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Depression, smoking abstinence and HPA function in women smokers

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To determine whether smokers with a history of depression are differentially susceptible to smoking withdrawal, depressed mood induction and/or hypothalamic–pituitary–adrenal (HPA) axis dysregulation during smoking abstinence, 24 women smokers with and without such a history were studied. During one 5-day interval, participants smoked *ad libitum*; during a second they abstained. On day 4, the participants were exposed to the Velten mood induction procedure (VMIP). Participants were then instructed to take 1 mg dexamethasone at 11 pm. At 4 pm on day 5, blood samples were withdrawn to determine the cortisol and ACTH response. Despite lower baseline cotinine levels, history-positive participants displayed more pronounced overall withdrawal distress than did history-negative participants, regardless of condition. The VMIP increased depression as well as negative responses on other profile of mood states subscales. Despite many overall group differences, no significant main effects for smoking condition nor interaction effects emerged. All participants evinced cortisol suppression in response to dexamethasone during both conditions, but the degree of suppression did not differ as a function of either abstinence or depression history. In history-positive smokers, however, ACTH levels trended toward overall elevation and showed almost no suppression during abstinence; thus exacerbation of HPA dysregulation in history-positive smokers during smoking abstinence cannot be ruled out. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — smoking; nicotine withdrawal; depression; dexamethasone suppression test (DST); cortisol; adrenocorticotropic hormone (ACTH)

INTRODUCTION

Considerable evidence has been presented that smoking is overrepresented in individuals with diagnosable or subclinical depression, or even with a history of depression (Anda *et al.*, 1990; Covey *et al.*, 1990; Glassman, 1993). And although the evidence is not unequivocal (e.g. Ginsberg *et al.*, 1995; Hall *et al.*, 1994; Hitsman *et al.*, 2001), a number of studies have shown that these smokers have greater difficulty in quitting (e.g. Glassman *et al.*, 1988; Glassman, 1993; Balabanis *et al.*, 2001). To the extent that they are successful, their quit attempts may be complicated by the emergence of greater and more persistent withdrawal symptomatology, particularly depressed mood (e.g. Borrelli *et al.*, 1996; Covey *et al.*, 1990; Hall *et al.*, 1991; Kinnunen *et al.*, 1996; Niaura *et al.*, 1999; Pomerleau *et al.*, 2001; Glassman *et al.*, 2001)—although a higher likelihood of episodes of depression in such smokers even when they are not attempting to quit has also been noted (Tsoh *et al.*, 2000). An additional consideration is that depression is more common in women than in men, with women accounting for 61.2% of the total in lifetime prevalence of depressive symptoms and 71.2% of major depressive disorder (MDD)/dysthymia (Johnson *et al.*, 1992; Weissman *et al.*, 1991). Moreover, although the association of smoking with depression has been shown to be significant for both men and women, data from the National Health and Nutrition Epidemiological Survey (Anda *et al.*, 1990), the St. Louis ECA study (Glassman *et al.*, 1990) and the San Francisco survey

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(Perez-Stable *et al.*, 1990) suggest that this relationship may be more pronounced in women than in men.

People with a history of MDD are more susceptible to HPA-axis dysregulation (Carroll *et al.*, 1981; Young *et al.*, 1991,) and clinical observations by Glassman (1993) suggest that chronic nicotine exposure may help to maintain affective equilibrium and 'normalize' HPA-axis function in certain people. Thus, when smokers with a history of MDD stop smoking, in addition to manifestations of clinical depression or severe dysphoria, there may be a rebound effect on the HPA-axis resulting in a loss of feedback inhibition of cortisol. Resumption of smoking has been found to terminate depression/dysphoria (Fagerström *et al.*, 1991)—within several hours in some cases (Glassman, 1993). While much uncertainty remains about biobehavioral mechanisms that might link smoking and depression (see Carmody, 1989), nicotine is known to have important effects on central acetylcholine and catecholamines (Pomerleau and Pomerleau, 1984), both of which have been shown to play a role in the etiology of depression (Siever, 1987; Janowsky and Risch, 1987); moreover, nicotine is known to affect brain regions that influence mood and well-being (Carmody, 1989; Pomerleau and Rosecrans, 1989). It is plausible, therefore, that the same genetic variations in brain neurotransmitter systems that influence the probability of major depression also increase the probability of smoking by enhancing the degree to which nicotine provides reinforcement via affective normalization (Kendler *et al.*, 1993). Further, in people whose psychological and/or physiological adaptability is compromised, nicotine may serve to maintain homeostasis in critical systems such as the HPA-axis; for such people, nicotine use may constitute a coping strategy for meeting the challenges of daily living (see Pomerleau and Pomerleau, 1984).

In order to determine whether the reinforcing value of nicotine self-administration is enhanced in depressed individuals by the drug's affect-normalizing properties and its ability to protect against the hypothalamic–pituitary–adrenal (HPA) axis dysregulation that often characterizes episodes of depression—as indicated by elevated cortisol and ACTH levels following dexamethasone administration—a laboratory test was conducted of women smokers with and without a history of depression. We also wished to determine susceptibility to induction of depressed mood in history-positive and history-negative women smokers. Participants were studied during *ad libitum* smoking and over the first few days of abstinence from smoking, the interval during which, despite considerable individual variability (Piasecki *et al.*, 2000), craving and cognitive/affective withdrawal symptomatology typically peak (Ward *et al.*, 2001).

Our expectations were as follows: (1) Over the course of 3 days of smoking abstinence, history-positive (HX+MDD) smokers would experience withdrawal symptomatology of greater magnitude and duration than history-negative (HX−MDD) smokers; (2) After 3 days of abstinence from smoking, history-positive smokers would be more susceptible to induction of dysphoria than would history-negative smokers; (3) After 4–5 days of abstinence from smoking, history-positive smokers would show HPA dysregulation as indicated by post-DST cortisol and ACTH levels, whereas history-negative smokers would show little or no evidence of HPA dysregulation.

METHODS

Participants

Twenty-four female smokers, 12 with and 12 without a history of depression, were recruited from the general community through local newspaper advertisements and posters. Participants were required to meet the following criteria: between 20 and 55 years of age; premenopausal; in good health; weight $\geq$ 100 pounds; score $\geq$ 3 on the Fagerström test of nicotine dependence (FTND; Fagerström *et al.*, 1991; Heatherton *et al.*, 1991; Pomerleau *et al.*, 1994); smoking at least 10 cigarettes per day; and smoking at the current rate for at least 1 year. Candidates were excluded for the following: current use of CNS or cardiovascular-acting drugs; current use of antidepressant or antipsychotic medication; cardiac, vascular, pulmonary or gastric disease; hypertension; history of throat irritation or severe sinus infection; allergy to nicotine; history of seizures; history of abuse of drug or alcohol within 1 year prior to the study; history of anorexia nervosa; $\geq$ 15% below normal weight; regular use of other tobacco products such as cigars or pipes; and current depression (episode within past 6 months). Candidates were also excluded if they were currently pregnant or breastfeeding, had been pregnant or breastfeeding within the past 3 months, or were at risk of becoming pregnant.

A total of 643 interested people were telephone-screened, 147 of whom met preliminary qualifications and were invited to come into the laboratory for a screening interview. Of these, 35 opted not to participate further, 24 failed to show up for an appointment, 41 kept the appointment but were disqualified due to

smoking criteria or medical reasons, and the remaining 47 candidates qualified for participation in the study. Of these, eight lost interest and/or did not show up for scheduled laboratory sessions, seven could not be re-contacted after the initial interview, two decided that they did not have enough time to participate, two smoked during the abstinence phase and had to be disqualified, two were dropped due to problems maintaining adequate blood flow during laboratory sessions, and two could not be enrolled because they failed to qualify for unfilled cells; ultimately, 24 participants completed the protocol.

Procedure

The protocol for this study was approved by the Institutional Review Board of the University of Michigan Medical School. All participants meeting preliminary qualifications from the telephone screen were scheduled for a screening interview and sent a packet that included the Milcom Health History Questionnaire and baseline questionnaires which included the following: general history (to assess demographics); smoking history; substance intake history; Center for Epidemiological Studies-Depression (CES-D; Radloff, 1977); and the Fagerstrom test of nicotine dependence (FTND; Fagerstrom *et al.*, 1991; Heatherton *et al.*, 1991; Pomerleau *et al.*, 1994).

At the screening interview, the study was explained and informed consent obtained. The Milcom was reviewed to determine medical exclusion, height, weight and blood pressure were measured, a pregnancy test was administered, and a 5 ml blood sample was withdrawn for baseline cotinine concentrations. The structured clinical interview for DSM-IV (SCID; First *et al.*, 1994) was conducted by a trained interviewer to determine history of major depressive disorder, mania, hypomania, dysthymia and anorexia nervosa. Acceptance into the HX+MDD or HX−MDD groups was made on the basis of this interview. To be categorized as HX+MDD, participants were required to have experienced at least one episode of MDD with five or more symptoms within the past 10 years. To rule out currently depressed individuals, they were required not to have had an episode of MDD or met criteria for dysthymia within the past 6 months. To qualify as HX−MDD, smokers could not have a history of any depression diagnosis.

The study consisted of two 5-day intervals separated by approximately a month and timed to coincide with the mid- to late-follicular phase (operationally, between the end of menses and day 11 of the menstrual cycle)—the time when affective, physiological and hormonal responses are known to be 'low' or neutral (Schechter *et al.*, 1989). During one 5-day interval the participant smoked *ad libitum*; during the other 5-day interval, she abstained from smoking; conditions were presented in counterbalanced order. CO levels ($CO \leq 10$) were measured on all 5 days, and a urine sample was obtained on day 3 to rule out pregnancy. On days 4 and 5 of the *ad libitum* smoking interval, to maintain a steady state of nicotine during laboratory testing, the participant was provided with two 15 mg Nicotrol® nicotine transdermal patches to be worn from 1100 h through to the end of the laboratory session. On days 3–5 of the abstinence interval, the participant also provided a urine sample for testing with a NicCheck™ test strip for nicotine and its metabolites for additional verification of abstinence.

For the first 3 days of each interval, the participant came into the laboratory to receive/drop off her daily diary questionnaire. This instrument was completed at bedtime and consisted of a 24-h retrospective assessment of smoking craving and withdrawal symptomatology as specified in DSM-IV (APA, 1994)—depressed mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, increased appetite—measured on a bipolar scale of −5 to +5 with values less than zero recoded as zero (Pomerleau *et al.*, 2001).

On day 4 of each phase, the participant reported for a laboratory session that began at 1500 h. The participant was seated in a recliner on one side of the one-way mirror; an intravenous catheter, attached to infusion-exfusion tubing to allow unobtrusive withdrawal in an adjacent room, was inserted 60 min prior to blood sampling to allow time for cortisol levels to stabilize. Samples for cortisol and nicotine/cotinine were withdrawn at 1600 h; samples for ACTH were withdrawn four times over a 20 min interval and pooled. The line was heparinized between draws to prevent clotting. Samples were collected in standard EDTA vacutainer tubes which were kept on ice during the session, centrifuged at 4°C, with the plasma stored at −80°C until assayed. Plasma cortisol levels were measured by RIA, using Diagnostic Product Corporation's cortisol CORT-A-COUNT kit. Plasma ACTH levels were determined using a Nichols Institute Allegro HS-ACTH immunoassay kit. Baseline cotinine was measured using high performance liquid chromatography (HPLC; Hariharan *et al.*, 1988).

The session lasted approximately 3 h, during which a modified version the Velten mood induction procedure (VMIP; Velten, 1968) was used as a provocative assessment of susceptibility to dysphoria. The standard VMIP induces affect by having participants read

a series of 50 emotional statements, with encouragement to actualize the feelings suggested by each statement. In the modified version, a pre-recorded tape was broadcast via speakers placed in the laboratory, consisting of 15 min of neutral statements followed by 15 min of dysphoric-mood statements. The Profile of Mood States (POMS; McNair *et al.*, 1971) was administered once before the neutral statements, once between the two segments, and once after the depression statements, with the following instructions: 'Please read EVERY word carefully. Then fill in ONE space under the answer which best describes how you feel RIGHT NOW. Mark the answer which is closest to how you feel RIGHT NOW using the following numbers . . . .'

Following the session, the participant was given a 1 mg dexamethasone tablet with instructions to take it at 2300 h—the standard protocol for the dexamethasone suppression test (DST; Carroll *et al.*, 1981). The DST, which involves monitoring the cortisol response to the administration of a small amount of the exogenous glucocorticoid, dexamethasone, was used to examine systematically the relationship between abstinence-induced dysphoria and dysregulation of inhibitory feedback mechanism in the hypothalamic–pituitary–adrenal (HPA) axis. Depressed individuals are less likely to show the normal response of cortisol suppression to levels below 1 μg/dl (Baumgartner *et al.*, 1985) and also tend to show enhanced variability in the range of cortisol response. ACTH release was also measured in order to provide additional information about inhibitory feedback mechanisms.

On day 5 of each phase, the participant reported to the laboratory at 1500 h and a catheter was inserted as described above. After 60 min, a single sample for post-dexamethasone cortisol was withdrawn, and four samples for ACTH were taken over a 20 min interval for subsequent pooling.

Data analysis

Baseline differences between diagnostic groups were compared using independent *t*-tests and ChiSquare tests as appropriate. Because of marginally significant differences in baseline cotinine levels, baseline concentrations were covaried in all subsequent analyses. Tests of withdrawal symptoms over the first 3 days were conducted using SAS PROC MIXED. Because preliminary testing revealed no higher-order interaction for any variable, diagnostic group, smoking condition, day and all first-order interactions were included in the model. Session POMS data were analysed including diagnostic group, smoking condition, time (pre- and post-mood induction), and all first-order interactions, using baseline (pre-neutral statements) as an additional covariate. Cortisol and ACTH values were log-transformed for the purpose of statistical testing. Because of the potential effect of age on DST results (Akil *et al.*, 1993), and because of substantial though nonsignificant group differences in age, this variable was also included as a covariate. Because of the possible impact of oral contraceptive use on cortisol and ACTH levels (Kirshbaum *et al.*, 1999), two oral contraceptive users matched for group and contraceptive type (Triphasic) were included in analyses of these variables; a third oral contraceptive user, in the HX+MDD group, could not be matched and was excluded. Data were analysed using SAS PROC MIXED, with diagnostic group, smoking condition, dexamethasone (pre vs post) and all first-order interactions included in the model.

RESULTS

Baseline group differences

Baseline characteristics for the two groups are shown in Table 1. CES-D scores for HX+MDD participants were higher than for HX−MDD. The only other significant difference was that cotinine levels were higher in HX−MDD participants.

In the HX+MDD group, four women had had a single episode of MDD, seven had had two episodes, and one had had three. The mean length of time since the most recent episode was 2.4 ± 2.4 years (range 0–8 years).

Compared with participants who completed the protocol, the 23 individuals who enrolled but either did not start or did not complete the protocol were significantly older (completers: 31.0 ± 9.5 years; non-completers: 39.1 ± 12.4 years; $t = -2.53$, $p < 0.05$) and more nicotine dependent as measured by the

Table 1. Participant characteristics (mean ± SEM or percent; *t*-test or ChiSquare)

	HX + MDD ($n = 12$)	HX − MDD ($n = 12$)	*p*-value
Age (years)	34.0 ± 2.7	28.0 ± 2.5	NS
Race (% white)	83%	83%	NS
BMI (kg/m^2)	25.2 ± 1.1	27.2 ± 1.6	NS
Smoking rate (cigarettes/day)	17.8 ± 2.3	20.0 ± 1.5	NS
Cotinine (ng/ml)	186.7 ± 27.2	324.3 ± 61.0	< 0.10
FTND (range 0–10)	4.2 ± 0.5	5.2 ± 0.5	NS
CES-D (range 0–60)	19.7 ± 3.5	6.6 ± 1.8	< 0.05

FTND (completers: 4.7 ± 1.8; noncompleters: 6.0 ± 2.2; $t = -2.26$, $p < 0.05$). They did not differ significantly with respect to race distribution or cigarettes/day.

Craving and withdrawal effects over the first three days

Craving and withdrawal symptomatology over the 3-day pre-session period are shown in Figure 1. For craving, a significant main effect emerged for condition (smoking vs abstinence; $F[1,20] = 21.94$, $p < 0.0001$), with a marginal interaction of condition with diagnostic group ($F[1,20] = 3.78$, $p < 0.10$), such that craving during abstinence was most strongly elevated in HX−MDD. Significant or marginal main effects were detected for both diagnostic group and condition for irritability (diagnostic group: $F[1,22] = 6.33$, $p < 0.05$; condition: $F[1,20] = 14.75$, $p < 0.01$), anxiety (diagnostic group: $F[1,22] = 3.45$, $p < 0.10$; condition: $F[1,20] = 19.38$, $p < 0.001$), difficulty concentrating (diagnostic group: $F[1,22] = 3.26$, $p < 0.10$; condition: $F[1,20] = 10.43$, $p < 0.01$), and restlessness (diagnostic group: $F[1,22] = 5.35$, $p < 0.05$; condition: $F[1,20] = 19.08$, $p < 0.001$). Significant or marginal main effects for diagnostic group only were detected for depression ($F[1,22] = 13.76$, $p < 0.01$) and insomnia ($F[1,22] = 3.27$, $p < 0.10$). Significant main effects for condition only were detected for increased appetite ($F[1,20] = 14.72$, $p < 0.01$). Except for a marginal diagnostic group by day interaction for insomnia ($F[2,44] = 2.74$, $p < 0.10$), no interaction effects for withdrawal symptoms were observed.

Response to mood induction

Response to mood induction is shown in Figure 2. A time effect was observed for the POMS elated/depressed subscale ($F[1,22] = 42.67$, $p < 0.0001$), indicating that the mood induction procedure was successful. Significant differences were also observed for diagnostic group ($F[1,22] = 9.05$, $p < 0.01$), with the HX+MDD group evincing a greater overall level of depression than the HX−MDD group. Regarding the remaining scales, significant time effects were also observed for composed/anxious ($F[1,22] = 4.72$, $p < 0.05$), agreeable/hostile ($F[1,22] = 15.80$, $p < 0.001$), onfident/unsure ($F[1,22] = 9.11$, $p < 0.01$) and energetic/tired ($F[1,22] = 18.81$, $p < 0.001$). Significant group differences were detected for agreeable/hostile ($F[1,22] = 7.28$, $p < 0.05$), with a trend towards significant differences for energetic/tired ($F[1,22] = 2.97$, $p < 0.10$). No significant effects for smoking condition or for any interaction for elated/depressed or any other POMS scale were observed.

Cortisol and ACTH

Data for 11 HX−MDD and 11 HX+MDD participants were available for analysis of cortisol; an additional participant had missing ACTH data, leaving 10 cases in the HX + MDD group available for ACTH analysis. The results for cortisol and ACTH are shown in Figure 3. Comparison of pre-session values showed no significant differences based on either smoking condition or depression status for either cortisol or ACTH (expressed as continuous variables). Comparisons of pre- vs post-dexamethasone administration showed highly significant post-dexamethasone suppression of both cortisol ($F[1,20] = 370.83$, $p < 0.0001$) and ACTH ($F[1,19] = 27.72$, $p < 0.0001$); no participant in either group exhibited DST nonsuppression during either the smoking or abstinence condition, using 5 μg/dl as the cutoff. For ACTH, but not cortisol, a trend towards significant between-groups differences was detected ($F[1,18] = 3.20$, $p < 0.10$), with levels for the HX+MDD group exceeding those for the HX−MDD MDD group. No significant differences or trends were detected for either cortisol or ACTH for smoking condition (*ad libitum* smoking vs abstinence) or any interaction.

DISCUSSION

Baseline characteristics for HX+MDD and HX−MDD women smokers were similar in most respects. The HX+MDD participants exhibited higher CES-D scores than the HX−MDD participants but this was expected given that they were selected on the basis of diathesis for depression. Cotinine levels showed a trend towards being higher in the HX−MDD participants, which was unrelated to the selection criteria and seems adventitious; differences in cigarettes/day or degree of dependence were in a consistent direction but fell short of being a trend.

As expected, significant main effects for condition (smoking vs abstinence) were detected for craving and most withdrawal symptoms. More surprisingly, regardless of smoking condition, we found greater overall levels of affective smoking-withdrawal symptomatology (irritability, anxiety, difficulty concentrating, restlessness, depression and insomnia) in history-positive participants despite their lower baseline levels of nicotine intake. Withdrawal symptomatology

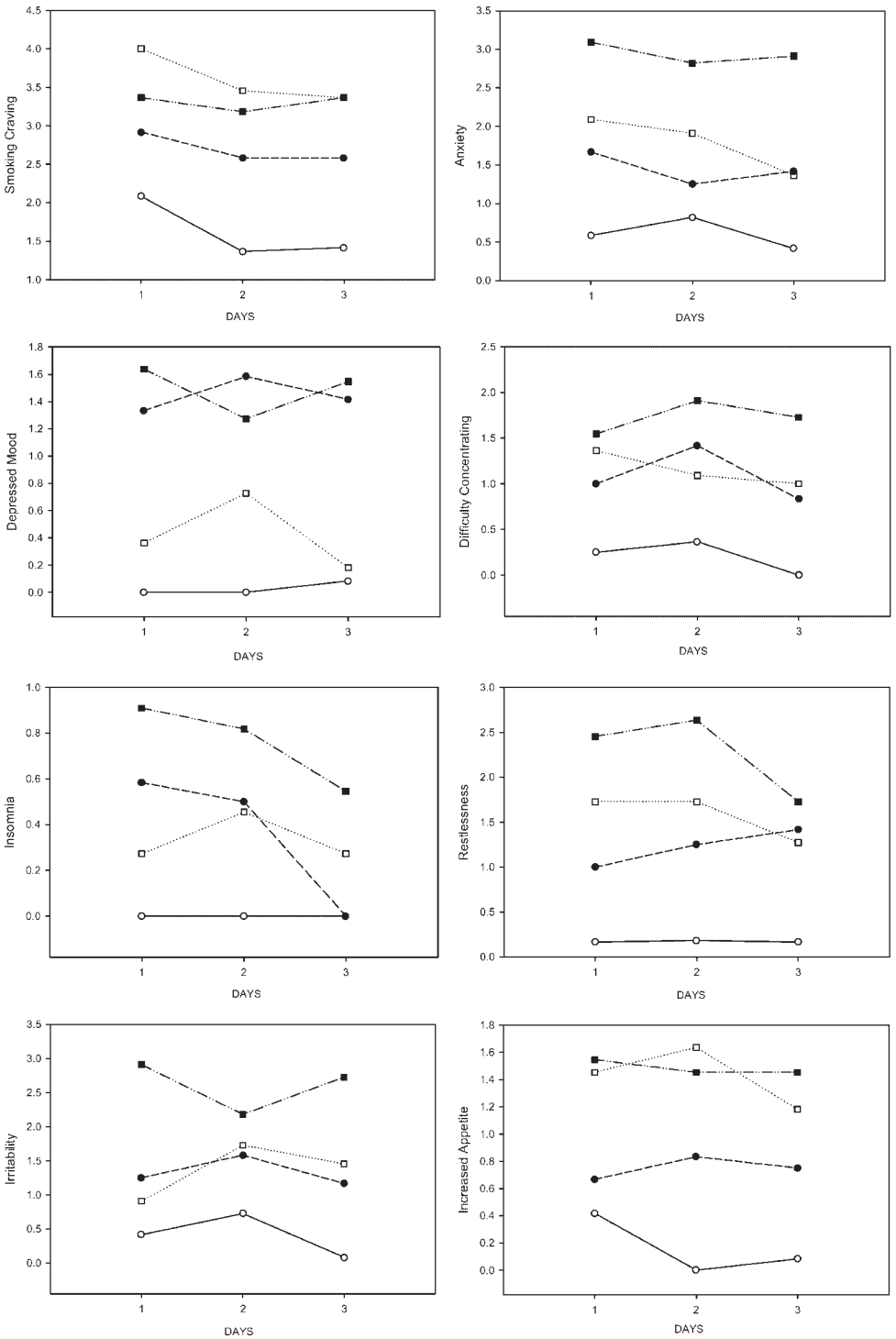

Figure 1. Craving and withdrawal symptoms over 3 days (means on a scale of 0–5). Open circles: HX−MDD, *ad libitum* smoking; open squares: HX−MDD, smoking abstinence; filled circles: HX+MDD, *ad libitum* smoking; filled squares: HX+MDD, smoking abstinence

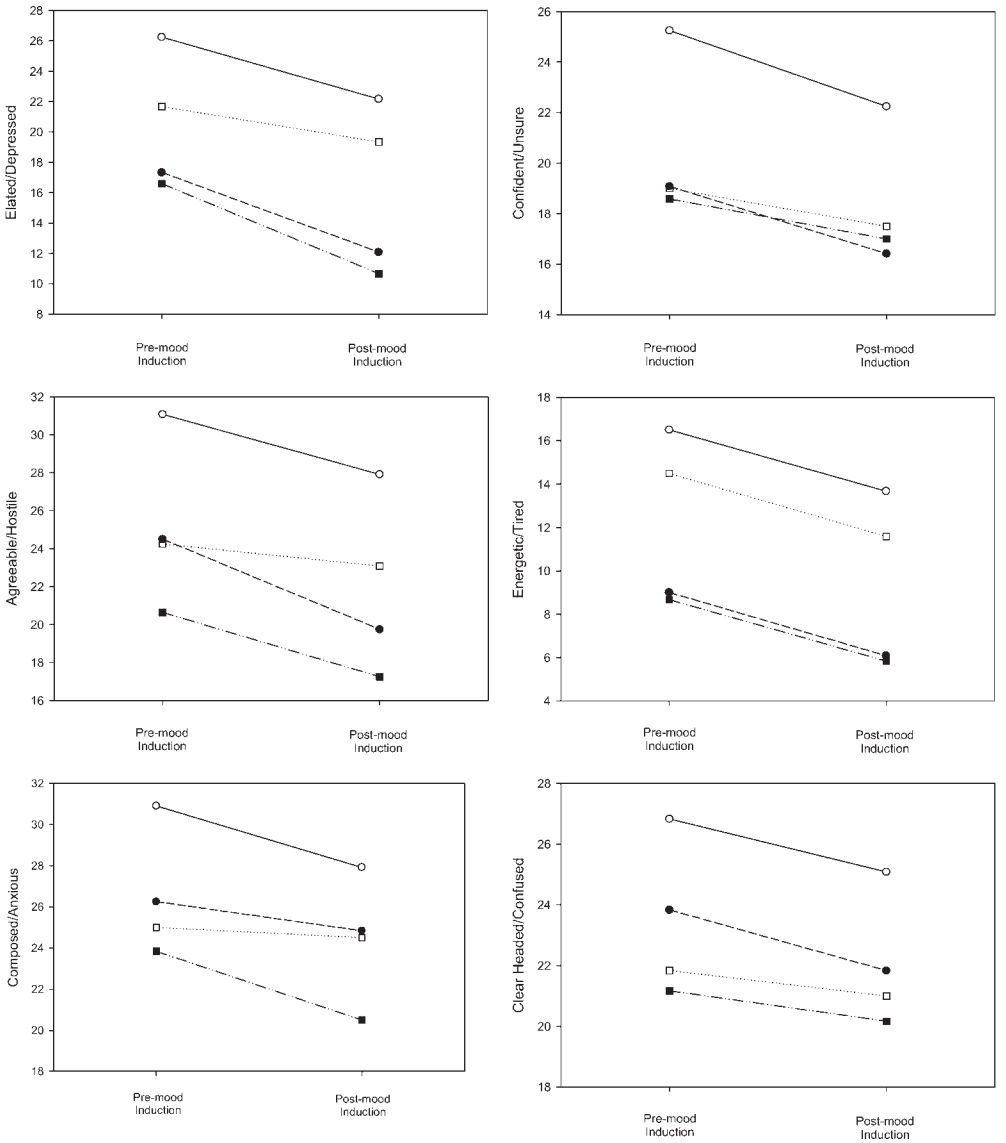

Figure 2. Mood ratings on POMS subscales (means on scales of 0–36) before and after the Velten mood induction procedure (day 4). Open circles: HX−MDD, *ad libitum* smoking; open squares: HX−MDD, smoking abstinence; filled circles: HX+MDD, *ad libitum* smoking; filled squares: HX+MDD, smoking abstinence

has been reliably demonstrated even in minimally deprived smokers, being lowest immediately after smoking and rising measurably within half an hour to an hour (Pomerleau *et al.*, 1983), at which point dependent smokers typically light up another cigarette. Although no differential effects were observed based on several days' abstinence vs *ad libitum* smoking, our findings suggest that individuals with a diathesis for depression may experience more chronic distress from withdrawal symptomatology than their nondepressed counterparts. This circumstance may contribute to relapse, unsuccessful quitting, or failure

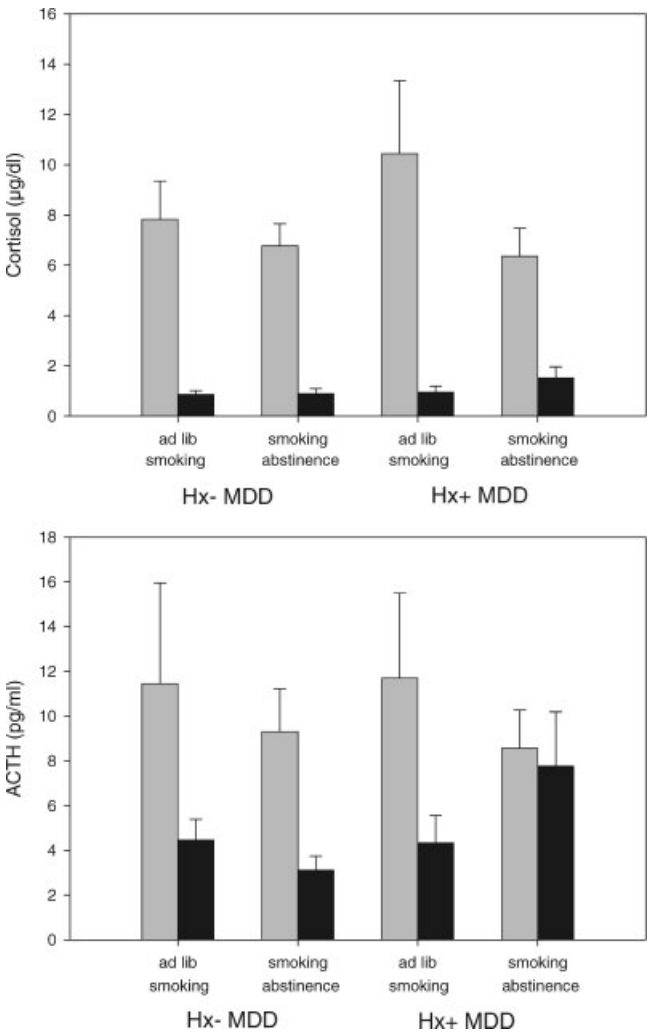

Figure 3. Pre- and post-DST levels of cortisol and ACTH (mean ± SEM) (days 4 and 5). Shaded bars: pre-dexamethasone condition; dark bars: post-dexamethasone condition

even to initiate a quit attempt in smokers with a history of depression. By contrast, craving did not differ based on diagnostic group, and indeed, a marginal interaction of condition with diagnostic group emerged such that craving during abstinence was most strongly elevated in nondepressed smokers—probably reflecting their higher nicotine intake as indicated by baseline cotinine levels. This disjunction between craving and affective withdrawal symptoms lends further support to our contention that these patterns may represent distinct phenotypes for smoking (e.g. Pomerleau *et al.*, 2000).

The modified Velten mood induction procedure was effective in increasing self-reported depressed mood, as measured by the POMS elated/depressed subscale in both history positive and history negative participants, and also increased negative responses on several other POMS subscales. A number of overall group differences were observed, suggesting that the HX+MDD group may have experienced greater depression than the HX−MDD group. No significant main effects for smoking condition nor any interaction effects emerged, however; little evidence was found for a differential effect of abstinence on susceptibility to acute mood induction by history of depression.

The results for HPA axis hormones are not as easily characterized. Regarding the effects of smoking

abstinence on cortisol, conflicting evidence has been presented in the literature. In two previous studies involving the DST in smokers, for example, Hughes *et al.* (1988) found a significant increase in baseline (pre-dexamethasone) cortisol in nondepressed laboratory participants after 1–2 days' abstinence, whereas Frederick *et al.* (1998) found a significant decrease in baseline cortisol in quitting smokers at 2 and 4 weeks. In our study, in which confirmed abstinence was required and history of depression was included as a grouping factor, there were no changes in baseline cortisol or ACTH levels after 4 days' abstinence. Although our findings cannot be regarded as conclusive in light of discrepancies in the previously cited studies, they indicate that investigations using repeated measures over both short- and long-term abstinence will be needed to resolve the issue.

All participants in our study evinced cortisol suppression in response to dexamethasone (i.e. none escaped from suppression) during both smoking and abstinence conditions (using 5 μg/dl as the cutoff), and no differences were found in degree of suppression as a function of either abstinence or history of depression. An explanation proposed by Hughes *et al.* (1988) upon failure to observe elevated cortisol levels following dexamethasone administration during 1–2 days' smoking abstinence in nondepressed smokers is that, as with baseline cortisol, a longer period of abstinence may be needed to elicit HPA dysregulation. No changes were found in degree of suppression over time over 5 days' abstinence, however, and Frederick *et al.* (1998) found no interaction for time by percent suppression over 2 and 4 weeks after quitting, suggesting that time alone may not be the critical variable.

Another and perhaps more likely possibility is that a negative bias may have been introduced by the study design: Not only were persons with current diagnosis of major depression and/or taking an antidepressant excluded, but also participants were told they would be abstaining only for a time-limited interval rather than actually quitting smoking. These methodological considerations, though conservative, may have limited the ability of the present design to elicit a degree of depression/dysphoria sufficient to precipitate escape from dexamethasone suppression. We note, moreover, that only 40%–50% of patients with current diagnosis of MDD typically exhibit escape from dexamethasone suppression when tested (Ribeiro *et al.*, 1993), suggesting that the DST in its present form may not be sensitive enough to detect more subtle degrees of HPA dysregulation accompanying moderate depression/dysphoria induced by smoking abstinence. Providing some support for this speculation are our findings on ACTH, a measure that provides additional information about pituitary control mechanisms for cortisol release. ACTH levels trended toward overall elevation in HX+MDD smokers and appear to show almost no suppression in the abstinence condition in this group, though the interaction effect failed to reach significance. It should be noted that interpretation of our findings is complicated by the fact that HX+MDD smokers included women with both single- and multiple episodes—which contribute variability in HPA axis response—and with recency ranging from zero to 8 years. Differences in age and BMI, though not significant, may also have contributed variability in our results. We conclude that research in a larger and/or more severely depressed sample in an inpatient setting, including men as well as women, and incorporating additional measures of HPA function and frequent sampling of cortisol and ACTH over a longer period of time, ought to be conducted before the possibility of exacerbation of HPA dysregulation during smoking abstinence is dismissed. We hope that the present report will stimulate further inquiry along these lines.

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