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Sex differences in negative affective response during nicotine withdrawal

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Abstract

This study examined physiological indicants of the neurobiological mediators of negative affect during acute nicotine withdrawal. Eighty subjects (41 male) were assigned to one of four groups (24-h deprived or nondeprived dependent smokers, occasional smokers, and nonsmokers) and participated in an instructed fear conditioning paradigm involving cued administration of electric shock. Negative affective response was measured with fear-potentiated startle during cues that signaled electric shock and during the postcue offset recovery period. Salivary cortisol and self-report measures were also collected. Fear-potentiated startle results indicated that affective recovery postcue offset was delayed in nicotine-deprived women. Nicotine-deprived women also displayed elevated cortisol levels throughout the fear conditioning procedure.

Descriptors: Smoking withdrawal, Negative affect, Sex differences, Fear-potentiated startle, Salivary cortisol

Numerous theorists have suggested that negative affect regulation is a primary motive for drug use in general, including nicotine use (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Koob & LeMoal, 2001). In particular, these recent (and longstanding, e.g., Solomon & Corbit, 1974) negative reinforcement accounts of drug dependence highlight the potentially important motivational contribution of *negative affect* during the *drug withdrawal syndrome*. Substantial evidence of the activation of the neurobiological mediators of negative affect during nicotine and other drug withdrawal has been obtained in animal models of drug dependence, but confirmation of these results in humans has been limited primarily to self-report methods to date. Physiological measures exist that reflect activation of negative-affect-related components of the neuroendocrine and central nervous systems, but the use of these measures has failed to yield evidence of significant activity in negative affect processing systems during drug withdrawal in humans. However, this preliminary research on drug withdrawal in humans has not examined negative affect in response to an affective challenge. It is possible that the effects of withdrawal in humans will be seen most clearly in the context of emotion regulation following a stressor, rather than on the basis of tonic levels of negative affect. Therefore, the research described in this article examined fear-potentiated startle and salivary cortisol in a fear conditioning paradigm involving threat of electric shock to document perturbations in the neurobiological mediators of negative affective response and regulation during nicotine withdrawal in humans.

Nicotine Use, Dependence, Withdrawal, and Negative Affect

Multiple independent lines of evidence suggest that one primary function for smoker's nicotine use is to regulate negative affect. Self-report questionnaires that specifically assess motives for smoking consistently identify negative affect reduction as an important motive for dependent smokers' use of nicotine (Brandon & Baker, 1991), and relative endorsement of this motive is a reliable predictor of smoking behavior (Brandon, Juliano, & Copeland, 1999). Nicotine-dependent smokers report greater expectation that smoking will successfully alleviate negative affect than do occasional smokers, ex-smokers, and nonsmokers (Brandon & Baker, 1991). Self-report of smoking urge has also been consistently observed to covary with smokers' affective state, regardless of whether affect is manipulated experimentally (Zinser, Baker, Sherman, & Cannon, 1992, experiment 2) or varies naturally (Zinser et al., 1992, experiment 1). Finally, increased negative affectivity is associated with reduced smoking cessation success (Patton, Barnes, & Murray, 1997) and is a potent setting event for relapse to nicotine use as well (Brandon, Tiffany, Obremski, & Baker, 1990).

Both classic (Solomon & Corbit, 1974) and current theories (Baker et al., 2004; Koob & LeMoal, 2001) of drug motivation emphasize that negative reinforcement is a critical motive for nicotine and other drug use. In other words, drug use is motivated to escape, avoid, or reduce aversive states such as drug withdrawal or stress. In particular, current negative reinforcement models emphasize that *negative affect* during drug withdrawal (rather than the physical symptoms such as tremor, hunger, or sleep disturbance) is the central motivational element

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of the drug withdrawal syndrome. That is, drug users take drugs to avoid, forestall, or reduce symptoms of negative affect that emerge during nicotine and other drug withdrawal.[1]

Unfortunately, much of what we know about these motivationally critical affective processes during nicotine withdrawal in humans is based on a narrow range of measures. In fact, as evidenced in the brief review above, the vast majority of the empirical research on affect during nicotine withdrawal in humans has been limited to self-report methods. Therefore, to address this significant shortcoming in the human literature on drug withdrawal, the present study used psychophysiological measures (startle response and salivary cortisol) to characterize central nervous system and neuroendocrine stress response in humans during nicotine withdrawal. We now briefly review empirical research and measurement of the central nervous system and neuroendocrine stress response in animals and humans as it is relevant to understanding the drug withdrawal syndrome.

Central Nervous System Mediated Negative Affect, Startle Response, and Drug Withdrawal

Substantial evidence from research with both animals and humans suggests that the amygdala is critically involved in the operations of the negative affect/aversive motivation system. Numerous studies have documented amygdala involvement in an array of processes involving negative affect (Ledoux, 1996). The startle response (Davis, Walker & Lee, 1999; Lang, Bradley, & Cuthbert, 1990) provides an attractive, cross-species, noninvasive measure for examining central nervous system/amygdala-mediated negative affect. Numerous empirical studies with human and animal participants have demonstrated that the startle response to an abrupt, intense stimulus (e.g., loud noise) increases when elicited in the presence of a cue that elicits acute negative affect (e.g., cue that has been paired with electric shock or other noxious stimulus; Curtin, Patrick, Lang, Cacioppo, & Birbaume, 2001; Davis et al., 1999). Substantial research implicates the amygdala in this potentiation of the startle response during negative affective states (Davis et al., 1999).

Converging lines of evidence indicate a key role for the amygdala and related neural structures in the negative affective concomitants of the drug withdrawal syndrome in animals (e.g., Isoardi, Martijena, Carrer, & Molina, 2004; Kelsey & Arnold, 1994; Tzavara, Monory, Hanoune, & Nomikos, 2002). Drug withdrawal studies that examine the startle response in animals have been critical in supporting this assertion. Numerous empirical studies have documented that overall startle response magnitude is tonically increased during spontaneous withdrawal from nicotine (Helton, Modlin, Tizzano, & Rasmussen, 1993; Rasmussen, Czachura, Kallman, & Helton, 1996), alcohol (Rassnick, Koob, & Geyer, 1992; van Erp, & Miczek, 2001), benzodiazepines (Miczek & Vivian, 1993; Rasmussen, Helton, Berger, & Scearce, 1993), and cocaine (Gordon & Rosen, 1999; Mutschler & Miczek, 1998) in chronically dependent rats and during naloxone-precipitated withdrawal during acute opiate dependence in rats (Harris & Gerwirtz, 2004, Harris, Hanes, & Gerwirtz, 2004). Moreover, administration of anxiolytic drugs blocks this increase in startle response in rats during withdrawal from nicotine (Rasmussen et al., 1996) and diazepam (Rasmussen et al., 1993).

In addition to tonic increases in the overall startle response magnitude, recent studies with animals have also documented that drug withdrawal increases the potentiation of the startle reflex in the presence of conditioned fear cues (Davis et al., 1999). For example, Fendt and Mucha (2001) demonstrated that after fear conditioning training sessions (repeated pairings of a light-conditioned stimulus with footshock), rats display significantly potentiated startle in the presence of the light-conditioned stimulus. Importantly, naloxone-precipitated opiate withdrawal significantly increased this fear potentiation of the startle response in that experiment. Similarly, Gordon and Rosen (1999) demonstrated increased fear-potentiated startle to a light-conditioned stimulus for footshock during cocaine withdrawal, although this effect was strongly moderated by the context in which drug exposure and withdrawal had occurred. Moreover, Borowski and Kokkinidis (1994) reported impaired extinction of fear-potentiated startle to previously established conditioned stimulus–footshock pairings during acute cocaine withdrawal.

Given the robust observations of a drug withdrawal effect on overall startle response magnitude and fear-potentiated startle in animals, it is striking that these effects have not been successfully replicated in humans. Numerous empirical studies with nicotine-dependent humans have failed to replicate the increase in overall startle during withdrawal that has been observed in animals (Casa, Hofer, Weiner, & Feldon, 1998; Duncan et al., 2001; Geier, Mucha, & Pauli, 2000; Mueller, Mucha, & Pauli, 1998; Postma, Kumari, Sharma, Hines, & Gray, 2001). Similarly, no significant increase in overall startle has been observed in humans during withdrawal from caffeine (Flaten & Elden, 1999; Swerdlow et al., 2000), cocaine (Efferen et al., 2000), or benzodizepines (i.e., oxazepam; Voshaar, Jan Verkes, van Luijtelaar, Edelbroek, & Zitman, 2005).

The research reported in the current article directly examined fear-potentiated startle during nicotine withdrawal in a fear conditioning paradigm similar to that used by Fendt and Mucha (2001). Fear-potentiated startle was measured both during the threat cue period and in the recovery period following termination of the threat cue to examine drug withdrawal effects on the initial negative affective response intensity and the subsequent regulation of this affective response poststress, respectively (see Davidson, 1998, for a discussion of the advantages of examining time course and parsing emotional response into its constituents). In addition to fear-potentiated startle, salivary cortisol response to this affective challenge was also collected to assess HPA-axis stress response during nicotine withdrawal. We now briefly review relevant research on the HPA-axis stress response.

Neuroendocrine Stress System, Salivary Cortisol, and Drug Withdrawal

The hypothalamic-pituitary-adrenal (HPA) axis is a component of the neuroendocrine system that is central to the coordination of an organism's response to stress (for a review, see McEwen, 2000). In contrast to the fast-acting aversive motivation system described above, this neuroendocrine stress response develops over the course of minutes to hours after stressor onset, but activity may persist for days to facilitate necessary longer lasting bodily response to stress. The HPA-axis stress response can be initiated by both psychological and physiological stressors (Cacioppo, 2000; Pomerleau & Pomerleau, 1990). Dysregulation of the HPA-axis stress response has been implicated as a key

[1]We do not intend to suggest that negative reinforcement is the sole determinant of drug use. Both positive reinforcement (e.g., Stewart, de Wit, & Eikelboom, 1984) and incentive salience (e.g., Robinson & Berridge, 1993) processes also likely contribute to drug use motivation, but these processes are not the focus of this current study.

contributor to the negative-affect-related motivational properties of drug withdrawal (Koob & LeMoal, 2001). Hyperactivation of the HPA-axis with increased cortisol secretion in humans and corticosterone in animals has been consistently observed during withdrawal from alcohol (e.g., Rasmussen et al., 2000) and opiates (e.g., Stine et al., 2002). Moreover, administration of a corticotrophin-releasing factor antagonist blocks the anxiety-like response observed during withdrawal from nicotine, alcohol, cocaine, and marijuana (Koob & LeMoal, 2001). Preliminary evidence also suggests that nicotine withdrawal in humans may affect HPA-axis regulation and cortisol levels, but these observations have been quite inconsistent (al'Absi, Amunrud, & Wittmers, 2002; al'Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003; Frederick, Reus, Ginsberg, Munoz, & Ellman, 1998; Pickworth, Baumann, Fant, Rothman, & Henningfield, 1996; Tsuda, Steptoe, West, Fieldman, & Kirschbaum, 1996). Cortisol levels during smoking and smoking deprivation predict withdrawal symptomatology (al'Absi, Hatsukami, & Davis, 2004; Cohen, Al'Absi, & Collins, 2004), but acute nicotine deprivation has been observed to increase, decrease, or not affect cortisol level across studies. However, none of these studies have involved significant affective challenge during the nicotine deprivation period. Thus, the present study measured nicotine withdrawal's effect on salivary cortisol in response to an affective challenge (threat of electric shock).

Sex Differences in Nicotine Dependence

Converging lines of evidence now suggest possible sex differences in affect-smoking relations (Perkins, Donny, & Caggiula, 1999). Importantly, women appear to have more difficulty quitting smoking than do men (Scharf & Shiffman, 2004; Wetter et al., 1999), and this difficulty may in part stem from differences in withdrawal-related negative affect. For example, women may be more likely than men to use smoking to cope with negative affect (Waldron, 1991). Negative affect may also be a stronger precipitant for smoking in women than men (Ikard & Tomkins, 1973). Nicotine's potentially negatively reinforcing properties may remain more salient for women than men even after cessation of use (Brandon & Baker, 1991; Wetter et al., 1999). Moreover, women appear to experience more problems with negative emotional states in general relative to men (Weissman, Bland, & Joyce, 1993). However, much research on affective processes related to smoking (including the research on the startle response and cortisol reviewed above) has used exclusively male samples, and when mixed sex samples have been available, formal tests for sex differences have frequently not been reported (Perkins, 1996). Given the available evidence, possible sex differences in the affective consequences of nicotine withdrawal were explicitly examined in the present study.

The Present Study

The present study was designed to examine physiological indicants of the negative affective concomitants of experimentally manipulated nicotine withdrawal during an explicit affective challenge. Specifically, affective response during an instructed fear conditioning paradigm involving threat of electric shock was examined in nicotine-deprived dependent smokers and nondeprived participants (nondeprived dependent smokers, nondependent/occasional smokers, and nonsmokers). The inclusion of occasional smoker and nonsmoker control groups (neither group will have recently smoked or be experiencing withdrawal) was critical to conclude that predicted affective differences between deprived and nondeprived dependent smokers could be unambiguously attributed to the nicotine withdrawal syndrome. Otherwise, results from restricted designs involving only deprived versus nondeprived dependent smokers could be caused by active smoking among the nondeprived smokers (Casa et al., 1998; Hughes, Higgins, & Hatsukami, 1990). This active smoking confound has not been consistently controlled in the nicotine withdrawal research reviewed above, and this failure is particularly troubling because active smoking has been documented to directly affect cortisol levels (Pomerleau & Pomerleau, 1990), and, in some contexts, negative affective response more generally (Kassel, Stroud, & Paronis, 2003). A multidimensional physiological assessment of affective response (including fear-potentiated startle during threat cue and recovery periods and salivary cortisol) was conducted to extend the limited support for negative affective concomitants of drug withdrawal from the self-report method available to date. Based on the preceding review, the following specific predictions were offered:

1. Nicotine-deprived dependent smokers will exhibit increased fear-potentiated startle to threat cues during the fear conditioning procedure relative to all three control groups (nondeprived, dependent smokers, occasional smokers, and nonsmokers). Two components of the fear-potentiated startle response (cue vs. recovery fear-potentiated startle) were assessed to examine both initial response intensity and the recovery of this fear response once the stressor was terminated, respectively.
2. Nicotine-deprived dependent smokers will exhibit increased salivary cortisol levels throughout the stressful fear conditioning procedure relative to all three control groups.
3. Given the available evidence indicating increased importance of and difficulty with negative affect associated with smoking in women, the above predicted nicotine withdrawal effects on fear-potentiated startle and salivary cortisol are expected to be greater in nicotine-deprived women than men.

Given the repeated confirmation of null effects in the existing literature, nicotine deprivation was not expected to alter overall startle response. However, to confirm these previous findings, analysis of overall startle response in the absence of threat cues was conducted.

Method

Participants

Eighty participants (39 female and 41 male) were recruited from the undergraduate psychology subject pool and the university community. Participants with uncorrected auditory or visual problems were excluded. The ethnic background of the participants reflected characteristics of the community. Potential subjects were screened to verify no history of adverse physical/medical reaction to nicotine use. Participants were admitted into the study based on their inclusion in one of three cigarette-use categories.

Dependent smokers. These participants reported smoking between 10 and 40 cigarettes per day, every day for at least the past year, had scores ≥ 3 on the Fagerstrom Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), and provided a carbon monoxide level of ≥ 10 ppm (obtained with a Bedfont piCO Breathalyzer) during an initial screening session. Dependent smokers were then randomly

assigned in equal numbers to one of two conditions during the screening session: *continuing (nondeprived) smokers* ($N = 20$; 10 male) or 24-h nicotine-deprived *withdrawn smokers* ($N = 20$; 11 male). Continuing smokers were asked to maintain their normal smoking pattern before the experimental session. Withdrawn smokers were asked to abstain completely from smoking for 24 h prior to the experimental session.

Occasional smokers ($N = 20$; 10 male). Occasional smokers reported smoking at least 12 cigarettes in their lifetime, with a minimum consumption of at least 1 cigarette per month over the past year. In addition, occasional smokers reported no current or past *regular* cigarette consumption (defined as average frequency of consumption in excess of 3 days per week for at least a 1 month period). Occasional smokers reported no current use of other tobacco products (e.g., smokeless tobacco, nicotine replacement systems). Finally, occasional smokers had to provide a maximum carbon monoxide level <10 ppm during the screening session.

Nonsmokers ($N = 20$; 10 male). Nonsmokers smoked less than five cigarettes in their lifetime, with no cigarette consumption in the last 6 months. They also reported no current use of other tobacco products (e.g., smokeless tobacco, nicotine replacement systems).

Procedure

Phone contact and screening session. During an initial phone contact, all participants provided information on smoking behavior and the Fagerstrom Test for Nicotine Dependence to verify eligibility for participation. Eligible participants were invited to attend a screening session during which informed consent was obtained, carbon monoxide level was assessed, and individual difference questionnaires were completed. As indicated above, dependent smokers were randomly assigned to withdrawn smoker and continuing smoker groups during this screening session.

Initial experimental session procedures. On arrival for the experimental session, carbon monoxide levels were assessed among all participants. Withdrawal compliance among withdrawn smokers was verified both by self-report and by measured carbon monoxide level (<10 ppm). Noncompliant withdrawn smokers were rescheduled. Participants in the continuing smoker group smoked a single cigarette to assure that they did not experience significant withdrawal during the experimental session. After this, all participants were escorted to the physiological session room and sensors were attached to measure the startle response (see Measures section below).

Shock sensitivity assessment. To control for individual differences in shock sensitivity, the intensity of shocks received during the experimental session was calibrated to participants' individual subjective shock sensitivity. Participants were administered a series of electric shocks of increasing intensity to the fingers of their left hand by a Farrall Mark300C electric shock stimulator that was modified to increase safety and allow for computer-controlled administration of a current range of 0 to 7 mA. Participants reported three intensity anchors: the first shock intensity they could detect, the first intensity that they considered uncomfortable, and the maximum intensity level that they could tolerate. The series was terminated when they reached their maximum intensity level. This assessment procedure was administered only once to minimize the number of shocks that participants received prior to the start of the actual experiment. Instructions strongly encouraged participants to provide accurate ratings and to tolerate the highest shock intensity possible. The shock intensity administered during the experimental session was calibrated to the midpoint intensity between their discomfort level and their maximum intensity level.

Instructed fear conditioning procedure. Participants completed two blocks of an instructed fear conditioning procedure, separated by a rest period that allowed for the collection of salivary cortisol and self-reported affect in response to each procedure (see Measures section).[2] During the procedure, participants viewed a series of colored square cues (50% blue and 50% yellow) presented on the computer monitor for 5 s each and separated by an average intertrial interval of 11 s (range 8–14 s). Participants were instructed that electric shocks would be administered during a subset of the CUE+ color squares (CUE+ color was constant across both procedures and counterbalanced across participants) and that no shocks would be administered during the other (CUE $-$) color or during the intertrial interval. Each block of the procedure began with four learning trials (two CUE+, two CUE– trials), in which both CUE+ trials were paired with electric shock. Participants then viewed an additional 60 trials (half CUE+), with electric shocks administered on 20% of CUE+ trials (six shocks). All shocks were administered at 4 s after CUE+ onset. Each block of the procedure lasted approximately 18 min.

Measures

Fear-potentiated startle. The eyeblink component of the startle reflex was elicited by an acoustic startle probe (50-ms 102-dB white noise with instantaneous rise time) and measured by recording activity over the orbicularis oculi muscle using miniature Ag-AgCl sensors filled with conductive gel and placed according to published guidelines (van Boxtel, Boelhouwer, & Bos, 1998). Startle probes were presented at 4 s after cue onset during the CUE+ and CUE $-$ trials to index fear-potentiated startle during the cue period (cue fear-potentiated startle) to assess initial negative affective response intensity. Additional startle probes were presented at 1, 3, and 5 s after cue offset to examine fear-potentiated startle during the recovery period after the threat of shock was terminated for that specific trial (recovery fear-potentiated startle). Startle probes were never presented on trials in which an electric shock was administered to avoid contamination of the startle response with movement and other noise artifact associated with reactions to the shock. It was expected that

[2]During the rest period between the first and second blocks of the procedure (approximately 55 min), withdrawn, continuing, and occasional smokers smoked one cigarette. This manipulation was included to test for nicotine effects on physiological indicants of negative affective response. However, preliminary analyses indicated that Block did not produce a main effect or significantly interact with any other independent variables for any of our primary dependent measures. Moreover, separate analyses within each block confirmed that the pattern of results across smoking groups was comparable in both blocks of the experiment for all dependent measures (as indicated by the absence of any significant Block interactions). Therefore, Block was not included as a factor in final reported analyses. This absence of a significant effect of smoking one cigarette is consistent with other research that has suggested that the administration of one cigarette is not sufficient to produce robust and detectable smoking effects in smokers (Mueller et al., 1998; Schuh & Stitzer, 1995).

affective response during this recovery period would be sensitive to emotion regulation effects. Six startle probes were presented within each condition, and a minimum of 15 s separated each probe presentation. Blink EMG activity was sampled (2000 Hz) with a bandpass filter (30 Hz high pass; 500 Hz low pass). Offline processing included signal rectification and smoothing (30 Hz low pass; 24 db/octave). Peak response (20–120 ms after probe onset) was scored relative to preprobe baseline. Fear-potentiated startle was indexed as the difference between CUE+ versus CUE − independently during cue and at 1, 3, and 5 s after cue offset recovery times within the procedure.

Salivary cortisol. Cortisol level was measured by obtaining saliva samples with Sarstedt salivettes from all participants at four times during the experimental session (immediately preceding and 25 min after each block of the procedure) to index HPA-axis activity in response to the anticipation and exposure to this "stressor" procedure. Samples were frozen at -80° until they were centrifuged and assayed using a ^{125}I radioimmunoassay at the Wisconsin Regional Primate Research Center Assay Services Unit. To control for diurnal variations in cortisol, all participants were asked to wake before 9:00 a.m. on the day of the experiment (verified via participant self-report on arrival at the laboratory), and every participant started the experimental procedure at 11:00 a.m. Female participants were included regardless of their oral contraceptive use. Women who were not using oral contraceptives were scheduled for the experimental session only during the follicular phase of their menstrual cycle. This choice was specifically designed to reduce variability associated with contraception use and menstrual cycle among women in the study. Specifically, Kirschbaum, Kudielka, Gaab, Schommer, and Hellhammer (1999) have observed that bioavailable, unbound (i.e., "free") cortisol response to a stressor measured via saliva samples varies as a function of both oral contraception use and menstrual cycle, with comparable response observed among women in their follicular phase and women using oral contraceptives. Kirschbaum et al. also noted that men displayed greater salivary cortisol response than women using oral contraceptives or during their follicular phase. Therefore, elevated salivary cortisol levels among male participants across all smoking groups were expected. Salivary cortisol data were missing for 1 man continuing smoker because his saliva sample volume was insufficient.

Self-reported affect and withdrawal. Self-reported positive and negative affect was measured with the Positive and Negative Affect Schedule (PANAS, 20-item version; Watson, Clark & Tellegen, 1988). As with the cortisol assessment described above, participants completed PANAS four times during the experimental session (immediately preceding and 25 min after each block of the procedure) to provide self-reported affect in response to the anticipation and exposure to the stressor procedure.

All participants completed the Wisconsin Smoking Withdrawal Scale (Welsch et al., 1999) immediately prior to the start of the procedure to document the success of the nicotine deprivation manipulation and to verify self-reported symptoms of withdrawal-related negative affect (consistent with the established self-report literature). The Wisconsin Smoking Withdrawal Scale is a 28-item scale that yields seven scales indicating the major self-reported affective and other components of the nicotine withdrawal syndrome (anger, anxiety, sadness, concentration, craving, sleep, and hunger). Previous research has confirmed that the individual scales are internally consistent (Cronbach's alphas range from .75 to .93), sensitive to smoking withdrawal, and predictive of smoking cessation outcomes (Welsch et al., 1999).

Results

Demographics and Smoking Behaviors

All individual differences (e.g., demographics, smoking behavior, and shock intensity thresholds) are presented by Smoking Group and Sex in Table 1. No significant Smoking Group, Sex, or interaction effects were observed for age. Screening session carbon monoxide levels were available for withdrawn and continuing dependent smokers and occasional smokers. As expected, a significant main effect of Smoking Group was observed, $F(2,54) = 43.96$, $p < .001$. Follow-up simple effects indicated that carbon monoxide levels were significantly lower in occasional smokers relative to withdrawn and continuing dependent smokers ($p < .001$), but not different between the two dependent smoker groups ($p = .783$ for withdrawn vs. continuing smoker contrast). No significant main effect or interaction involving Sex was observed for screening session carbon monoxide levels. Information on cigarettes per day, years of daily smoking, and Fagerstrom dependence scores were available for withdrawn and continuing smokers. No significant Smoking Group, Sex, or interaction effects were observed for these two measures among the two dependent smoker groups. No significant Smoking Group, Sex, or interaction effects were observed for the shock intensities administered during the experimental session based on the shock intensity assessment procedure.

Table 1. *Individual Differences by Smoking Group and Sex*

	Men				Women			
	Withdrawn smokers	Continuing smokers	Occasional smokers	Nonsmokers	Withdrawn smokers	Continuing smokers	Occasional smokers	Nonsmokers
Age (years)	24.4 (4.9)	22.5 (6.2)	20.2 (1.0)	21.5 (5.2)	21.2 (6.8)	23.2 (5.9)	23.4 (6.1)	21.2 (2.7)
Carbon monoxide (ppm)	18.6 (6.3)	21.3 (9.8)	2.0 (0.8)		18.6 (6.5)	19.3 (9.1)	2.5 (2.6)	
Cigarettes/day	20.8 (7.6)	17.3 (3.9)			20.5 (8.1)	20.2 (6.5)		
Fagerstrom Test of Nicotine Dependence	5.3 (2.4)	4.1 (1.8)			4.8 (2.0)	4.4 (1.9)		
Years smoking	6.7 (3.5)	6.3 (7.7)			7.1 (9.6)	7.1 (5.3)		
Shock intensity (mA)	3.7 (1.3)	4.1 (1.1)	4.5 (1.1)	4.7 (1.2)	3.9 (1.1)	4.4 (1.1)	3.9 (0.7)	3.9 (0.8)

Note: Mean (*SD*); carbon monoxide level during screening session measured in parts per million (ppm).

General Analytic Strategy

For all dependent measures, the Smoking Group effect was examined with planned orthogonal contrasts to maximize power to detect nicotine withdrawal effects. The Smoking Group planned orthogonal contrasts we used were: a *withdrawn smoker* contrast (withdrawn smokers vs. continuing, occasional, and nonsmokers), a *dependent smoker* contrast (continuing vs. occasional and nonsmokers), and an *occasional smoker* contrast (occasional vs. nonsmokers). This set of contrasts provided the most informative tests of the effects of withdrawal and dependence status. Specifically, the withdrawn smoker contrast directly compared withdrawn smokers to all other groups who were not experiencing nicotine withdrawal. Thus, examination of this contrast provided the primary tests of the effect of nicotine withdrawal on emotion processes. The clearest support for a withdrawal effect on dependent measures would be offered by a significant withdrawn smoker contrast combined with nonsignificant dependent and occasional smoker contrasts (i.e., comparable responding across continuing, occasional, and nonsmoker groups). However, these latter two contrasts also provided exploratory but potentially interesting tests of the effects of nicotine dependence (in the absence of withdrawal; dependent smoker contrast) and occasional smoking status (occasional smoker contrast) on emotion processes. Finally, focused withdrawn smoker versus continuing smoker simple effects are also reported when appropriate (when a significant overall withdrawal smoker contrast was detected).

Startle Response

Mean startle response for CUE+ and CUE − trials and fear-potentiated startle (startle response for CUE+ minus CUE −) during cue presentation and recovery periods (1–5 s after cue offset) are presented in Table 2.

Overall startle response magnitude. Overall startle response magnitude was analyzed with a two-way factorial ANOVA with Smoking Group Contrasts and Sex as between-subjects variables. A significant main effect of Sex was observed, with women displaying significantly larger startle response magnitude ($M = 124.6$, $SD = 94.0$) across all trials relative to men ($M = 77.5$, $SD = 68.1$), $F(1,72) = 6.18$, $p\eta^2 = .08$, $p = .015$. Most importantly, the critical withdrawn smoker contrast was not significant, $F(1,72) = 1.30$, $p\eta^2 = .02$, $p = .258$. A comparable analysis of overall startle response magnitude limited only to CUE − trials yielded a comparable pattern of results with a significant main effect of Sex, $p\eta^2 = .08$, $p = .014$, but no significant Withdrawn Smoker Contrast, $p\eta^2 = .02$, $p = .266$. No other effects were significant in either analysis.

Cue fear-potentiated startle. Fear-potentiated startle during cue presentation was examined to index effects on central nervous system instantiated initial negative affective response intensity. Cue fear-potentiated startle was analyzed within a two-way factorial ANOVA with Smoking Group Contrasts and Sex as between-subjects variables. No significant Smoking Group, Sex, or interaction effects were observed, indicating comparable negative affective response across smoking groups and sexes. Most importantly, the critical Withdrawn Smoker Contrast was not significant, $F(1,72) = 0.93$, $p\eta^2 = .01$, $p = .337$. A one-sample t test indicated that overall Cue fear-potentiated startle was significantly different from zero among all participants, $t(79) = 10.23$, $p < .001$, confirming that the shock threat manipulation did produce reliable potentiation of the startle reflex during shock cue presentation as expected (see Figure 1, black bar). No other significant effects were observed in these analyses.

Recovery fear-potentiated startle. Mean startle response for CUE+ and CUE − trials and fear-potentiated startle (startle response for CUE+ minus CUE −) during the recovery period are presented in Table 2. Fear-potentiated startle during the recovery period was examined to index effects on emotion regulation processes that affected the duration of affective response. Recovery fear-potentiated startle was analyzed within a mixed model ANCOVA with Smoking Group and Sex as between-subjects variables and Recovery Time (1 s vs. 3 s vs. 5 s) as a within-subject variable. Cue fear-potentiated startle was included as a covariate to control for individual differences in initial affective response to the cues. As expected, a significant main effect of Recovery Time was observed, $F(2,144) = 15.21$, $p\eta^2 = .17$, $p < .001$, with fear-potentiated startle linearly decreasing across the three recovery times (see Figure 1, gray bars). The Sex effect and the Dependent Smoker and Occasional Smoker Contrasts were not significant. However, the Withdrawn Smoker Contrast

Table 2. *Startle Response during CUE+, CUE −, and Fear-Potentiated Startle in Cue and Recovery Periods by Smoking Group and Sex*

	Men				Women			
	Withdrawn smokers	Continuing smokers	Occasional smokers	Nonsmokers	Withdrawn smokers	Continuing smokers	Occasional smokers	Nonsmokers
During cue presentation								
Fear-potentiated startle	51.4	54.6	48.8	44.3	50.5	84.7	70.3	83.0
	(36.6)	(50.3)	(21.2)	(35.3)	(36.6)	(66.6)	(63.0)	(67.0)
CUE+	120.2	114.6	101.7	112.8	181.8	159.6	173.3	177.4
	(110.3)	(85.5)	(57.6)	(111.7)	(106.3)	(97.1)	(98.4)	(139.5)
CUE −	68.8	60.0	52.9	68.6	131.3	74.9	102.9	94.4
	(69.6)	(42.9)	(42.8)	(83.1)	111.7	(56.1)	(79.6)	(88.0)
During recovery period								
Fear-potentiated startle,	6.7	6.3	5.3	7.1	22.1	8.6	3.3	12.9
recovery	(18.2)	(10.2)	(11.3)	(8.2)	(17.2)	(12.8)	(22.5)	(16.7)
CUE+ recovery	84.7	78.4	63.3	82.8	163.0	97.3	120.0	120.9
	(79.0)	(54.6)	(41.7)	(91.2)	(120.1)	(70.4)	(83.0)	(108.6)
CUE − recovery	78.0	72.0	58.0	75.7	141.8	88.7	116.7	108.0
	(83.9)	(52.7)	(46.8)	(87.1)	(115.2)	(69.9)	(85.1)	(104.6)

Note: Mean (*SD*); CUE+: cue paired with shock; CUE − : cue no paired with shock. Top section of table displays scores during the cue presentation (i.e., startle probes presented 4 s into a 5-s cue period. Bottom section displays scores during the recovery period (i.e., average to probes presented 1, 3, and 5 s after cue offset). The units for all scores are microvolts.

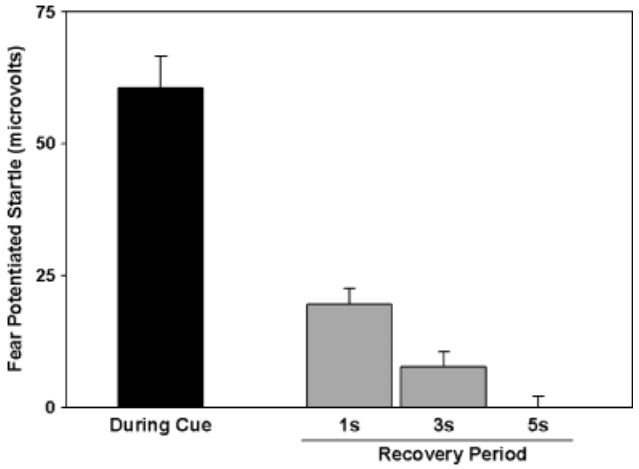

Figure 1. Fear potentiated startle during cue and recovery periods. Fear-potentiated startle is calculated as the difference between startle response magnitude during CUE+ minus CUE − . Mean fear-potentiated startle across Smoking Groups and Sex is displayed both during the cue period and at 1, 3, and 5 s into the postcue recovery period. Fear-potentiated startle means for recovery period are covariate adjusted for individual differences in fear-potentiated startle during cue presentation period. Error bars represent between-subjects standard errors.

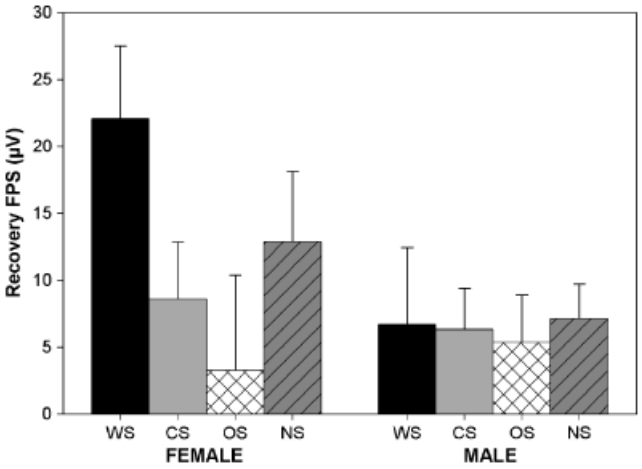

Figure 2. Recovery fear potentiated startle by smoking group and sex. Mean fear-potentiated startle for the three postcue offset probe times (1, 3, and 5 s postcue offset) is displayed. Means are covariate adjusted for individual differences in fear-potentiated startle during cue presentation period. WS: withdrawn smokers; CS: continuing smokers; OS: occasional smokers; NS: nonsmokers. Error bars represent between-subjects standard errors.

was significant, $F(1,72) = 4.53$, $p\eta^2 = .06$, $p = .037$, with greater overall fear-potentiated startle during the postcue recovery period in the withdrawn group relative to all other groups. Moreover, Sex moderated (interacted with) the magnitude of this Withdrawn Smoker Contrast, $F(1,72) = 4.23$, $p\eta^2 = .06$, $p = .043$ (see Figure 2).

To decompose this interaction, the Withdrawn Smoker Contrast was tested separately among men and women. A significant Withdrawn Smoker Contrast was observed among women, $F(1,35) = 6.80$, $p\eta^2 = .16$, $p = .013$. In contrast, the Withdrawn Smoker Contrast was not significant among men, $F(1,37) = 0.003$, $p\eta^2 = .00$, $p = .953$.[3] Finally, this pattern of simple effects is replicated if withdrawn smokers are compared only to continuing smokers (rather than all other smoking groups). Specifically, female withdrawn smokers displayed significantly greater fear-potentiated startle during the recovery period than female continuing smokers, $t(17) = 2.33$, $p = .032$. In contrast, no significant differences were observed for fear-potentiated startle during the recovery period between male withdrawn smokers and male continuing smokers, $t(19) = 0.09$, $p = .926$. No other significant effects were observed in these analyses.

Salivary Cortisol

Overall salivary cortisol level during the experiment was analyzed within a three-way factorial ANOVA with Smoking Group Contrasts and Sex as between-subjects variables and Assessment Time (1–4) as a within-subject variable. A trend level Withdrawn Smoker Contrast effect was observed, $F(1,71) = 3.42$, $p\eta^2 = .05$, $p = .068$, with higher cortisol levels in the withdrawn group relative to all other groups. However, consistent with above recovery fear-potentiated startle analyses, Sex significantly moderated the magnitude of this Withdrawn Smoker Contrast, $F(1,71) = 5.07$, $p\eta^2 = .07$, $p = .027$ (see Figure 3).

To decompose this interaction, the Withdrawn Smoker Contrast was tested separately among men and women. A significant Withdrawn Smoker Contrast was observed among women, $F(1,35) = 8.70$, $p\eta^2 = .20$, $p = .006$. In contrast, the Withdrawn Smoker Contrast was not significant among men, $F(1,36) = 0.08$, $p\eta^2 = .00$, $p = .781$. This pattern of simple effects is replicated if withdrawn smokers are compared only to continuing smokers. Specifically, female withdrawn smokers displayed significantly higher cortisol levels than female continuing smokers, $t(17) = 2.36$, $p = .031$. In contrast, no significant differences were observed for cortisol levels between male withdrawn smokers and male continuing smokers, $t(18) = 0.49$, $p = .630$. No other significant effects were observed in these analyses.

Supplemental Analyses of Self-Reported Withdrawal and Affect Measures

Self-reported withdrawal. The Wisconsin Smoking Withdrawal Scales was completed on arrival at the laboratory and yields seven individual scores that index the affective (anger, anxiety, sadness) and other components (craving, concentration, hunger, and sleep) of the nicotine withdrawal syndrome (see Table 3 for means and standard deviations by Smoking Group and Sex). Each of these scales was examined within a factorial ANOVA with Smoking Group Contrasts and Sex (male vs. female) as between-subjects variables. Significant Withdrawn Smoker Contrasts were observed on five of the seven scales, with withdrawn smokers reporting increased anger, anxiety, sadness, and craving, and decreased concentration relative to all other groups, Fs(1,72) = 6.94, 11.07, 8.06, 133.08, and 17.47, respectively; all ps $< .01$. Significant Dependent Smoker and Occasional Smoker Contrasts were also observed for the craving scale, with nondeprived dependent continuing smokers reporting more craving than occasional and nonsmokers, and occasional smokers reporting more craving than nonsmokers, Fs(1,72) = 50.10 and 17.11, respectively; both ps $< .001$.

[3]Comparable results are obtained for these contrasts if they are conducted without Cue fear-potentiated startle as a covariate. Specifically, the Withdrawn Smoker Contrast was significant among women, $p\eta^2 = .11$, $p = .041$), but not among men, $p\eta^2 = .00$, $p = .925$.

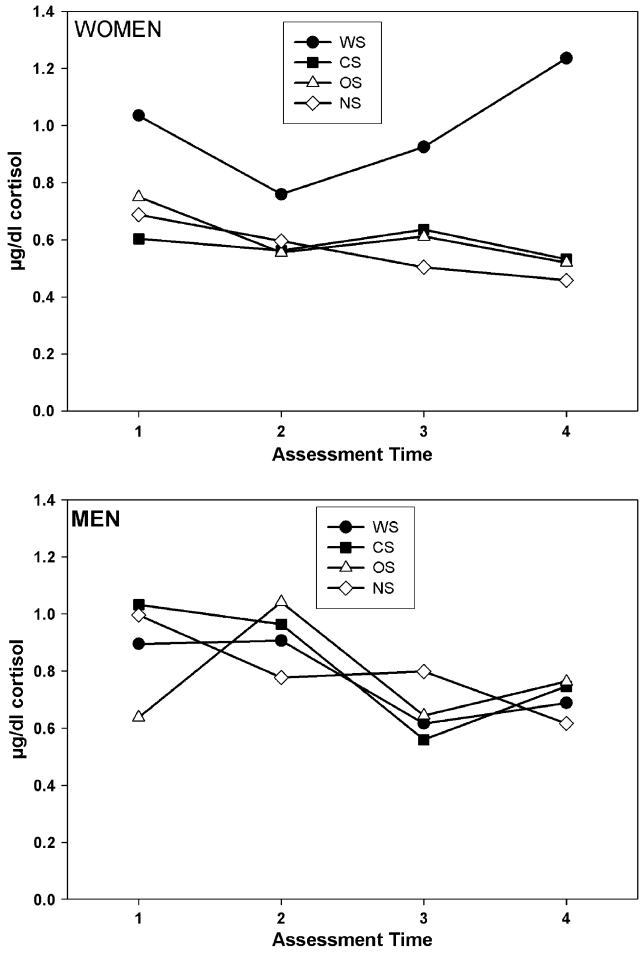

Figure 3. Salivary cortisol level by smoking group and time for women and men. WS: withdrawn smokers; CS: continuing smokers; OS: occasional smokers; NS: nonsmokers. Approximate time of assessments: Time 1, 11:30 a.m.; Time 2, 12:00 noon; Time 3, 1:00 p.m.; Time 4, 1:30 p.m. Fear conditioning procedures occurred between Time 1–2 and Time 3–4.

Main effects of Sex were observed for both the anger and anxiety scales, with women reporting overall increased anger and anxiety relative to men, Fs(1,72) = 8.76 and 9.58, respectively; both ps < .01. Moreover, Sex × Withdrawn Smoker Contrast interactions were observed for both anger and sleep, Fs(1,72) = 5.47 and 10.35, respectively; both ps < .05. Separate follow-up contrasts within Sex indicated that the Withdrawal Contrast was significant for both anger and sleep among women (increased anger and impaired sleep among withdrawn female smokers; ps < .05) but the Withdrawal Contrast was not significant for either scale among men. No other significant effects were observed from the analyses of the self-reported withdrawal scales.

PANAS self-reported affect. PANAS Negative Affect and Positive Affect scales were analyzed separately within three-way factorial ANOVAs with Smoking Group and Sex as between-subjects variables and Assessment Point (1–4) as a within-subject variable. For PANAS Negative Affect, there was a significant effect of Time, $F(3,216) = 34.79$, $p\eta^2 = .33$, $p < .001$, with negative affect increased at Time 2 ($M = 19.2$, $SD = 6.9$) relative to all other assessment points (Time 1: $M = 15.4$, $SD = 4.8$; Time 3: $M = 14.5$, $SD = 5.4$; Time 4: $M = 14.4$, $SD = 4.9$). More importantly, there was a significant Sex × Withdrawn Smoker × Time interaction, $F(3,216) = 4.40$, $p\eta^2 = .06$, $p = .005$.

To decompose this interaction, Smoking Group × Time analyses were conducted separately for men and women. A significant Withdrawn Smoker Contrast × Time interaction was observed for women, $F(3,105) = 3.93$, $p = .001$, but not for men. Follow-up simple Withdrawn Smoker Contrasts among women at each assessment time revealed that female withdrawn smokers reported significantly more negative affect at Time 1 (immediately prior to the start of the first procedure; $M = 19.1$, $SD = 5.7$) than females in all other smoking groups ($M = 14.5$, $SD = 3.5$), $F(1,35) = 8.75$, $p = .006$. The Withdrawn Smoker Contrast was not significant for women at any of the subsequent assessment points. Female withdrawn smokers also displayed descriptively elevated negative affect when compared to only female continuing smokers ($M = 15.33$, $SD = 4.1$), but this more focused contrast failed to reach conventional levels for significance, $t(17) = 1.64$, $p = .119$.

For PANAS Positive Affect, a significant effect of Sex was observed, $F(1,72) = 6.58$, $p\eta^2 = .08$, $p = .012$, with men reporting higher overall positive affect than women. A significant effect of Time was also observed, $F(3,216) = 12.27$, $p\eta^2 = .15$, $p < .001$, with reduced positive affect at Time 2 ($M = 23.8$, $SD = 7.8$) and Time 3 ($M = 22.8$, $SD = 7.7$) relative to Time 1 ($M = 25.9$, $SD = 7.5$) and Time 4 ($M = 24.2$, $SD = 7.9$). More importantly, there was a significant Withdrawn Smoker Contrast for positive affect, $F(1,72) = 5.72$, $p\eta^2 = .07$, $p = .019$, with lower positive affect among withdrawn smokers relative to the other smoking groups across all assessment times.

In addition, Sex significantly moderated the magnitude of the Withdrawn Smoker Contrast, $F(1,72) = 4.19$, $p\eta^2 = .06$,

Table 3. *Self-Reported Withdrawal Scales by Smoking Group and Sex*

	Men				Women			
	Withdrawn smokers	Continuing smokers	Occasional smokers	Nonsmokers	Withdrawn smokers	Continuing smokers	Occasional smokers	Nonsmokers
Anger	1.3 (1.1)	1.6 (1.0)	1.3 (1.1)	0.8 (0.8)	2.8 (0.5)	1.8 (0.9)	1.3 (0.8)	1.6 (1.2)
Anxiety	2.2 (0.8)	1.8 (0.9)	1.8 (0.5)	1.5 (0.7)	2.8 (0.6)	2.3 (0.7)	2.0 (0.6)	2.1 (0.8)
Sadness	1.4 (0.6)	1.4 (1.0)	0.9 (0.4)	0.7 (0.6)	1.9 (0.9)	1.3 (1.0)	1.0 (0.5)	1.3 (1.0)
Concentration	2.1 (1.0)	1.2 (0.6)	1.2 (0.6)	1.1 (0.8)	2.0 (0.8)	1.4 (0.9)	1.3 (0.7)	1.2 (0.6)
Craving	2.8 (1.2)	1.7 (0.6)	1.0 (0.7)	0 (0)	3.2 (0.7)	1.9 (0.7)	0.9 (0.8)	0 (0)
Sleep	1.2 (0.6)	1.7 (0.8)	1.9 (0.9)	1.3 (0.8)	2.3 (1.2)	1.7 (0.9)	1.3 (0.8)	1.1 (0.5)
Hunger	2.1 (1.1)	2.2 (0.6)	2.4 (0.8)	1.9 (0.6)	2.3 (1.1)	2.0 (0.7)	1.7 (0.8)	1.8 (0.6)

Note: Mean (*SD*); withdrawal scales are from the Wisconsin Smoking Withdrawal Scales. PANAS positive and negative scales are averaged across all four assessment times.

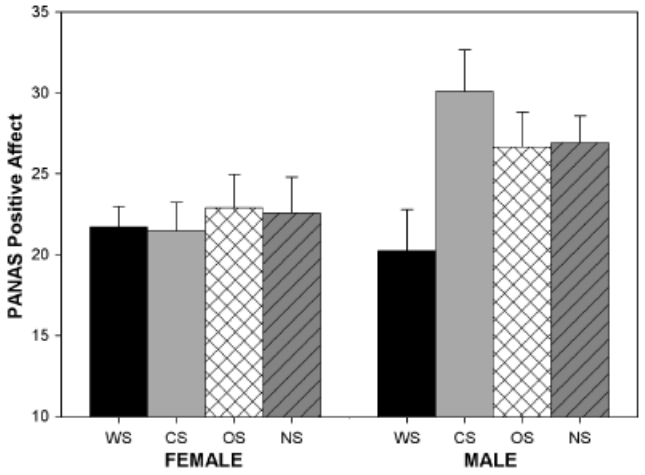

Figure 4. Positive and negative affect schedule (PANAS) positive affect by smoking group and sex. WS: withdrawn smokers; CS: continuing smokers; OS: occasional smokers; NS: nonsmokers. Error bars represent between-subjects standard errors.

$p = .044$ (see Figure 4). The Withdrawn Smoker Contrast was significant among men, $F(1,37) = 8.19$, $p\eta^2 = .18$, $p = .007$, but not women, $F(1,35) = 0.08$, $p\eta^2 = .00$, $p = .785$, indicating that male withdrawn smokers reported lower positive affect compared to the other male groups across all assessment times, with no differences in positive affect among female smoker groups. This pattern of simple effects is replicated if withdrawn smokers are compared only to continuing smokers. Specifically, male withdrawn smokers displayed significantly lower positive affect than male continuing smokers, $t(19) = 2.71$, $p = .014$. In contrast, no significant differences were observed for positive affect between female withdrawn smokers and female continuing smokers, $t(17) = 0.12$, $p = .905$.

Discussion

One central goal of this study was to use fear-potentiated startle to examine the effect of nicotine withdrawal on two constituents of central nervous system negative affective response: initial negative emotional response intensity and subsequent negative emotional response recovery. Fear-potentiated startle data indicated no effect of withdrawal on the magnitude of the initial response component of the stress response (fear-potentiated startle *during* the cue). In other words, while in the presence of the fear cue the abstinent participants displayed comparably intense initial negative emotional response relative to all other groups. Although we believe that this is the first examination of nicotine withdrawal on fear-potentiated startle in a fear conditioning paradigm, this null finding is consistent with other recent results reported by Geier and colleagues (2000) wherein nicotine withdrawal did not alter the modulation of the startle response measured *during* the presentation of affectively valent photographic stimuli. Such findings suggest that nicotine withdrawal does not alter the intensity of a smoker's initial negative affective response to an acute stressor.

However, nicotine withdrawal did impair recovery from the negative affective response to the stressor. Nicotine-deprived female smokers displayed increased fear-potentiated startle during the recovery period after the fear cue had been terminated. These differential nicotine withdrawal effects across initial emotional response intensity versus recovery highlight the importance of examining the time course of emotional response and the potential contribution that a constituent process approach can offer to clarify the affective problems experienced during withdrawal. It appears that when female smokers report increased negative affect during withdrawal, their self-report does not result from experiencing an exacerbated initial negative response to stressors in their environment. Instead, they may be reporting on disturbances in other constituents of their overall affective experience such as their ability to subsequently recover from or otherwise effectively regulate their negative affective response, or their ability to experience relief when no shock was administered during that particular CUE+ trial.

This fear-potentiated startle emotional recovery component may be particularly sensitive to emotion regulation processes. Numerous emotion theorists have highlighted the need to examine potentially separable processes related to initial emotional response versus the subsequent regulation of emotion (Davidson, 1998; Gross, 1999). Emotion regulation includes a broad array of automatic and volitional processes that are designed to enhance, suppress, or maintain the strength of an initial emotional response. Thus, deficient emotion regulation may likely underlie female smokers' delayed recovery with respect to fear-potentiated startle once the trial was complete and the stressor terminated. In fact, many theorists have argued that nicotine and other drug use is motivated primarily to regulate emotion (Baker et al., 2004). Current results suggest that nicotine use may be particularly important to overcome deficits in emotion regulation that occur during acute nicotine withdrawal, at least for women.

A second central goal of this study was to examine nicotine withdrawal effects on neuroendocrine stress response. The primary function of the HPA-axis is to regulate bodily systems to adaptively respond to stress (McEwen, 2000). The current results revealed significant withdrawal effects on HPA-axis function, which were also moderated by sex. Specifically, nicotine withdrawal heightened cortisol response to the stressor, but only among women. No withdrawal effect was observed for men. To date, a handful of other studies have examined nicotine withdrawal effects on cortisol to index HPA-axis stress response, but no consistent pattern of results has been observed (e.g., al'Absi et al., 2002, 2003; Frederick et al., 1998; Pickworth et al., 1996; Tsuda et al., 1996). However, this is not surprising given the diversity in methodologies and measurement approaches used. For example, many of these projects examined only basal cortisol levels in the absence of a stressor (al'Absi et al., 2002; Frederick et al., 1998; Pickworth et al., 1996) or phasic response to an, at best, mild stressor (e.g. visual matricies, Tsuda et al., 1996). Additionally, our data indicate that consideration of sex-related sample characteristics and procedures are critical. However, past studies have restricted the sample to male participants (Tsuda et al., 1996), not reported analysis of sex as a factor (al'Absi et al., 2003; Frederick et al., 1998; Pickworth et al., 1996), or not indicated any control for menstrual phase among women, which contributes significantly to variability in cortisol reactivity (Kirschbaum et al., 1999). This study therefore describes a first test of nicotine withdrawal's effect on cortisol response to a potent stressor that included critical controls for sex-related issues, with results indicating increased HPA-axis response during nicotine withdrawal for women.

Implications for Theories of Drug Dependence

Baker and his colleagues (2004) report that anxiety, irritability, depression, and dysphoria are common elements of the

withdrawal syndrome for all major drugs of abuse. Moreover, these and other researchers (e.g., Koob & LeMoal, 2001) suggest that this negative affect plays a critical role in understanding drug use motivation. However, to date, the majority of the evidence to document this increased negative affect during nicotine withdrawal in humans has relied on self-report methods. Current results substantiate, clarify, and limit these claims that were previously based primarily on self-report through the use of two additional measurement methods, fear-potentiated startle and salivary cortisol. Specifically, physiological results suggest that negative affect problems during nicotine withdrawal are characterized by deficits in the recovery from a stress, not the intensity of response to that stressor. Moreover, current results limit these claims about negative affect problems during withdrawal to female smokers, although obviously this result requires replication. Furthermore, these results more readily facilitate the search for the neurobiological mechanisms that can account for these negative affective symptoms during nicotine withdrawal.

Koob and LeMoal (2001) report evidence from animal models that negative affect is regulated through homeostatically balanced functional interactions of glucocorticoids (e.g., cortisol/corticosterone) and corticotropin-releasing factor in central (e.g., amygdala and bed nucleus of the stria terminalis) and HPA-axis stress systems. They argue that this exquisite balance is disrupted by adaptations of these stress systems to the allostatic load produced by chronic drug administration. As a result of these allostatic adaptations, significant negative affective symptoms are observed on cessation of drug use. Results from the indices of stress system activation in the current study complement Koob's thesis. Recovery fear-potentiated startle and salivary cortisol level measures suggest impaired function in both central and HPA-axis stress systems, respectively, during nicotine withdrawal in women. However, further research is necessary to determine if recovery fear-potentiated startle and cortisol effects represent two independent affective consequences of nicotine withdrawal. Alternatively, recovery fear-potentiated startle deficits may result from sensitization of the central stress system due to HPA-axis dysregulation in withdrawal. Conversely, prolonged central stress activation during withdrawal may have potentiated the HPA-axis stress response (Koob & LeMoal, 2001).

Koob and colleagues also suggest that hypofunctioning of the neurochemicals (dopamine, opioid peptides) involved in positive reinforcement contribute importantly to the motivational significance of drug withdrawal (Epping-Jordan, Watkins, Koob, & Markou, 1998; Koob & LeMoal, 2001). For example, these researchers have provided intriguing evidence to suggest an increase in brain reward thresholds in rats during nicotine withdrawal (Epping-Jordan et al., 1998). Though speculative, our PANAS self-report results are consistent with this if decreased positive reinforcement associated with increased reward threshold detrimentally affects positive affective experience. Withdrawn male smokers self-reported significantly lower positive affect on the PANAS than did men in all other conditions in this study. No group differences in positive affect were observed among women. Thus, in contrast to the increased negative affective symptoms observed among withdrawn women, men may instead experience decreased positive reinforcement from natural and conditioned reinforcers in their environment with coincident reduced positive affect during nicotine withdrawal.

Sex Differences

Important sex differences were noted for both central and neuroendocrine stress response and self-reported positive affect (and, to a lesser extent, self-reported negative affect). Of course, increased confidence in the reliability of these sex differences must await replication. However, these sex differences have already been foreshadowed in the existing literature on nicotine dependence in humans. For example, other research has suggested men appear to be more sensitive than women to the rewarding effects of nicotine (Perkins et al., 1999). Conversely, negative affect regulation appears to be a stronger motivation for women's nicotine use (Ikard & Tomkins, 1973; Waldron, 1991). Moreover, preliminary evidence suggests that some pharmacological treatments for mood and anxiety disorders may be more effective for smoking cessation for women than men (e.g., Clonidine: Hughes, 1993; Bupropion: Perkins et al., 1999; but see Scharf & Shiffman, 2004).

Interestingly, basic research has indicated sex differences in the distribution of glucocorticoid receptors (GRs) in the brain, with a greater number of GRs observed in the brains of female rats (Karandrea, Kittas, & Kitraki, 2000). This observation, combined with the sex differences in withdrawal's effect on salivary cortisol (a primary glucocorticoid) reported here, points to one potential mechanism to account for sex differences in nicotine's motivational properties. Regardless, development of better treatment and prevention strategies require greater understanding of the critical mechanisms underlying nicotine dependence (Shiffman, 1993). Continued use of measures and paradigms that serve to bridge basic animal and human research on nicotine dependence will likely advance research toward this important clinical goal.

Limitations and Future Directions

Limitations of the current study point to important next steps for systematic research. As discussed previously, nicotine withdrawal significantly reduced self-reported positive affect among men. However, in contrast to the physiological measures of negative affect, PANAS self-report cannot effectively parse the dynamic positive affective response into distinct constituents across the time course (e.g., initial emotional response intensity vs. emotional recovery). Therefore it is unclear what components of emotion contribute to this self-reported decrement in positive affect for withdrawn men. Future research could take advantage of the temporal specificity of emotion modulated startle to facilitate the identification of these components within the on-going positive emotional response. Specifically, the use of startle methodology in conjunction with direct manipulations of positive affect could more effectively assess withdrawal effects on the components of positive affective response.

Another limitation of the self-report positive affect results is its relatively distal relationship to the neurobiological systems underlying positive affective response. For negative affect, results from fear-potentiated startle and salivary cortisol measures suggested withdrawal effects on both central nervous system and neuroendocrine stress response. Future research should include measures that are more proximal to the brain systems involved in positive affect to further understanding of nicotine withdrawal's effect at this level of analysis. Due to recent advances in affective neuroscience, more central indices of positive affect are now available (e.g., anterior EEG asymmetry, fMRI). In fact, initial evidence suggests that anterior EEG asymmetry may be sensitive to changes in activity in prefrontal brain areas associated with

approach motivation during nicotine withdrawal (Zinser, Fiore, Davidson, & Baker, 1999). Human neuroimaging research can provide even more direct examination of the neural systems affected by withdrawal, but to our knowledge, no such research has been published to date.

Consideration of the duration and nature of the stressor may also be important. The stressor presented in this experiment involved a punctate stimulus intended to elicit an acute stress response. Though quitting smokers may encounter similarly brief, intense stressors, much of the evidence points toward more chronic and longer-lasting periods of stress leading to cessation failures (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996). Therefore, the acute stressor manipulation employed in this study represents only one point along the full spectrum of stressors a quitting smoker may experience. That said, withdrawal-related regulatory failures appear to have prolonged our female participants' experience of the punctate stressor. Therefore, distinctions between acute and chronic stress may be blurred and perhaps less meaningful among smokers in withdrawal.

Conclusions about the results involving salivary cortisol must remain somewhat speculative. The contrast of study results with previous research suggests that an important difference in the current methods was the inclusion of a stressor challenge. As noted earlier, none of the previous studies on nicotine withdrawal have measured salivary cortisol during a significant affective challenge. However, we are not able to unambiguously conclude that female withdrawn smokers displayed increased salivary cortisol response to the stressor because of the absence of a true no-stress condition (i.e., all measurements were collected after informing participants about the impending electric shocks). Future studies will need to measure cortisol across multiple days and/or prior to informing participants about the nature of the stressor they will be exposed to.

Consideration of the duration of the withdrawal period may be important. Withdrawn participants in this study were abstinent for 24 h prior to the experimental session. Research has shown that the first 24 h of a quit attempt may be a critical period, as relapse frequently occurs during the first day postcessation (Westman, Behm, Simel, & Rose, 1997). However, recent studies also have indicated that withdrawal may be a lengthy and dynamic process that lasts for days or even weeks beyond the quit date (Piasecki, Fiore, & Baker, 1998; Piasecki, Jorenby, Smith, Fiore, & Baker, 2003). For example, Gilbert et al. (1999) found that some physiological effects of smoking withdrawal failed to resolve after 31 days of abstinence. Piasecki and colleagues (2003) have shown that quitting smokers with more severe and long-lasting withdrawal profiles are at increased risk for relapse. Therefore, future laboratory studies might use the current methodology to examine withdrawal effects on emotion over an extended time course to compare effects across acute and protracted withdrawal periods. Future research also could have withdrawn smokers smoke denicotinized cigarettes to confirm that the effects observed among our withdrawn smokers are indeed due specifically to nicotine deprivation rather than more general cessation of smoking behavior.

As discussed earlier, withdrawal effects on negative affect during the recovery period suggested overall deficits in emotion regulation during nicotine withdrawal. Research has suggested that homeostatic regulatory processes may aid an organism in maintaining balance within affect systems much like other homeostatic processes control body temperature within an adaptive range (Solomon & Corbit, 1974). In contrast to these more automatic homeostatic regulatory processes, individuals are also able to regulate their emotions volitionally. However, volitional regulation may involve different neurobiological systems and processes than automatic regulation. Although it is difficult to establish definitively in this study, the time course of the observed recovery effects and the nature of the affect manipulation in general (repeated short stressor presentations) suggest that the fear-potentiated startle recovery effects index automatic/homeostatic regulatory processes. Future systematic attention to this potential important distinction between automatic and voluntary emotion regulation may clarify the mechanisms that account for withdrawal effects on emotion. In fact, methods have been developed to systematically manipulate volitional regulation through instruction (Jackson, Malmstadt, Larson, & Davidson, 2000) and preliminary evidence suggests that volitional emotion regulation is not impaired during nicotine withdrawal (Piper & Curtin, 2006). More generally, future research on affective processes in addiction will benefit from careful attention to the rapid conceptual and methodological advances that are occurring in the basic affective sciences.

REFERENCES

al'Absi, M., Amunrud, T., & Wittmers, L. E. (2002). Psychophysiological effects of nicotine abstinence and behavioral challenges in habitual smokers. *Pharmacology, Biochemistry and Behavior*, *72*, 707–716.

al'Absi, M., Hatsukami, D., & Davis, G. L. (2004). Prospective examination of effects of smoking abstinence on cortisol and withdrawal symptoms as predictors of early smoking relapse. *Drug & Alcohol Dependence*, *73*, 267–278.

al'Absi, M., Wittmers, L. E., Erickson, J., Hatsukami, D., & Crouse, B. (2003). Attenuated adrenocortical and blood pressure responses to psychological stress in ad libitum and abstinent smokers. *Pharmacology, Biochemistry and Behavior*, *74*, 401–410.

Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R., & Fiore, M. C. (2004). Addiction motivation reformulated: An affective processing model of negative reinforcement. *Psychology Review*, *111*, 33–51.

Borowski, T. B., & Kokkinidis, L. (1994). Cocaine preexposure sensitizes conditioned fear in a potentiated acoustic startle paradigm. *Pharmacology, Biochemistry & Behavior*, *49*, 935–942.

Brandon, T. H., & Baker, T. B. (1991). The Smoking Consequences Questionnaire: The subjective expected utility of smoking in college students. *Psychological Assessment*, *3*, 484–491.

Brandon, T. H., Juliano, L. M., & Copeland, A. L. (1999). Expectancies for tobacco smoking. In I. Kirsch (Ed.), *How expectancies shape experience* (pp. 263–299). Washington, DC: American Psychological Association.

Brandon, T. H., Tiffany, S. T., Obremski, K. M., & Baker, T. B. (1990). Postcessation cigarette use: The process of relapse. *Addictive Behaviors*, *15*, 105–114.

Cacioppo, J. T. (2000). Autonomic, neuroendocrine, and immune responses to psychological stress. *Psychologische Beitrage*, *42*, 4–23.

Casa, V. D., Hofer, I., Weiner, I., & Feldon, J. (1998). The effects of smoking on acoustic prepulse inhibition in healthy men and women. *Psychopharmacology*, *137*, 362–368.

Cohen, L. M., Al'Absi, M., & Collins, F. L. (2004). Salivary cortisol concentrations are associated with acute nicotine withdrawal. *Addictive Behaviors*, *29*, 1673–1678.

Curtin, J. J., Patrick, C. J., Lang, A. R., Cacioppo, J. T., & Birbaume, N. (2001). Alcohol affects emotion through cognition. *Psychological Science*, *12*, 527–531.

Davidson, R. J. (1998). Affective style and affective disorders: Perspectives from affective neuroscience. *Cognition and Emotion*, *12*, 307–330.

Davis, M., Walker, D. L., & Lee, Y. (1999). Neurophysiology and neuropharmacology of startle and its affective modification. In M. Dawson, A. Schell, & M. Bohmelt (Eds.), *Startle modification: Implications for neuroscience, cognitive science, and clinical science* (pp. 95–113). Cambridge: Cambridge University Press.

Duncan, E., Madonick, S., Chakravorty, S., Parwani, A., Szilagyi, S., Efferen, T., et al. (2001). Effects of smoking on acoustic startle and prepulse inhibition in humans. *Psychopharmacology*, *156*, 266–272.

Efferen, T. R., Duncan, R. J., Szilagyi, S., Chakravorty, S., Adams, J. U., Gonzenbach, S., et al. (2000). Diminished acoustic startle in chronic cocaine users. *Neuropsychopharmacology*, *22*, 89–96.

Epping-Jordan, M. P., Watkins, S. S., Koob, G. F., & Markou, A. (1998). Dramatic decreases in brain reward function during nicotine withdrawal. *Nature*, *393*, 76–79.

Fendt, M., & Mucha, R. (2001). Anxiogenic-like effects of opiate withdrawal seen in the fear potentiated startle test, an interdisciplinary probe for drug related motivational states. *Psychopharmacology*, *155*, 242–250.

Flaten, M. A., & Elden, A. (1999). Caffeine and prepulse inhibition of the acoustic startle reflex. *Psychopharmacology*, *147*, 322–330.

Frederick, S. L., Reus, V. I., Ginsberg, D., Hall, S. M., Munoz R, . F., & Ellman, G. (1998). Cortisol and response to dexamethasone as predictors of withdrawal distress and abstinence success in smokers. *Biological Psychiatry*, *43*, 525–530.

Geier, A., Mucha, R. F., & Pauli, P. (2000). Appetitive nature of drug cues confirmed with physiological measures in a model using pictures of smoking. *Psychopharmacology*, *150*, 283–291.

Gilbert, D. G., McClernon, F. J., Rabinovich, N. E., Dibb, W. D., Plath, L. C., Hiyane, S., et al. (1999). EEG, physiology, and task-related mood fail to resolve across 31 days of smoking abstinence: Relations to depressive traits, nicotine exposure, and dependence. *Experimental and Clinical Psychopharmacology*, *7*, 427–443.

Gordon, M. K., & Rosen, J. B. (1999). Lasting effects of repeated cocaine administration on acoustic and fear-potentiated startle in rats. *Psychopharmacology*, *144*, 1–7.

Gross, J. J. (1999). Emotion regulation: Past, present, future. *Cognition & Emotion*, *13*, 551–573.

Harris, A. C., & Gewirtz, J. C. (2004). Elevated startle during withdrawal from acute morphine: A model of opiate withdrawal and anxiety. *Psychopharmacology*, *171*, 140–147.

Harris, A. C., Hanes, S. L., & Gewirtz, J. C. (2004). Potentiated startle and hyperalgesia during withdrawal from acute morphine: Effects of multiple opiate exposures. *Psychopharmacology*, *176*, 266–273.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction*, *86*, 1119–1127.

Helton, D. R., Modlin, D. L., Tizzano, J. P., & Rasmussen, K. (1993). Nicotine withdrawal: A behavioral assessment using schedule controlled responding, locomotor activity, and sensorimotor reactivity. *Psychopharmacology*, *113*, 205–210.

Hughes, J. R. (1993). Pharmacotherapy for smoking cessation: Unvalidated assumptions, anomalies, and suggestions for future research. *Journal of Consulting and Clinical Psychology*, *61*, 751–760.

Hughes, J. R., Higgins, S. T., & Hatsukami, D. (1990). Effects of abstinence from tobacco: A critical review. In L. T. Kozlowski, H. M. Annis, H. D. Cappell, F. B. Glaser, M. S. Goodstadt, Y. Israel, & H. Kalant, et al. (Eds.), *Research advances in alcohol and drug problems* (*Vol. 10*, pp. 317–398). New York: Plenum Press.

Ikard, F. F., & Tomkins, S. (1973). The experience of affect as a determinant of smoking behavior: A series of validity studies. *Journal of Abnormal Psychology*, *81*, 172–181.

Isoardi, N. A., Martijena, I. D., Carrer, H. F., & Molina, V. A. (2004). Increased fear learning coincides with neuronal dysinhibition and facilitated LTP in the basolateral amygdala following benzodiazepine withdrawal in rats. *Neuropsychopharmacology*, *29*, 1852–1864.

Jackson, D. C., Malmstadt, J. R., Larson, C. L., & Davidson, R. J. (2000). Suppression and enhancement of emotional responses to unpleasant pictures. *Psychophysiology*, *37*, 515–522.

Karandrea, D., Kittas, C., & Kitraki, E. (2000). Contribution of sex and cellular context in the regulation of brain corticosteroid receptors following restraint stress. *Neuroendocrinology*, *71*, 343–353.

Kassel, J. D., Stroud, L. R., & Paronis, C. A. (2003). Smoking, stress, and negative affect: Correlation, causation, and context across stages of smoking. *Psychological Bulletin*, *129*, 270–304.

Kelsey, J., & Arnold, S. (1994). Lesions of the dorsomedial amygdale, but not the nucleus accumbens, reduce the aversiveness of morphine withdrawal in rats. *Behavioral Neuroscience*, *108*, 1119–1127.

Kirschbaum, C., Kudielka, B. M., Gaab, J., Schommer, N. C., & Hellhammer, D. H. (1999). Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. *Psychosomatic Medicine*, *61*, 154–162.

Koob, G. F., & LeMoal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, *24*, 97–129.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention and the startle reflex. *Psychological Review*, *97*, 377–398.

LeDoux, J. (1996). *The emotional brain: The mysterious underpinnings of emotional life*. New York: Touchstone.

McEwen, B. S. (2000). The neurobiology of stress: From serendipity to clinical relevance. *Brain Research*, *886*, 172–189.

Miczek, K. A., & Vivian, J. A. (1993). Automatic quantification of withdrawal from 5-day diazepam in rates: Ultraconic distress vocalizations and hyperreflexia to acoustic startle stimuli. *Psychopharmacology*, *110*, 379–382.

Mueller, V., Mucha, R. F., & Pauli, P. (1998). Dependence on smoking and the acoustic startle response in healthy smokers. *Pharmacology, Biochemistry & Behavior*, *59*, 1031–1038.

Mutschler, N. H., & Miczek, K. A. (1998). Withdrawal from IV cocaine binges in rats: Ultrasonic distress calls and startle. *Psychopharmacology*, *135*, 161–168.

Patton, D., Barnes, G. E., & Murray, R. P. (1997). A personality typology of smokers. *Addictive Behaviors*, *22*, 269–273.

Perkins, K. A. (1996). Sex differences in nicotine versus nonnicotine reinforcement as determinants of tobacco smoking. *Experimental and Clinical Psychopharmacology*, *4*, 166–171.

Perkins, K. A., Donny, E., & Caggiula, A. R. (1999). Sex differences in nicotine effects and self-administration: Review of human and animal evidence. *Nicotine & Tobacco Research*, *1*, 301–315.

Piasecki, T. M., Fiore, M. C., & Baker, T. B. (1998). Profiles in discouragement: Two studies of variability in the time course of smoking withdrawal symptoms. *Journal of Abnormal Psychology*, *107*, 238–251.

Piasecki, T. M., Jorenby, D. E., Smith, S. S., Fiore, M. C., & Baker, T. B. (2003). Smoking withdrawal dynamics: I. Abstinence distress in lapsers and abstainers. *Journal of Abnormal Psychology*, *112*, 3–13.

Pickworth, W. B., Baumann, M. H., Fant, R. V., Rothman, R. B., & Henningfield, J. E. (1996). Endocrine responses during acute nicotine withdrawal. *Pharmacology, Biochemistry & Behavior*, *55*, 433–437.

Piper, M. E., & Curtin, J. J. (2006). Tobacco withdrawal and negative affect: An analysis of initial emotional response intensity and voluntary emotion regulation. *Journal of Abnormal Psychology*, *115*, 96–102.

Pomerleau, O. F., & Pomerleau, C. S. (1990). Cortisol response to a psychological stressor and/or nicotine. *Pharmacology, Biochemistry & Behavior*, *36*, 211–213.

Postma, P., Kumari, V., Sharma, T., Hines, M., & Gray, J. A. (2001). Startle response during smoking and 24 h after withdrawal predicts successful smoking cessation. *Psychopharmacology*, *156*, 360–367.

Rasmussen, D. D., Boldt, B. M., Bryant, C. A., Mitton, D. R., Larsen, S. A., & Wilkinson, C. W. (2000). Chronic daily ethanol and withdrawal: 1. Long-term changes in the hypothalamo-pituitary-adrenal axis. *Alcoholism: Clinical & Experimental Research*, *24*, 1836–1849.

Rasmussen, K., Czachura, J. F., Kallman, M. J., & Helton, D. R. (1996). The CCK-B antagonist LY288513 blocks the effects of nicotine withdrawal on auditory startle. *NeuroReport*, *7*, 1050–1052.

Rasmussen, K., Helton, D. R., Berger, J. E., & Scearce, E. (1993). The CCK-B antagonist LY288513 blocks the effects of diazepam withdrawal on auditory startle. *NeuroReport*, *5*, 154–156.

Rassnick, S., Koob, G. F., & Geyer, M. A. (1992). Responding to acoustic startle during chronic ethanol intoxication and withdrawal. *Psychopharmacology*, *106*, 351–358.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Review*, *18*, 247–291.

Scharf, D., & Shiffman, S. (2004). Are there gender differences in smoking cessation, with and without bupropion? Pooled- and meta-analyses of clinical trials of Bupropion SR. *Addiction*, *99*, 1462–1469.

Schuh, K. J., & Stitzer, M. L. (1995). Desire to smoke during spaced smoking intervals. *Psychopharmacology*, *120*, 289–295.

Shiffman, S. (1993). Smoking cessation treatment: Any progress? *Journal of Consulting and Clinical Psychology*, *61*, 718–722.

Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. A., & Hickcox, M. (1996). First lapses to smoking: Within-subjects analysis of real-time reports. *Journal of Consulting & Clinical Psychology*, *64*, 366–379.

Solomon, R. L., & Corbit, J. D. (1974). An opponent-process theory of motivation: I. Temporal dynamics of affect. *Psychological Review*, *81*, 119–145.

Stewart, J., de Wit, H., & Eikelboom, R. (1984). Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychological Review*, *91*, 251–268.

Swerdlow, N. R., Eastvold, A., Gerbranda, T., Uyan, K. M., Hartman, P., Doan, Q., et al. (2000). Effects of caffeine on sensorimotor gating of the startle reflex in normal control subjects: Impact of caffeine intake and withdrawal. *Psychopharmacology*, *151*, 368–378.

Tsuda, A., Steptoe, A., West, R., Fieldman, G., & Kirschbaum, C. (1996). Cigarette smoking and psychophysiological stress responsiveness: Effects of recent smoking and temporary abstinence. *Psychopharmacology*, *126*, 226–233.

Tzavara, E. T., Monory, K., Hanoune, J., & Nomikos, G. G. (2002). Nicotine withdrawal syndrome: Behavioural distress and selective up-regulation of the cyclic AMP pathway in the amygdala. *European Journal of Neuroscience*, *16*, 149–153.

van Boxtel, A., Boelhouwer, A. J. W., & Bos, A. R. (1998). Optimal EMG signal bandwidth and interelectrode distance for the recording of acoustic, electrocutaneous and photic blink reflexes. *Psychophysiology*, *35*, 690–697.

van Erp, A. M. M., & Miczek, K. A. (2001). Persistent suppression of ethanol self-administration by brief social stress in rats and increased startle response as index of withdrawal. *Physiology & Behavior*, *73*, 301–311.

Voshaar, R. C. O., Jan Verkes, R., van Luijtelaar, G. L. J. M., Edelbroek, P. M., & Zitman, F. G. (2005). Effects of additional oxazepam in long-term users of oxazepam. *Journal of Clinical Psychopharmacology*, *25*, 42–50.

Waldron, I. (1991). Patterns and causes of gender differences in smoking. *Social Science Medicine*, *32*, 989–1005.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality & Social Psychology*, *54*, 1063–1070.

Weissman, M. M., Bland, R., & Joyce, P. R. (1993). Sex differences in rates of depression: Cross-national perspectives. *Journal of Affective Disorders*, *29*, 77–84.

Welsch, S. K., Smith, S. S., Wetter, D. W., Jorenby, D. E., Fiore, M. C., & Baker, T. B. (1999). Development and validation of the Wisconsin Smoking Withdrawal Scale. *Experimental and Clinical Psychopharmacology*, *7*, 354–361.

Westman, E. C., Behm, F. M., Simel, D. L., & Rose, J. E. (1997). Smoking behavior on the first day of a quit attempt predicts long-term abstinence. *Archives of Internal Medicine*, *157*, 335–340.

Wetter, D. W., Kensford, S. L., Smith, S. S., Fiore, M. C., Jorenby, D. E., & Baker, T. B. (1999). Gender differences in smoking cessation. *Journal of Consulting and Clinical Psychology*, *67*, 555–562.

Zinser, M. C., Baker, T. B., Sherman, J. E., & Cannon, D. S. (1992). Relation between self reported affect and drug urges and cravings in continuing and withdrawing smokers. *Journal of Abnormal Psychology*, *101*, 617–629.

Zinser, M. C., Fiore, M. C., Davidson, R. J., & Baker, T. B. (1999). Manipulating smoking motivation: Impact on an electrophysiological index of approach motivation. *Journal of Abnormal Psychology*, *108*, 240–254.

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