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Early Life Adversity Influences Stress Response Association with Smoking Relapse

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Abstract

Rationale—We examined the hypothesis that stress-related blunting of cortisol in smokers is particularly pronounced in those with history of severe life adversity.

Objectives—The 2 aims of this study were first to examine hormonal, craving, and withdrawal symptoms during ad libitum smoking and after the first 24 hours of abstinence in smokers who experienced high or low levels of adversity. Secondly, we sought to examine the relationship between adversity and HPA hormones to predict relapse during the first month of a smoking cessation attempt.

Methods—Hormonal and self-report measures were collected from 103 smokers (49 women) during ad libitum smoking and after the first 24 hours of abstinence. Hypothalamic-pituitary-adrenal (HPA) hormones were measured during baseline rest and in response to acute stress in both conditions. All smokers were interested in smoking cessation, and we prospectively used stress response measures to predict relapse during the first four weeks of the smoking cessation attempt.

Results—The results showed that high adversity was associated with higher distress and smoking withdrawal symptoms. High level of early life adversity was associated with elevated HPA activity, which was found in both salivary and plasma cortisol. Enhanced adrenocorticotrophic hormone (ACTH) stress response was evident in high adversity but not in low adversity relapsers.

Conclusions—This study demonstrated that early life adversity is associated with stress-related HPA responses. The study also demonstrated that, among smokers who experienced a high level of life adversity, heightened ACTH and cortisol responses were linked with increased risk for smoking relapse.

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Conflict of Interest

The authors have no conflicts of interest to report.

Keywords

Life adversity; stress; HPA

Introduction

Exposure to adverse life experiences may contribute to increased negative affect (Kim et al. 2013; Young et al. 2007), which may, in turn, increase vulnerability to and risk for maintenance of addictive behaviors (Farris and Zvolensky 2016; Muscatello et al. 2016). Large epidemiological, cross-sectional, and, more recently, prospective studies have documented a link between early exposure to adversity and smoking (Bellis et al. 2014a; Edwards et al. 2007; Elliott et al. 2014; Ford et al. 2011; Fuller-Thomson et al. 2013; Xie et al. 2012). Research has consistently linked negative affect with intensity of smoking withdrawal and with challenges during smoking cessation (Kassel et al. 2007; Killen et al. 1996), leading to increased risk for early smoking relapse (al'Absi et al. 2007; Nakajima and al'Absi 2012). Stress-related negative emotions may also decrease an individual's ability to resist the urge to smoke (al'Absi et al. 2004) and increase the number and intensity of puffs taken while smoking a cigarette (McKee et al. 2011).

Multiple studies demonstrate that chronic smoking is associated with dysregulation in the HPA stress response (al'Absi et al. 2002; al'Absi et al. 2005; al'Absi et al. 2015; al'Absi et al. 2003; Nakajima and al'Absi 2012; Potretzke et al. 2014). Smokers demonstrate elevated resting cortisol relative to nonsmokers, but they fail to demonstrate a cortisol rise in response to acute smoking abstinence despite cognitive, psychological, and cardiovascular evidence that abstinence is a stressful experience (al'Absi et al. 2002). In more controlled laboratory stress manipulations, both abstinent smokers and smokers smoking at their customary rate (ad libitum) show a negative change in cortisol following public speaking stress while nonsmokers show a positive change (al'Absi et al. 2003). Smokers who demonstrate HPA non-response (no change or a decline in cortisol or ACTH rather than the expected increase in response to stress) relapse faster following cessation than those who show a normal response (al'Absi et al. 2005). Smoking abstinence is stressful for all smokers, but men and women differ in their experience. These differences in psychological correlates translate into different risk patterns based on sex whereby depressive affect and stress predict relapse for women, but craving tobacco predicts relapse for men (Nakajima and al'Absi 2012).

HPA dysregulation, in the form of hypersecretion of ACTH in response to exogenous corticotropin-releasing factor (CRF) and blunted adrenocortical stress response, has been noted in individuals with history of trauma and early life adversity (Heim et al. 2001; Sinha 2008). Stress-related blunting of cortisol in smokers may be particularly pronounced in those with history of severe adversity. To date, however, the relationship between adversity and stress-related mechanisms that mediate risk for smoking relapse has not been investigated. The aim of this study was to examine hormonal, craving, and withdrawal symptoms during ad libitum smoking and after the first 24 hours of abstinence in smokers (seeking cessation) who experienced high or low levels of adversity. HPA hormones were measured during rest and in response to acute stress under both conditions. The second aim was to examine the

relationship between adversity and ACTH and cortisol levels to predict relapse during the first month of a smoking cessation attempt. We hypothesized that the association between stress and relapse would vary as a function of early life adversity.

Methods

Participant recruitment and eligibility criteria

Participants were recruited via flyers and social media advertisements in Duluth and Minneapolis, Minnesota. To be eligible, smokers completed both a telephone-screening interview and an on-site medical examination supervised by a study physician. Potential participants had to smoke at least 10 cigarettes per day for the past 2 years, have a baseline carbon monoxide level of > 12 ppm, have stable mental health, and be medically fit. Any participant requiring maintenance of a chronic medical condition (hypertension, renal or liver disease, cardiac disease, endocrine or metabolic disease) or receiving current (past year) mental health treatment of any kind, including drug or alcohol treatment, was excluded by physician review of history. Drug and alcohol histories, including current use rates, were collected both via phone interview and in-person. Pregnancy was also an exclusion criterion. Detailed review of prescription and over-the-counter medications was conducted to rule-out any potential use of medications that could influence the HPA axis, including newly initiated psychiatric medications (stable maintenance prescriptions > 1 year with no change) and contraceptives were included). All participants expressed a strong desire to quit smoking (4 or higher on a 5-point scale). Social drinking (no more than 2 drinks per day) was allowed. All participants signed an informed consent approved by the University of Minnesota Institutional Review Board.

Procedure

General study flow—During the medical screening, participants completed measures of demographics, health, psychosocial tendencies, and smoking history. Following a successful screening interview, participants set a quit date and completed stress reactivity laboratory sessions before and 24 hours post-cessation. Before each laboratory session, participants were questioned regarding recent (past 72 hours) use of prescription or over-the-counter medications. Relapse status was monitored following cessation at 24 hours and at four weekly visits thereafter via smoking diaries, self-report, exhaled carbon monoxide (abstinence cutoff was 8 ppm), and saliva cotinine (at least 50% decline from baseline levels). Details of the stress labs, including Figure 1, can be found in the Supplementary Materials.

Measures

Psychological traits—Measures of adversity, mood, and psychological traits were assessed at baseline during medical screening. Participants completed the Adverse Childhood Experiences (ACE) questionnaire (Felitti et al. 1998; Ford et al. 2011). Participants indicated whether they had ever experienced psychological abuse, physical abuse, sexual abuse, neglect, substance abuse, mental illness in a household member, suicide attempt by a household member, incarceration of a household member, and whether they had ever witnessed their mother's domestic violence victimization. Baseline mood was

assessed using the Patient Health Questionnaire-9 (PHQ-9) for depressive affect (Kroenke et al. 2001) and the State-Trait Anxiety Inventory-Trait Scale (Spielberger et al. 1983). Scores on the PHQ-9 range from 0 to 27 with 0–4 indicating minimal symptoms, 5–9 mild, 10–14 moderate, and 15–19 moderate-severe depressive affect. The State-Trait Anxiety Inventory-Trait Scale (STAI-T) has a score range from 20 to 80.

Smoking variables—Self-report of craving and withdrawal were collected at baseline (medical screening) and at each lab session using the Minnesota Withdrawal Scale (MNWS: (Hughes and Hatsukami 1986)). The MNWS assesses psychological discomfort related to nicotine withdrawal (i.e., irritability, anger, anxiety, difficulty concentrating, restlessness, low mood, and hunger). An additional item related to craving was also administered (Toll et al. 2007). The brief Questionnaire of Smoking Urges (QSU-B: (Cox et al. 2001; Tiffany and Drobes 1991)) further quantified appetitive smoking urges and aversive smoking urges. Severity of nicotine dependence was assessed using the Fagerström Test of Nicotine Dependence (FTND: (Heatherton et al. 1991)). Positive and negative affect scales of the subjective state scale (al'Absi et al. 2005; al'Absi et al. 2004) included 5 and 4 items, respectively. Details of the score ranges on each are available in the Supplementary Materials. They were administered at each of the four time points during the lab (baseline, post-stress, recovery 1 and recovery 2). Smoking history and daily functioning were collected via interview questions related to age of smoking onset, current smoking rate (cigarettes per day), sleep patterns, and diet. Relapse was defined as smoking 1 or more cigarettes per day for 7 consecutive days within the first four weeks of abstinence (verified using biomarkers; see below). This definition of relapse reflects a return to daily smoking, which was based on the consensus statement of the 2003 Society for Research on Nicotine and Tobacco workgroup (Hughes et al. 2003).

Biological measures—HPA axis function was measured by cortisol (both saliva and plasma) and ACTH (plasma) levels. Saliva samples were collected using Salivette® tubes at the time points outlined above; and salivary cortisol was assayed using time-resolved fluorescence immunoassay (cortisol-biotin conjugation). The assay kits (IBL International) had a sensitivity of 0.4 nmol/L and inter- and intra-assay coefficients of variation less than 10% and 12%, respectively. Plasma cortisol and ACTH were assayed at a local hospital lab (Fairview Hospital, Minneapolis, MN) using chemiluminescent immunoassays using the ADVIA Centaur® cortisol kit and the Immulite® 2000 ACTH kit (Siemens Medical Solutions USA, Malvern, PA). Smoking was assessed via exhaled CO (MicroCO™ monitors; Micro Direct, Inc.) and saliva cotinine. Relapse was confirmed biologically using CO (>8 ppm) during the 24-hour and 4-week follow-up sessions. In addition, enzyme linked immunoassays (DRG Diagnostics) were used to assess cotinine levels (inter- and intra-assay variability < 12%), to confirm successful abstinence.

Working Definitions and Data Analysis

We defined high early adversity as an ACE score of 4 or more, consistent with other smoking studies (Bellis et al. 2014b; Edwards et al. 2007; Strine et al. 2012). Low early adversity was defined as 0 to 3. Although it may be desirable to examine each adversity type, it is important to note that adversity factors are highly correlated (Anda et al. 1999;

Dong et al. 2004); and the current study did not have the sample size sufficient for examining each ACE.

All hormones were log transformed. Demographic factors and smoking patterns were examined using independent t-tests between relapsers and successful abstainers. The main analytical approach consisted of mixed repeated measures Analysis of Variances (ANOVAs) using SPSS v22 (p-value = 0.05). The repeated factors consisted of lab (ad libitum smoking, 24-hour abstinence) and period within a lab (baseline, post-stress, recovery 1, and recovery 2) for salivary cortisol, plasma cortisol, and ACTH. The between subjects factors for all analyses consisted of early adversity level (low, high) and relapse status (successful abstainers, relapsers). Sex was not included in the analysis of biological measures due to small sample size. Withdrawal and subjective state scale factors for positive and negative affect were square root transformed and assessed with similar mixed repeated measures ANOVAs. Significant interactions were examined with simple univariate ANOVAs and/or Bonferroni corrected t-tests. Planned contrasts were used to assess the repeated period factor nested within each lab. Descriptive variables were examined using ANCOVAs with relapse status and ACE level as independent variables and sex as a covariate.

In addition, logistic regressions were performed to predict relapse status from adversity, HPA stress response, and their interaction. Sex was included as covariate and median splits were calculated for all HPA axis factors (saliva cortisol, plasma cortisol, and ACTH) such that high values indicated a strong response and low or negative values indicated a weak response or decline. Associations between smoking urges, craving, withdrawal symptoms, and HPA hormones were assessed. A hormonal stress index was created by subtracting the baseline cortisol sample from the post-stress cortisol sample (higher numbers indicate a stronger stress response), which served as the outcome variable. Sex, age, and smoking variables consisting of the three measures of craving - craving for nicotine, aversive urges (QSU-B F1), and appetitive urges (QSU-B F2), and withdrawal symptoms were used as predictors. Sex and age were entered first as covariates, followed by the smoking variables. These regression models were run for both sessions on low and high early adversity participants separately for comparison.

Results

Sample description

Only those who completed both the lab sessions were included (see the Supplementary Materials for detailed accounting of attrition). Participants were, on average, 40 years old (SE = 1.23), with an average of 14 years of education (SE = .27). The average days between the two sessions was 12.60 days (SE = .79), with most at exactly one week apart (mode = 7.00). The time between the lab sessions did not differ by sex, ACE level, nor relapse status. Also shown in Table 1 is the equal distribution of sex by relapse status and early adversity (all χ^2 p-values > .10).

Baseline differences between relapsers and abstainers

At the one-month post-quit session, 25 females and 32 males had relapsed. Relapsers did not differ from successful abstainers at baseline in age, education, body mass index (BMI), average sleep, nicotine addiction (FTND), depressive affect, anxiety, nor cigarettes smoked per day. The relapsers did, however, have higher baseline CO than the successful abstainers, $t(101) = 2.06$, $p < .05$ (see Table 1). Cotinine was not substantially different at baseline between relapsers and successful abstainers (relapsers $M = 299.16$, $SE = 32.88$; successful abstainers $M = 259.67$, $SE = 35.54$). Cotinine changed in the expected manner based on relapse status, $F(2, 69) = 21.58$, $p < .001$. Successful abstainers had decreased cotinine at the 24-hour abstinence lab ($M = 79.48$, $SE = 14.59$); and cotinine remained low until the one-month post-quit session ($M = 53.70$, $SE = 16.27$; comparison $p > .10$). The initial 24-hour abstinence lab decline in cotinine for the relapsers ($M = 96.45$, $SE = 12.86$; decline $p < .001$) returned to a level comparable to baseline by the one-month post-quit session ($M = 241.99$, $SE = 31.86$; baseline comparison $p > .10$; 24-hour abstinence lab comparison $p < .001$). Among these descriptive variables, only depressive affect ($F(1,97) = 6.15$, $p < .05$) and anxiety ($F(1,90) = 7.76$, $p < .01$) differed by early adversity group (see Table 1). In addition to continuous scores, the use of cutoff scores for clinical relevance indicated that those in the high early adversity group had higher rates of clinically relevant depressive affect ($\chi^2(1) = 6.96$, $p < .01$) and anxiety ($\chi^2(1) = 7.92$, $p < .01$) than those in the low early adversity group; but there were no differences based on relapse status.

Within the relapsers, there were 33 participants with low adversity and 24 participants with high adversity. Similarly, within the successful abstainers there were 25 participants with low adversity and 20 high adversity participants ($p > .10$).

Changes in stress hormones across time

Salivary cortisol—Salivary cortisol changed significantly across the low- (baseline) and high-stress periods within each lab ($F(4, 78) = 29.18$, $p < .001$) and across the two (ad libitum, 24-hour abstinence) lab sessions ($F(1,81) = 4.11$, $p < .05$), but there was no interaction between lab session and period ($p > .10$). Cortisol levels during ad libitum smoking were higher ($M = .69$, $SE = .06$) than after the 24-hours of abstinence ($M = .57$, $SE = .05$); however, this effect was primarily attributable to the high early adversity group who relapsed, as evident by a significant three-way lab session by relapse status by early adversity group interaction, $F(1, 81) = 4.74$, $p < .05$. Within the high early adversity group (interaction $F(1, 38) = 4.83$, $p < .05$), but not the low early adversity groups (interaction $p > .10$), saliva cortisol was higher during the ad libitum period ($M = .72$, $SE = .07$) than after 24 hours of abstinence ($M = .52$, $SE = .07$).

There was no significant effect of lab session for low early adversity ($p > .10$; ad libitum $M = .66$, $SE = .08$, abstinence $M = .61$, $SE = .06$); however, there was a significant period by relapse status by early adversity interaction ($F(4, 78) = 2.57$, $p < .05$). As shown in Figure 2, there was no significant difference for low early adversity successful abstainers nor relapsers across the sampling periods ($ps > .10$; Figure 2 left panel). Within the high early adversity participants (Figure 2 right panel), however, the relapsers had higher saliva cortisol than the

successful abstainers at the post-stress ($t(39) = 2.065$, $p < .05$) and the second recovery ($t(39) = 2.51$, $p < .05$) periods.

The logistic regression indicated no significant effects per individual lab session, but there was a significant interaction between adversity group and saliva cortisol ($p = .05$). High early adversity group, but not for the low early adversity group, showed a positive stress response (increase from baseline to post-stress) more than tripled the risk of relapse ($p < .05$, OR = 3.25, CI = .92 – 11.51; referenced to negative values or a baseline to post-stress decrease).

Plasma cortisol—There was a marginal main effects for lab sessions ($F(1, 83) = 3.62$, $p = .06$) and a significant main effect of period ($F(3, 81) = 36.09$, $p < .001$). Similar to saliva, the plasma cortisol during ad libitum smoking was marginally higher ($M = 1.87$, $SE = .05$) than after 24 hours of abstinence ($M = 1.78$, $SE = .04$). Within the stress periods, there was a significant increase of plasma cortisol from baseline to post-stress ($p < .001$), which subsequently declined to below baseline levels (all contrasts $p < .01$). The between subject relapse status by early adversity group effect also demonstrated a significant interaction ($F(1,83) = 5.36$, $p < .05$). As shown in Figure 3, the high early adversity relapsers (Figure 3, grey bar, right comparison) had higher plasma cortisol ($M = 1.97$, $SE .09$; $p < .05$) than the high adversity successful abstainers ($M = 1.70$, $SE = .08$), but there was no difference between low early adversity successful abstainers and relapsers ($p > .10$). Logistic regressions for plasma cortisol were not significant.

ACTH—There was a main effect of period ($F(3, 61) = 5.46$, $p < .002$), indicating that ACTH was responsive to the stress task. The time effect for period was also qualified by a significant four-way lab by early adversity by period by relapse status interaction ($F(3, 61) = 2.70$, $p = .05$). During ad libitum smoking in the low early adversity group (top left panel of Figure 4), only those who maintained successful abstinence showed a significant stress response ($p < .05$). This stress effect is evidenced by a significant rise in ACTH from baseline to post-stress ($p < .001$), which consistently declined across the two recovery periods (contrasts $p < .001$). During ad libitum smoking within the high early adversity group (lower left panel of Figure 3), successful quitters exhibited a marginal ACTH stress response (main effect of period $p = .07$), but relapsers did not ($p > .10$). During the 24 hours of abstinence, low early adversity successful abstainers also showed a stress effect as evident but as a main effect of period ($p < .05$; all contrasts $p < .05$). Although slopes are similar, the low early adversity relapsers showed no stress effect in ACTH during the 24-hours of abstinence, as evidenced by a non-significant main effect of period. Logistic regression revealed that relapse was six times less likely with a positive ACTH stress ($p < .01$, OR = .149, CI = .04 – .56; reciprocal OR = 6.71) relative to negative or no ACTH stress response. Smoking urges and craving did not show early adversity effects, though there were expected effects by relapse and time. Interested readers are referred to the Supplementary Materials.

Affect and withdrawal symptoms—Main effects of early adversity (high early adversity > low early adversity) were seen for withdrawal ($F(1, 94) = 9.16$, $p < .01$) and distress ($F(1, 94) = 8.40$, $p < .01$), but not for positive affect. Significant period by lab interactions were found for withdrawal ($F(5, 85) = 6.34$, $p < .001$). All participants reported

higher withdrawal during the 24-hour abstinence period relative to ad libitum smoking (lab effect $F(1, 94) = 5.94, p < .05$); there was also evidence of a significant stress response on withdrawal at each lab (baseline to post-stress $ps < .01$). The mean differences were larger during the ad libitum lab than during the 24-hour abstinence lab; and the two recovery periods did not differ for either lab (See Table 2 Supplementary Materials).

The negative affect score was further qualified by period and lab main effects, $F(3, 92) = 12.14, p < .001$ and $F(1, 94) = 8.74, p < .01$, respectively. Distress was higher during the 24-hour abstinence lab as opposed to the ad libitum lab. Distress rose from baseline samples to all subsequent samples ($p > .001$), but the two recovery periods were not different from one another (See Table 2 Supplementary Materials). Finally, a significant lab by period interaction ($F(3, 92) = 3.82, p < .05$) revealed that, during both ad libitum and 24-hour abstinence labs, there was a decline in positive affect from baseline to post-stress ($p < .001$); however, by the final recovery period during the ad libitum lab ($p < .05$) and during the 24-hour abstinence lab ($p < .001$), positive affect showed significant increases relative to post-stress.

Regression analyses for the ad libitum lab predicting saliva cortisol were not significant for either level of early adversity ($ps > .10$). In contrast, during the 24-hour abstinence lab, saliva cortisol was reliably predicted using the aforementioned regression models for those who experienced low early adversity ($F(6, 42) = 2.86, p < .05$) but not for those who experienced high early adversity ($p > .10$). Examination of the coefficients indicates that for the low early adversity smokers, craving (Std. Beta = $-.32, p < .05$) and withdrawal symptoms (Std. Beta = $.31, p < .05$) predicted saliva cortisol. No other predictors were significant. The same patterns of significance were observed for plasma cortisol and ACTH during the 24-hour abstinence lab, but not during ad libitum, was evident for the low early adversity, but not high early adversity, smokers. Plasma cortisol during the 24-hour abstinence lab was predicted by craving (Std. Beta = $-.37, p < .01$), appetitive urges (Std. Beta = $.47, p < .05$), and aversive urges (Std. Beta = $-.42, p < .05$) among low early adversity smokers ($F(6, 41) = 4.26, p < .01$), but not among high early adversity smokers ($p > .10$). Likewise, ACTH during the 24-hour abstinence lab was predicted by appetitive (Std. Beta = $.68, p < .01$) and aversive urges (Std. Beta = $-.61, p < .01$) among low early adversity smokers ($F(6, 36) = 2.60, p < .05$), but not among high early adversity smokers ($p > .10$).

Discussion

This study demonstrated, for the first time, a link between early adversity and stress-related HPA response in the context of smoking relapse in several ways. First, there is a convergence of evidence from both saliva and plasma cortisol that relapsed, high early adversity smokers demonstrate an enhanced stress response. While a high saliva cortisol stress response was associated with increased probability of relapse among those with high early adversity, there was no difference in ACTH responses between relapsers and successful abstainers among those who experienced high early adversity. Regardless of adversity level, ACTH was less variable during the 24-hour abstinence period and heightened ACTH stress responses were associated with a decreased probability of relapse. These results are maintained when important covariates, such as contraception use (females), psychiatric

meds, or psychiatric dysfunction (depressive symptoms and anxiety) are included in the models (see Supplementary Materials). In fact, including depressive affect and anxiety, two common correlates of adversity, enhanced the ACTH results, which suggests that these symptoms are independent of the effects seen here.

The results presented here for ACTH are similar to the results of previous CRF and ACTH stimulation challenges (Heim et al. 2001) wherein the most robust ACTH response was in the context of childhood adversity without psychiatric dysfunction. Our sample excluded those with active psychiatric dysfunction; and we show that controlling for subclinical depressive affect and anxiety led to further strengthening of the ACTH and adversity findings. We further qualify the findings by showing that smoking in the context of early adversity and acute stress may be driving the ACTH hypersecretion. The difference between the results of these two studies may be related to the fact that Heim's study (Heim et al. 2001) used a direct manipulation of ACTH and did not report controlling for smoking in its sample of abused women. This is relevant given that smoking has been associated with high early adversity (Bellis et al. 2014a; Edwards et al. 2007; Elliott et al. 2014; Ford et al. 2011; Fuller-Thomson et al. 2013) and further clarified in this report. We found evidence that HPA indices (saliva cortisol) predicted more than a three-fold increase in risk of relapse for those with high early adversity and a six-fold decrease in risk of relapse (ACTH) without regard to early adversity. The low early adversity groups produced patterns consistent with those observed in our earlier research (al'Absi et al., 2005), but we found here that these patterns of association were different for the high early adversity group. High early adversity was associated with higher distress and smoking withdrawal symptoms. Despite having higher distress and withdrawal symptoms, the patterns of association between all three HPA factors and smoking withdrawal symptoms were evident only in the low early adversity group and only during the more challenging 24-hour abstinence period. Past studies have shown that relapse groups (defined at 4 weeks post quit initiation) differ in multiple withdrawal symptoms both at the ad libitum and abstinent period (Nakajima & al'Absi, 2013). The study reported herein is the first study to examine these patterns in the context of adversity; therefore, it is unclear why these associations were evident in low early adversity, but not in high early adversity, smokers. These results do, however, support previous reports of associations between HPA functioning and withdrawal symptoms, including craving and smoking urges. It is theoretically possible that the association between HPA functioning and smoking variables in the high early adversity smokers is influenced by long-term effects of adversity on stress response systems and will require further analysis and mediation designs to reveal.

This study provides novel findings on potential mechanisms mediating the link between exposure to early adversity, smoking, and risk for smoking relapse. While the connection between HPA stress response and relapse risk confirmed previously reported studies for those who experienced low early adversity, the results from the high early adversity group appeared to be in the opposite direction, high saliva and plasma cortisol stress responses were associated with increased risk for early relapse (al'Absi et al., 2002; al'Absi et al., 2003; al'Absi et al., 2005). The fact that these findings were obtained across two hormonal measures (e.g., total cortisol from plasma and free cortisol from saliva), supports the robustness of these findings. It is important to note that our sample was not a clinical sample

of psychiatric patients. Thus, past demonstrations of cortisol blunting may be secondary to trauma-related psychopathology, which is also known to show cortisol blunting (Sriram et al. 2012).

These results extend previous findings from our, as well as others', laboratories, which indicate that early adversity increases an individual's risk of early smoking initiation and lifetime smoking (Edwards et al. 2007; Ford et al. 2011; Lemieux et al. 2016; Topitzes et al. 2010; Walsh and Cawthon 2014). To that end, it is important to note that a high level of early adversity was associated with higher withdrawal and distress in this study. Consistent with this finding, a recent study with a larger sample of smokers found that individuals who relapsed earlier reported higher level of early adversity (Lemieux et al. 2016). This study was also partially consistent with another study that showed a relationship between early adversity and smoking initiation (van Loon et al. 2005). The current study included a more carefully conducted assessment of stress reactivity before and after cessation and it included biological and prospectively monitored outcomes. As such, our findings advance understanding of the potential sensitizing role of early adversity in the impact of stress on addictive processes. A variety of adverse early life experiences lead to centrally driven dopaminergic over-reactivity to reward and under-reactivity to punishment. These patterns of reactivity set the stage for childhood and adolescent impulsivity, reward-seeking behaviors, and, for some, drug exploration and addiction (Leyton and Vezina 2014).

The current study had some limitations related to the retrospective assessment of early adversity, namely, exclusion of a comprehensive analysis of sex differences in both relapse and stress responsivity. Preclinical and clinical research has demonstrated the significance of sex differences in HPA responding, (Kosten et al. 2005), drug self-administration (Kosten and Kehoe 2007), and other rewarding behaviors (Kosten et al. 2000; Zhang et al. 2005). Consistent clinical and epidemiological reports indicate sex differences stress occurrence and motivation for drug use, maintenance, and relapse (Najavits et al. 1998; Shaw and al'Absi 2010). Secondly, our lack of urine testing for drugs or alcohol abstinence is a limitation, particularly as researchers have demonstrated that adversity exposed women exhibit a fourfold increase in risk for lifetime addiction (Wilsnack et al. 1997; Winfield et al. 1990). Because we were unable to examine the full interaction of sex, early adversity, and relapse due to sample size limitations, future research should more carefully consider potential sex differences in the association between early adversity and risk for smoking relapse. This is particularly important in light of previous work showing sex differences in risk for smoking relapse (al'Absi 2006; al'Absi et al. 2015; Bohadana et al. 2003; Cepeda-Benito et al. 2004; Jarvis et al. 2013; Nakajima and al'Absi 2012; Torchalla et al. 2012; van Loon et al. 2005).

Despite its limitations, we note several strengths of this study, including comprehensive assessment of the effects of acute stress, mood, craving, and withdrawal symptoms in the context of smoking cessation. For the first time, we demonstrate that previous reports of craving, smoking urges, and withdrawal symptoms as predictors of HPA functioning are contingent on early adversity experience. Another strength is our use of a prospective design to predict relapse. Finally, there are two approaches to studying adversity and ours was a conscious choice based on theory and clinical application, though arguably it has its

limitations. For example, one approach seeks to examine and quantify the impact of each individual adversity type (for example sexual abuse or neglect or physical abuse). The second approach, the approach we utilized here, recognizes the covariance of abuse types and instead seeks to examine the cumulative effect of across multiple types of adversity. This approach has a rich research history supporting the dose-response effect of cumulative adversity and its impact on physical, mental and substance use disorders. The interested reader is directed to one of several systematic or meta-analytic reviews available on this concept (Danese and McEwen 2012; Danese and Tan 2014; Huang et al. 2015; Kalmakis and Chandler 2015; Su et al. 2015).

In conclusion, this study demonstrated, for the first time, that early adversity may influence associations between stress-response and risk for smoking relapse. These results further indicate that minimal abstinence (24 hours) from smoking among those who experienced high early adversity is associated with cortisol levels similar to their low early adversity peers. This further supports the literature indicating that HPA blunting predicts relapse (al'Absi et al. 2005), but it also suggests that hypo-responsiveness to stress inductions may be particularly true for smokers who experience low early adversity. High early adversity smokers demonstrated robust cortisol stress responses and heightened negative affect; therefore, these smokers might benefit from additional psychosocial support during attempted cessation. There is now sufficient evidence of a link between adversity and addictive behaviors to warrant a recent policy and treatment statement by the U. S. Substance Abuse and Mental Health Services Administration (Center for Substance Abuse Treatment 2014). Our study is one of very few studies to prospectively examine potential mechanisms that might account for this adversity and addictive behavior link to provide critical clinical information for tailoring smoking cessation treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 2.

Saliva cortisol demonstrated a significant three-way period by relapse status by early adversity group interaction ($p < .05$) with high early adversity relapsers having higher saliva cortisol post-stress (marginal means for period averaging across lab sessions).

Fig. 3.

Plasma cortisol demonstrated a significant relapse status by early adversity group interaction ($p < .05$) where the high, but not low, early adversity relapsers produced more plasma cortisol than the successful abstainers ($p < .05$).

Fig. 4.

The low early adversity (upper panel), but not high early adversity (lower panel), successfully abstaining smokers showed a significant stress effect for ACTH during the ad libitum session ($p < .05$). The high early adversity successful abstainers did not demonstrate a significant lab effect but there was a main effect of stress-induced ACTH response ($p < .05$). Relapsers showed a significant period by early adversity group interaction whereby the high early adversity smokers showed a significant stress induction of ACTH ($p < .05$).

Table 1

Sample description

	Low ACE 0-3						High ACE 4+					
	Successful Abstainer			Relapser			Successful Abstainer			Relapser		
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
Age (years)	25	39.92	2.60	33	41.24	2.35	20	39.65	2.68	24	37.71	2.36
Education (years)	22	14.02	0.57	32	13.45	0.41	20	13.33	0.81	23	13.85	0.49
BMI	22	26.96	1.13	32	28.12	1.06	18	29.60	2.28	20	26.03	1.34
Average sleep (hours)	24	7.43	0.23	31	7.34	0.21	19	7.05	0.24	24	7.10	0.19
Nicotine dependence	25	4.60	0.37	32	5.59	0.35	20	4.95	0.41	22	4.82	0.40
Baseline expired CO ^{*a} (ppm)	25	22.00	2.80	33	32.85	3.26	20	25.00	3.58	24	27.33	2.92
Cigarettes per day	25	12.12	0.96	33	14.00	0.88	19	12.39	0.98	24	13.50	1.23
Baseline cotinine (ng/ml)	20	214.67	42.81	18	292.12	40.38	18	311.84	59.52	17	306.62	53.76
Depressive Affect ^{*b}	25	2.76	0.75	33	2.44	0.47	20	4.45	1.08	24	4.33	0.81
Trait Anxiety ^{**}	24	34.29	1.66	29	34.29	1.59	19	39.79	2.05	23	38.96	1.80
Clinical cut off scores:	N (%) Above cut off			N (%) Above cut off			N (%) Above cut off			N (%) Above cut off		
Depressive affect ^{**c}	1 (4%)			0 (0%)			3 (15%)			4 (16.7%)		
Trait anxiety ^{**d}	6 (25%)			8 (27.6%)			10 (52.6%)			13 (56.5%)		
Sex distribution	Female			Male			Female			Male		
	12			13			12			12		

^{*a} p < .05 successful abstainer versus relapser,^{*b} p < .05 low versus high ACE,^{**} p < .01 low versus high early adversity,^{**c} p < .000 Adversity by PHQ-9 cut off only, no relapse effect,^{**d} p < .01 Adversity by STAI cut off only, no relapse effect.