could further delineate the true effect of sex differences in withdrawal and could contribute to menstrual cycle effects of cessation success (Allen et al., 2010; Franklin & Allen, 2009; Franklin et al., 2008), which we could not do in this study.

In this study, we did not collect self-report measures throughout the delay and self-administration periods. Although this approach avoided disrupting natural smoking processes or draw attention to craving, it limited our ability to provide information about potential sex differences in the decisions to smoke and continue to smoke. Given previous reports suggesting that self-reports collected during the end of the delay period are predictive of smoking lapse in this task (McKee, 2009), collection of this data could provide more predictive validity for the measures and decision to smoke. Furthermore, measures taken during the self-administration period could provide information regarding sex differences in the alleviation of withdrawal.

Additionally, the magnitude of effects should be taken into consideration. The direct effect of abstinence on a number of scales (i.e., QSU, MNWS, POMS Anxiety, Elation, Friendliness, Vigor, and time delay for smoking) showed Cohen's *d* effect size estimates suggestive of a medium to large effect of abstinence, which is consistent with prior literature quantifying the effect sizes of tobacco abstinence (Leventhal et al., 2010). Sex differences on these scales were in the small to medium range, which is also consistent with prior work on this topic (Leventhal et al., 2007). Given that negative affect mediated lapse behavior in this study coupled with extant literature suggesting the importance of negative affect (Perkins et al., 2012; Weinberger & McKee, 2012) and anger (Allen et al., 2010; Patterson et al., 2008; Rose & Behm, 2013) in smoking behavior and relapse risk, it is likely that the effects demonstrated in this study although small may be likely to impact smoking behavior and thus could be clinically relevant.

Another limitation of the study is that the participants in this study were nontreatment seeking. Whether or not the findings would translate to those attempting to quit is unclear. However, extant research has found that tobacco withdrawal severity during experimentally induced abstinence predicts withdrawal in a subsequent naturalistic self-initiated quit attempt (Strong et al., 2011) suggesting that findings from research employing this design may perhaps generalize outside the laboratory. An additional limitation is the number of tests performed. Although this increases the chances of Type I error, the fact that we saw a consistent pattern specific to negative affect outcomes and effects of sex on abstinence induced changes in negative affect composite scores and anxiety persisted after a type-I error correct for multiple tests makes it unlikely that the results were merely a false positive. Similarly, some of the results occurred only at the trend level and should be interpreted with caution.

In summary, women appear to experience more severe exacerbations in negative affect during tobacco abstinence, which may in turn impact motivation to resume smoking. Extending these findings to clinical settings would be of value to explore their relevance to smoking cessation interventions. Further exploring the mechanisms underlying the sex-withdrawal association (e.g., neuroendocrine interactions with nicotine, beliefs regarding the effects of tobacco abstinence, loss of the sensorimotor ritual of smoking) could prove valuable for advancing both models of addiction etiology and addiction treatment tailored by sex.

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References

- al' Absi M, Amunrud T, Wittmers LE. Psychophysiological effects of nicotine abstinence and behavioral challenges in habitual smokers. *Pharmacology, Biochemistry and Behavior*. 2002; 72:707–716.10.1016/S0091-3057(02)00739-6
- al' Absi M, Hatsukami D, Davis GL, Wittmers LE. Prospective examination of effects of smoking abstinence on cortisol and withdrawal symptoms as predictors of early smoking relapse. *Drug and Alcohol Dependence*. 2004; 73:267–278.10.1016/j.drugalcdep.2003.10.014 [PubMed: 15036549]
- Allen AM, Allen SS, Lunos S, Pomerleau CS. Severity of withdrawal symptomatology in follicular versus luteal quitters: The combined effects of menstrual phase and withdrawal on smoking cessation outcome. *Addictive Behaviors*. 2010; 35:549–552. S0306-4603(10)00022-5[pii]. 10.1016/j.addbeh.2010.01.003 [PubMed: 20167436]
- Allen SS, Bade T, Hatsukami D, Center B. Craving, withdrawal, and smoking urges on days immediately prior to smoking relapse. *Nicotine & Tobacco Research*. 2008; 10:35–45. 789473953[pii]. 10.1080/14622200701705076 [PubMed: 18188743]
- Allen SS, Hatsukami D, Christianson D, Brown S. Effects of transdermal nicotine on craving, withdrawal and premenstrual symptomatology in short-term smoking abstinence during different phases of the menstrual cycle. *Nicotine & Tobacco Research*. 2000; 2:231–241.10.1080/14622200050147493 [PubMed: 11082823]
- Baker TB, Piper ME, McCarthy DE, Bolt DM, Smith SS, Kim SY. Time to first cigarette in the morning as an index of ability to quit smoking: Implications for nicotine dependence. *Nicotine & Tobacco Research*. 2007; 9:S555–S570. 788258006[pii]. 10.1080/14622200701673480 [PubMed: 18067032]
- Borrelli B, Papandonatos G, Spring B, Hitsman B, Niaura R. Experimenter-defined quit dates for smoking cessation: Adherence improves outcomes for women but not for men. *Addiction*. 2004; 99:378–385.10.1111/j.1360-0443.2004.00648.xADD648[pii] [PubMed: 14982551]
- Borrelli B, Spring B, Niaura R, Hitsman B, Papandonatos G. Influences of gender and weight gain on short-term relapse to smoking in a cessation trial. *Journal of Consulting and Clinical Psychology*. 2001; 69:511–515.10.1037/0022-006X.69.3.511 [PubMed: 11495180]
- Burgess DJ, Fu SS, Noorbaloochi S, Clothier BA, Ricards J, Widome R. Employment, gender, and smoking cessation outcomes in low-income smokers using nicotine replacement therapy. *Nicotine & Tobacco Research*. 2009; 11:1439–1447. ntp158[pii]. 10.1093/ntr/ntp158 [PubMed: 19875765]
- Cepeda-Benito A, Reynoso JT, Erath S. Meta-analysis of the efficacy of nicotine replacement therapy for smoking cessation: Differences between men and women. *Journal of Consulting and Clinical Psychology*. 2004; 72:712–722. [PubMed: 15301656]
- Cigarette Smoking in Los Angeles County: Local Data to Inform Tobacco Policy. Los Angeles: Los Angeles County Department of Public Health, Office of Health Assessment and Epidemiology; 2010.
- Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine & Tobacco Research*. 2001; 3:7–16.10.1080/14622200020032051 [PubMed: 11260806]
- Evans SE, Blank M, Sams C, Weaver MF, Eissenberg T. Transdermal nicotine-induced tobacco abstinence symptom suppression: Nicotine dose and smokers' gender. *Experimental and Clinical Psychopharmacology*. 2006; 14:121–135. 2006-07129-003[pii]. 10.1037/1064-1297.14.2.121 [PubMed: 16756416]
- Field M, Duka T. Cue reactivity in smokers: The effects of perceived cigarette availability and gender. *Pharmacology, Biochemistry and Behavior*. 2004; 78:647–652.10.1016/j.pbb.2004.03.026

- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM–IV–TR Axis I Disorders, Research Version, Non-Patient Edition. (SCID-I/NP). New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
- Franklin TR, Allen SS. Influence of menstrual cycle phase on smoking cessation treatment outcome: A hypothesis regarding the discordant findings in the literature. *Addiction*. 2009; 104:1941–1942. ADD2758[pii]. 10.1111/j.1360-0443.2009.02758.x [PubMed: 19832791]
- Franklin TR, Ehrman R, Lynch KG, Harper D, Sciortino N, O'Brien CP. Menstrual cycle phase at quit date predicts smoking status in an NRT treatment trial: A retrospective analysis. *Journal of Women's Health*. 2008; 17:287–292.10.1089/jwh.2007.0423
- Gunn RC. Reactions to withdrawal symptoms and success in smoking cessation clinics. *Addictive Behaviors*. 1986; 11:49–53. 0306-4603(86)90008-0[pii]. [PubMed: 3716916]
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction*. 1991; 86:1119–1127.10.1111/j.1360-0443.1991.tb01879.x [PubMed: 1932883]
- Hughes JR. Effects of abstinence from tobacco: Valid symptoms and time course. *Nicotine & Tobacco Research*. 2007; 9:315–327. 772841444[pii]. 10.1080/14622200701188919 [PubMed: 17365764]
- Hughes JR, Gust SW, Skoog K, Keenan RM, Fenwick JW. Symptoms of tobacco withdrawal. A replication and extension. *Archives of General Psychiatry*. 1991; 48:52–59.10.1001/archpsyc.1991.01810250054007 [PubMed: 1984762]
- Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry*. 1986; 43:289–294.10.1001/archpsyc.1986.01800030107013 [PubMed: 3954551]
- Hyland A, Li Q, Bauer JE, Giovino GA, Steger C, Cummings KM. Predictors of cessation in a cohort of current and former smokers followed over 13 years. *Nicotine & Tobacco Research*. 2004; 6:S363–S369.10.1080/14622200412331320761 [PubMed: 15799599]
- Japuntich SJ, Leventhal AM, Piper ME, Bolt DM, Roberts LJ, Fiore MC. Smoker characteristics and smoking-cessation milestones. *American Journal of Preventive Medicine*. 2011; 40:286–294. S0749-3797(10)00714-2[pii]. 10.1016/j.amepre.2010.11.016 [PubMed: 21335259]
- Japuntich SJ, Piper ME, Leventhal AM, Bolt DM, Baker TB. The effect of five smoking cessation pharmacotherapies on smoking cessation milestones. *Journal of Consulting and Clinical Psychology*. 2011; 79:34–42. 2011-01388-004[pii]. 10.1037/a0022154 [PubMed: 21261432]
- Jarvis MJ, Cohen JE, Delnevo CD, Giovino GA. Dispelling myths about gender differences in smoking cessation: Population data from the USA, Canada and Britain. *Tobacco Control*. 2012 tobaccocontrol-2011-050279[pii]. 10.1136/tobaccocontrol-2011-050279
- Leeman RF, O'Malley SS, White MA, McKee SA. Nicotine and food deprivation decrease the ability to resist smoking. *Psychopharmacology*. 2010; 212:25–32.10.1007/s00213-010-1902-z [PubMed: 20585761]
- Leventhal AM. Do individual differences in reinforcement smoking moderate the relationship between affect and urge to smoke? *Behavioral Medicine*. 2010; 36(1):1–6. 682222426118J450[pii]. 10.1080/08964280903521347 [PubMed: 20185395]
- Leventhal AM, Waters AJ, Boyd S, Moolchan ET, Lerman C, Pickworth WB. Gender differences in acute tobacco withdrawal: Effects on subjective, cognitive, and physiological measures. *Experimental and Clinical Psychopharmacology*. 2007; 15:21–36. 2007-01684-002[pii]. 10.1037/1064-1297.15.1.21 [PubMed: 17295582]
- Leventhal AM, Waters AJ, Moolchan ET, Heishman SJ, Pickworth WB. A quantitative analysis of subjective, cognitive, and physiological manifestations of the acute tobacco abstinence syndrome. *Addictive Behaviors*. 2010; 35:1120–1130. S0306-4603(10)00243-1[pii]. 10.1016/j.addbeh.2010.08.007 [PubMed: 20807673]
- MacKinnon DP, Fritz MS, Williams J, Lockwood CM. Distribution of the product confidence limits for the indirect effect: Program PRODCLIN. *Behavior Research Methods*. 2007; 39:384–389.10.3758/BF03193007 [PubMed: 17958149]
- Masson CL, Gilbert DG. Cardiovascular and mood responses to quantified doses of cigarette smoke in oral contraceptive users and nonusers. *Journal of Behavioral Medicine*. 1999; 22:589–604.10.1023/A:1018793729594 [PubMed: 10650538]

- McKee SA. Developing human laboratory models of smoking lapse behavior for medication screening. *Addiction Biology*. 2009; 14:99–107.10.1111/j.1369-1600.2008.00135.x [PubMed: 18855800]
- McNair, D.; Lorr, M.; Droppleman, DL. Profile of mood states. San Diego, CA: EdITS; 1971.
- Nakajima M, al'Absi M. Predictors of risk for smoking relapse in men and women: A prospective examination. *Psychology of Addictive Behaviors*. 2012; 26:633–637. 2012-04369-001[pii]. 10.1037/a0027280 [PubMed: 22352701]
- Patterson F, Kerrin K, Wileyto EP, Lerman C. Increase in anger symptoms after smoking cessation predicts relapse. *Drug and Alcohol Dependence*. 2008; 95:173–176. S0376-8716(08)00052-5[pii]. 10.1016/j.drugalcdep.2008.01.013 [PubMed: 18328642]
- Pergadia ML, Agrawal A, Heath AC, Martin NG, Bucholz KK, Madden PA. Nicotine withdrawal symptoms in adolescent and adult twins. *Twin Research and Human Genetics*. 2010; 13:359–369.10.1375/twin.13.4.35910.1375/twin.13.4.359[pii] [PubMed: 20707706]
- Perkins KA, Giedgowd GE, Karelitz JL, Conklin CA, Lerman C. Smoking in response to negative mood in men versus women as a function of distress tolerance. *Nicotine & Tobacco Research*. 2012 nts075[pii]. 10.1093/ntr/nts075
- Perkins KA, Levine M, Marcus M, Shiffman S, D'Amico D, Miller A. Tobacco withdrawal in women and menstrual cycle phase. *Journal of Consulting and Clinical Psychology*. 2000; 68:176–180.10.1037/0022-006X.68.1.176 [PubMed: 10710853]
- Piper ME, Schlam TR, Cook JW, Sheffer MA, Smith SS, Loh WY. Tobacco withdrawal components and their relations with cessation success. *Psychopharmacology*. 2011; 216:569–578.10.1007/s00213-011-2250-3 [PubMed: 21416234]
- Pomerleau CS, Tate JC, Lumley MA, Pomerleau OF. Gender differences in prospectively versus retrospectively assessed smoking withdrawal symptoms. *Journal of Substance Abuse*. 1994; 6:433–440.10.1016/S0899-3289(94)90376-X [PubMed: 7780301]
- Rose, JE.; Behm, FM. Combination varenicline/bupropion treatment benefits male NRT-nonresponders. Paper presented at the Society for Nicotine and Tobacco Research; Boston, MA. 2013.
- Shafer AB. Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung. *Journal of Clinical Psychology*. 2006; 62:123–146.10.1002/jclp.20213 [PubMed: 16287149]
- Strong DR, Kahler CW, Ramsey SE, Abrantes A, Brown RA. Nicotine withdrawal among adolescents with acute psychopathology: An item response analysis. *Nicotine & Tobacco Research*. 2004; 6:547–557.10.1080/14622200410001696484 [PubMed: 15203788]
- Strong DR, Leventhal AM, Evatt DP, Haber S, Greenberg BD, Abrams D. Positive reactions to tobacco predict relapse after cessation. *Journal of Abnormal Psychology*. 2011; 120:999–1005. 2011-10192-001[pii]. 10.1037/a0023666 [PubMed: 21574668]
- Svikis DS, Hatsukami DK, Hughes JR, Carroll KM, Pickens RW. Sex differences in tobacco withdrawal syndrome. *Addictive Behaviors*. 1986; 11:459–462.10.1016/0306-4603(86)90028-6 [PubMed: 3544698]
- Swan GE, Ward MM, Jack LM. Abstinence effects as predictors of 28-day relapse in smokers. *Addictive Behaviors*. 1996; 21:481–490. 0306-4603(95)00070-4[pii]. [PubMed: 8830906]
- Walitzer, K.; Deffenbacher, J.; Slawiak, L.; Stasiewicz, P. Developing anger management treatment for alcoholic outpatients. Paper presented at the International Conference on Violence, Abuse, and Trauma; San Diego, CA. 2011.
- Waters AJ, Shiffman S, Sayette MA, Paty JA, Gwaltney CJ, Balabanis MH. Cue-provoked craving and nicotine replacement therapy in smoking cessation. *Journal of Consulting and Clinical Psychology*. 2004; 72:1136–1143.10.1037/0022-006X.72.6.1136 [PubMed: 15612859]
- Weinberger AH, McKee SA. Gender differences in smoking following an implicit mood induction. *Nicotine & Tobacco Research*. 2012; 14:621–625. ntr198[pii]. 10.1093/ntr/ntr198 [PubMed: 21908458]
- Wetter DW, Fiore MC, Young TB, McClure JB, de Moor CA, Baker TB. Gender differences in response to nicotine replacement therapy: Objective and subjective indexes of tobacco withdrawal.

Experimental and Clinical Psychopharmacology. 1999a; 7:135–144.10.1037/1064-1297.7.2.135 [PubMed: 10340153]

Wetter DW, Kenford SL, Smith SS, Fiore MC, Jorenby DE, Baker TB. Gender differences in smoking cessation. Journal of Consulting and Clinical Psychology. 1999b; 67:555–562.10.1037/0022-006X.67.4.555 [PubMed: 10450626]

Xu J, Azizian A, Monterosso J, Domier CP, Brody AL, Fong TW. Gender effects on mood and cigarette craving during early abstinence and resumption of smoking. Nicotine & Tobacco Research. 2008; 10:1653–1661. 905082643[pil]. 10.1080/14622200802412929 [PubMed: 18988078]

Table 1

Baseline Sample Characteristics

	Full sample (<i>N</i> = 199) <i>M</i> (<i>SD</i>) or %	Women (<i>N</i> = 68) <i>M</i> (<i>SD</i>) or %	Men (<i>N</i> = 131) <i>M</i> (<i>SD</i>) or %	<i>t</i> or χ^2
Age	43.4 (10.2)	43.5 (9.9)	43.3 (10.4)	n.s.
Race				n.s.
Black	53.5	51.6	54.4	
White	38.0	37.1	38.4	
Other	8.5	11.3	7.2	
Hispanic	15.7	20.6	10.8	n.s.
Cigarettes/day	16.7 (6.5)	16.4 (6.5)	16.9 (6.6)	n.s.
FTND, range 0–9	5.3 (1.9)	5.2 (1.7)	5.3 (10.4)	n.s.
Age onset regular smoking	19.24 (5.30)	20.06 (5.92)	18.80 (4.89)	n.s.
BMI	27.54 (5.42)	28.70 (5.97)	26.95 (5.04)	2.10*
Education				n.s.
Less than high school	11.6	14.7	10.0	
High school diploma or GED	29.3	27.9	30.0	
Some college	42.4	38.2	44.6	
College degree or higher	16.7	19.1	15.4	
CES-D, range 0–60	9.99 (8.09)	9.96 (8.62)	10.01 (7.83)	n.s.

Note. Men and women did not significantly differ in age, race (Black vs. non-Black), rates of Hispanic, cigarettes/day, nicotine dependence age started smoking regularly, education level, or baseline depressive symptomatology. Males and females had significantly different body mass indexes (BMIs, * $p < .05$). FTND = Fagerström Test of Nicotine Dependence; GED = general educational development test; CES-D = The Center for Epidemiologic Studies Depression Scale.

Table 2

Sex Differences in Acute Tobacco Abstinence Effects

Measure	Women (N = 68)				Men (N = 131)				Sex effect ^a β
	Nonabstinent		Abstinent		Nonabstinent		Abstinent		
	M (SD)	M (SD)	M (SD)	d ^b	M (SD)	M (SD)	M (SD)	d ^b	
QSU	1.06 (1.16)	3.42 (1.20)	2.36 (1.39)	1.70****	0.93 (1.10)	3.29 (1.04)	2.36 (1.19)	1.98****	-.04
MNWS	1.25 (1.18)	2.17 (1.23)	0.92 (1.29)	0.71****	0.99 (0.93)	1.80 (1.04)	0.81 (0.93)	0.87****	-.11 [†]
POMS									
Anger	0.51 (0.84)	0.94 (1.04)	0.43 (0.91)	0.47****	0.37 (0.58)	0.58 (0.69)	0.21 (0.65)	0.32****	-.18***
Anxiety	0.85 (0.89)	1.50 (1.18)	0.66 (1.09)	0.61****	0.69 (0.71)	1.05 (0.81)	0.36 (0.77)	0.47****	-.20***
Confusion	0.87 (0.76)	1.14 (0.93)	0.27 (0.93)	0.29*	0.77 (0.67)	0.87 (0.71)	0.10 (0.68)	0.15 [†]	-.14*
Depression	0.46 (0.68)	0.67 (0.86)	0.21 (0.71)	0.30*	0.43 (0.66)	0.46 (0.61)	0.03 (0.58)	0.05	-.15*
Fatigue	1.06 (1.09)	1.09 (1.10)	0.03 (0.90)	0.03	0.77 (0.84)	0.78 (0.81)	0.01 (0.82)	0.01	3-.09
Elation	2.00 (0.90)	1.42 (0.94)	-0.59 (0.88)	0.67****	1.96 (0.86)	1.53 (0.78)	-0.43 (0.77)	0.56****	.08
Friendliness	2.73 (1.03)	2.22 (1.07)	-0.50 (0.84)	0.6****	2.73 (0.84)	2.19 (0.91)	-0.54 (0.76)	0.71****	-.01
Vigor	2.20 (1.09)	1.73 (1.05)	-0.46 (0.82)	0.56****	2.28 (0.94)	1.89 (0.93)	-0.39 (0.80)	0.49****	.06
NA composite	0.73 (0.75)	1.07 (0.93)	0.32 (0.79)	0.41***	0.61 (0.62)	0.75 (0.63)	0.14 (0.57)	0.25**	-.17***
PA composite	2.30 (0.93)	1.79 (0.95)	-0.52 (0.76)	0.68****	2.31 (0.84)	1.87 (0.81)	-0.44 (0.70)	0.63****	0.54
Smoking lapse									
Analogue task									
Time delay (min)	40.9 (16.5)	21.4 (22.5)	-19.5 (23.3)	0.84****	39.8 (17.4)	26.0 (23.1)	-13.8 (22.7)	0.61****	.11 [†]
Cigs smoked	1.25 (0.95)	1.60 (0.90)	.34 (1.09)	0.31*	1.24 (1.00)	1.51 (0.96)	.27 (0.96)	0.28***	-.03

Note. QSU = Questionnaire of Smoking Urges (range 0–5); MNWS = Minnesota Nicotine Withdrawal Scale (range 0–5); POMS = Profile of Mood States (range 0–5); NA = negative affect; PA = positive affect; Time Delay (range 0–50 minutes); Cigarettes smoked (range 0–8). Bold β values signify significance after correcting for multiple comparisons for the sex effect on abstinence induced changes.

^a Standardized coefficient for sex effect from regression models predicting abstinence induced changes controlling for nonabstinent scores and Fagerström Test of Nicotine Dependence (women coded 0, men coded 1).

^b Abstinence induced change score significantly departs from 0.

[†] $p < .10$.

* $p < .05$.
 ** $p < .01$.
 *** $p < .001$.
 **** $p < .0001$. (not corrected for multiple comparisons).

Table 3
Mediational Pathways of Sex → Abstinence-Induced Change in Withdrawal Symptoms → Willingness to Delay Smoking

Mediating variable	Sex → abstinence induced changes on mediator			Abstinence induced changes in mediator → abstinence induced changes in time to delay smoking			Indirect mediating effect		
	β^a	SE		β^b	SE		β	LL	UL
MNWS	-.11	.06		-.12	.07		.013	-.003	.040
POMS									
Anger	-.18	.07		-.18	.07		.032*	.003	.075
Anxiety	-.20	.07		-.10	.07		.02	-.007	.057
Confusion	-.14	.06		-.09	.07		.013	-.007	.040
Depression	-.15	.06		-.09	.07		.014	-.007	.042
NA composite	-.17	.07		-.14	.07		.024	-.001	.061

Note. MNWS = Minnesota Nicotine Withdrawal Scale; POMS = Profile of Mood States; NA = negative affect.

^a Standardized coefficient for sex effect from regression models predicting abstinence induced changes controlling for nonabstinent scores and Fagerström Test of Nicotine Dependence (women coded 0, men coded 1).

^b Standardized coefficient for abstinence induced changes in mediator from regression model predicting abstinence induced changes in willingness to delay smoking for money not controlling for any variables. The lower limit (LL) and upper limit (UL) make up the 95% confidence intervals around the mediational effect.

* $p < .05$.