Published in final edited form as:

Exp Clin Psychopharmacol. 2010 April ; 18(2): 167–174. doi:10.1037/a0018864.

Subjective effects of transdermal nicotine among nonsmokers

Rebecca L. Ashare, M.A.,

University at Buffalo

Joseph S. Baschnagel, Ph.D., and

Rochester Institute of Technology

Larry W. Hawk Jr., Ph.D.

University at Buffalo

Abstract

The subjective experience of nicotine, which may be influenced by personality traits as well as environmental factors, may be important for understanding the factors associated with the initiation and maintenance of nicotine dependence. The present study examined the effects of 7 mg transdermal nicotine among a relatively large sample ($n=91$; 44 female) of college-aged nonsmokers. Using a placebo controlled, double-blind, within-subjects design, nicotine's effects were examined at rest and again after participants completed a sustained attention task. Sex and personality factors (Behavioral Inhibition and Behavioral Approach; BIS/BAS) were examined as potential moderators. Overall, the effects of nicotine were generally modest and unpleasant. In the context of the cognitive task, nicotine increased nausea and negative affect but reduced fatigue, relative to placebo. In contrast, effects of nicotine during the initial 4 hours of patch administration, in which participants were in their natural environments, were moderated by individual differences in behavioral approach. Neither behavioral inhibition nor gender reliably moderated any subjective effects of nicotine. The present work suggests transdermal nicotine exerts only modest, mostly negative effects among nonsmokers. Future work should examine both contextual and personality moderators in large samples of participants who are exposed to nicotine through multiple routes of administration.

Keywords

subjective effects; transdermal nicotine; nonsmokers; affect; smoking

The factors that contribute to nicotine reinforcement are important for understanding, preventing, and treating tobacco dependence. Though rats and humans self-administer nicotine (Harvey et al., 2004; Perkins, 1999; USDHHS, 1988), relative to other drugs of abuse, nicotine may be a weak primary reinforcer (Caggiula et al., 2002). Given the purported mood-enhancing effects of smoking and nicotine (see Kalman, 2002), these subjective effects may be an important aspect of nicotine reinforcement (e.g., Kalman & Smith, 2005; Perkins, 1998). Indeed, subjective effects have been related to initiation (Acosta, Eissenberg, Nichter, & Balster, 2008) and maintenance of smoking behavior (Kassel, Stroud, & Paronis, 2003).

Not surprisingly, most research on the subjective effects of nicotine focuses on smokers. In general, the effects of nicotine are dose-dependent, with lower doses rated more positively,

but higher doses resulting in negative effects (Kalman, 2002). Many smokers report that smoking alleviates negative affect associated with withdrawal and stress. However, evidence regarding the true mood enhancing effects of smoking is mixed (Conklin & Perkins, 2005). This may be due in part to difficulties interpreting smokers' responses. Specifically, although comparing deprived and non-deprived states has many strengths, it does not allow one to disentangle whether the effects of nicotine are due to genuine affect enhancement or to withdrawal relief (e.g., Kalman, 2002; Kassel et al., 2003).

To address this problem, researchers increasingly consider the effects of nicotine in nonsmokers, among whom withdrawal relief is eliminated as an alternative hypothesis (Kalman & Smith, 2005). Since the subjective effects of smoking cannot ethically be examined in nonsmokers, alternate routes of nicotine administration have been employed, including subcutaneous, intravenous, transdermal, nasal spray, and gum (for a review, see Kalman, 2002). Nasal nicotine has been used most frequently. Although the rapid onset of nasal nicotine nicely parallels that of smoking, it may also result in the generally aversive effects observed among nonsmokers (Perkins et al., 1993; Grobe et al., 1998).

Therefore, it is important to consider additional routes of administration to test the generalizability of the subjective effects of nicotine among nonsmokers. Slower routes of administration, such as transdermal nicotine, may be better tolerated among nonsmokers and its pharmacokinetic properties provide a relatively long (~5 hours) window of action (Benowitz, 1998). This may also mimic the steady state effects of nicotine, comparable to those experienced by smokers who regulate their nicotine levels throughout the day via smoking. Furthermore, this long window of action provides a way to examine the influence of context on the subjective experience of nicotine. To date, the subjective effects of transdermal nicotine have not been well characterized. Although one study found that transdermal nicotine enhanced self-reported vigor (Levin et al., 1998), others have found no significant effects of transdermal nicotine on mood in nonsmokers (Gillin, Lardon, Ruiz, Golshan, & Salin-Pascual, 1994; Jamner, Girdler, Shapiro, & Jarvik, 1998).

The relatively weak subjective effects observed among nonsmokers for nicotine in general, and transdermal nicotine in particular, may simply mean that nicotine has only subtle influences on mood and related constructs. Alternatively, there may be important moderators at work, including individual differences such as personality traits (Acosta et al., 2008; Jamner, Shapiro, & Jarvik, 1999; McCrae, Costa Jr, & Bosse, 1978; Terracciano & Costa, 2004) and sex (Perkins, Jacobs, Sanders, & Caggiula, 2002), as well as situational or contextual factors (Perkins, 1995, 1999). Gilbert's (1995) Situation $\times$ Trait Adaptive Response (STAR) model considers interactions among biological and cognitive processes, trait-specific characteristics such as personality, situational variables (e.g., exposure to stressful stimuli), and individual differences in nicotine sensitivity.

Broadly consistent with the STAR framework, individual differences in personality, including impulsivity, sensation-seeking, hostility, and neuroticism, appear to moderate the subjective effects of nicotine (Acton, 2003). For example, nonsmokers scoring higher on some aspects of sensation-seeking reported greater increases in pleasantness and vigor from nasal nicotine, which in turn predicted greater nicotine self-administration (Perkins, Gerlach, Broge, Grobe, & Wilson, 2000). More broadly, the Behavioral Inhibition and Behavioral Approach Scales (BIS/BAS; Carver & White, 1994) are thought to index sensitivity to aversive and appetitive motivation, respectively. Because constructs associated with BIS (e.g., neuroticism) and BAS (e.g., sensation-seeking) are related to smoking behavior and distinguish smokers and nonsmokers (Acton, 2003; Elkins et al., 2006; Gilbert, 1995), the present study examined whether individual differences in BIS and BAS moderate the subjective effects of nicotine among nonsmokers.

Beyond individual differences, the STAR model suggests that contextual factors play an important role in nicotine's effects (Gilbert, 1995). For example, nicotine may be most reinforcing when it normalizes mood (i.e., decreases stress or increases low arousal; Perkins, 1995; 1999). To further understand these processes, subjective effects were measured at rest and after participants completed a boring sustained attention task (the effects of nicotine on attention are the focus of a separate report; Baschnagel & Hawk, 2008). Although context is confounded with duration of patch administration, it provides at least preliminary information regarding subjective effects of nicotine under two different contexts.

The present study extends prior research examining the subjective effects of nicotine among nonsmokers in several important ways. Although a recent meta-analysis pooled a total sample of 102 nonsmokers, individual studies typically included fewer than 20 subjects (Kalman & Smith, 2005). The present work examines the subjective effects of transdermal nicotine among a relatively large sample of young adult nonsmokers ($N=91$), providing improved power to examine the subjective effects of nicotine. We considered the five domains derived from Perkins and colleagues (2003) – Head rush, Positive affect, Negative affect, Fatigued, and Energized – organized within the two-dimensional valence and arousal framework proposed by Kalman and Smith (2005; see also Lang, Bradley & Cuthbert, 1997; Watson & Tellegen, 1985).

We expected the subjective effects of transdermal nicotine to be modest and unpleasant (Hypothesis 1). Because women may be less sensitive to nicotine than men (Perkins, 1995), we hypothesized that men would report greater subjective effects than women (Hypothesis 2). Given the relationship between BAS and sensation-seeking and BIS and negative emotionality, we hypothesized that participants higher in behavioral approach would endorse more positive effects of nicotine (Hypothesis 3a), whereas those higher in behavioral inhibition would endorse more negative subjective effects (Hypothesis 3b). Finally, based on the STAR model, we hypothesized that the subjective effects of nicotine would be influenced by context such that more positive effects would be observed following the boring vigilance task, relative to the pre-task rest period (Hypothesis 4).

Methods

Participants

Participants were 91 young adult nonsmokers (44 female). As in prior work on subjective effects in nonsmokers (see Kalman & Smith, 2005), participants denied any use of nicotine in the past year, but reported modest prior exposure (i.e., at least 1 puff, but less than 100 cigarettes lifetime; Center for Disease Control, 2002). Participants earned course credit towards a research requirement in Introductory Psychology. Additional participants (not included in the 91) withdrew due to nausea when wearing the nicotine patch ($n=3$), attended only the first of the two experimental sessions ($n=13$), or were excluded due to incomplete self-report data ($n=4$). Males tended to be older than females, mean age (SD) = 19.5(2.3) vs. 18.6(.8), $F(1,88) = 5.5$, $p < .05$, but there were no significant differences in race/ethnicity between males and females, $p > .2$. The majority of participants were Caucasian, non-Hispanic (70%) and the remainder identified as Asian (10%), African-American (8%), Hispanic (6%), or Middle Eastern (2%), or refused to provide race/ethnicity (5%).

Measures/Materials

Subjective effects—To assess the subjective effects of nicotine, participants completed a series of computerized visual analog scales (VAS) and a pair of standardized affect measures within MediaLab® (New York, NY) software. On each VAS, participants rated the degree to which they currently felt the descriptor on a scale from 0 (not at all) to 100

(extremely). This response format has been used widely in prior research (Perkins, Fonte, Sanders, Meeker, & Wilson, 2001; Perkins, Sanders, D'Amico, & Wilson, 1997). Specific items were drawn from factors described by Perkins et al. (2003): head rush (buzzed, head rush, lightheaded, jittery), positive affect (comfortable, relaxed, satisfied, pleasant), negative affect (anger, depression, tension), fatigue (tired, sedated), and energy (stimulated, vigor). Nausea, sometimes included as a component of positive affect (Perkins et al., 2003) was considered separately because it does not consistently load on any single factor (Kalman, 2002).

The 20-item Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988) measures two primary dimensions of affect: Positive Affect (PA; e.g., “interested,” “alert,” “enthusiastic”) and Negative Affect (NA; e.g., “afraid,” “upset”). The PANAS is sensitive to fluctuations in mood when “short-term” instructions (i.e., “How do you feel right now?”) are used and both scales have demonstrated high internal consistency ($\alpha=.87$ for PA and $\alpha=.84$ for NA; Watson, Clark, & Tellegen, 1988). Figure 1 depicts the organization of the VAS and PANAS measures along two general dimensions of emotion, valence (e.g., positive versus negative) and arousal (e.g., high versus low).

Personality—The Behavioral Inhibition Scale (BIS) and Behavioral Approach Scale (BAS) assess motivational systems that guide behavior and emotion (Carver & White, 1994). The BIS assesses sensitivity to cues for punishment or non-reward and is associated with the experience of anxiety. The BAS assesses sensitivity to cues for reward and non-punishment and is associated with subjective pleasure. Both scales have adequate internal consistency ($\alpha = .66$ to $.76$; Carver & White, 1994). Since BIS and BAS test-retest reliabilities were high, $r = .76$ and $.82$, respectively, BIS and BAS were averaged across the two sessions. Although males and females did not differ on average BAS scores, $F<1$, females had higher BIS scores than males (means[SDs] = 21 and 19 [2.6 and 2.9]), $F(1,89) = 11.1, p < .01$.

Nicotine Patches—Nicotine patches were Habitrol® 7-mg (Novartis, New Jersey, USA). This brand has a slow-rise nicotine transfer rate (Benowitz, 1993), with blood nicotine levels reaching about 50% of peak levels within 4 hours, which minimizes nausea relative to fast-rise nicotine patches (Gilbert, Rabinovich, & Rosenberger, 2003). Placebo patches were manufactured by SmithKline Beecham and purchased from 1-800-patches.com.

Procedures

Participants completed two experimental sessions, one week apart, and received either the nicotine patch or placebo patch during Session 1 and the alternate drug condition in Session 2. Patch order was counterbalanced across subjects. Subjective effects measures were completed three times: before patch application (pre-patch *baseline*), before the sustained attention task (4 hours post-patch; *pre-task*), and after the task (5 hours post-patch; *post-task*). Participants signed an informed consent during the first session and received a debriefing following completion of the second session. Sessions were otherwise identical except for the patch condition.

During the pre-patch baseline, BIS/BAS and subjective effects were assessed and the patch was then applied to the upper arm. Participants were informed of possible side effects, given emergency contact information, and instructed to return to the lab in 4 hours. To maintain the double-blind, different research assistants ran the baseline and task portions of the study.

When participants returned to the lab (pre-task), subjective effects were reassessed. Participants then completed a sustained attention task during which behavioral and psychophysiological responses were assessed. During the task, participants attended to tones

of one pitch, responding to occasional longer-duration targets (i.e., 8 s tones vs 5 s), and could ignore tones of the other pitch¹. Tones were separated by inter-trial intervals (average = 30 s), during which participants simply sat quietly. Intermittently, startling bursts of noise were presented over headphones. The effects of nicotine on attention and additional details about the attention task are the focus of a separate manuscript (Baschnagel & Hawk, 2008). Following the task, participants completed another set of subjective effects measures (post-task).

Data Analysis

Repeated measures ANCOVAs were conducted for measures in each of the four quadrants of affective space shown in Figure 1. Since High Arousal Negative and Positive Affect consisted of multiple correlated measures (details available from the authors), doubly-multivariate repeated measures ANCOVAs were conducted to protect against Type-I error (Tabachnick, Fidell, & Osterlind, 2001). Sex and patch order (nicotine first vs. placebo first) were between-subjects factors, and patch (nicotine vs. placebo) and time (pre-patch baseline, pre-task, post-task) were within-subjects factors. Based on the STAR model (Gilbert, 1997) and Perkins' (1995; 1999) findings suggesting the importance of context (i.e., at rest vs. task) on the subjective effects of nicotine, significant multivariate interactions were followed with pre-patch baseline vs. pre-task and pre-task vs. post-task contrasts. BIS and BAS were continuous between-subjects predictors (mean-centered within sex). Significant interactions involving BIS or BAS were probed to examine effects conditioned on High and Low BAS or BIS, defined as one standard deviation above and below the mean, respectively. All 2-way and 3-way interactions among between-subjects factors were eliminated from all models to conserve degrees of freedom, as we had no between $\times$ between hypotheses.

Results

High Arousal Negative Affect

There were no significant main effects of patch or sex across measures of high arousal negative affect, p s > .7. However, a significant increase in negative affect over time, p < .01, Patch $\times$ BAS interaction, p = .05 and a marginal Patch $\times$ Time interaction, p = .06, were qualified by a Patch $\times$ Time $\times$ BAS interaction, Wilks Lambda $F(6,340) = 2.2$, p < .05. Separate multivariate analyses were examined for each time contrast². There was a significant effect for the Patch $\times$ Baseline vs. Pre-task contrast $\times$ BAS Wilks Lambda $F(3,84) = 3.6$, p < .02, but not for the pre- vs. post-task contrast, p = .3. Contrary to Hypothesis 3a, follow-up tests for the baseline vs. pre-task contrast revealed that the interaction was significant for Low BAS individuals, $F(3,87) = 2.9$, p < .05, but not for High BAS individuals, p = .36. Univariate tests conditioned for Low BAS suggested that although headrush increased during both patch conditions, p s < .001 and .005 for nicotine and placebo, respectively, the increase tended to be greater for nicotine, Patch $\times$ Baseline vs. Pre-task contrast $F(1,89) = 2.9$, p = .09. Similarly, for Low BAS changes in VAS NA tended to be influenced by patch, Patch $\times$ Baseline vs. Pre-task contrast $F(1,89) = 3.3$, p = .07, with the baseline-to-pre-task decrease in VAS NA evident in placebo, p < .02, eliminated by nicotine, p = .18. The univariate Patch $\times$ Baseline vs. Pre-task interaction for PANAS NA

¹Approximately half the participants ($n = 43$) had the opportunity to earn a small monetary incentive (up to US\$5) for accurate task performance, while the remaining participants were simply asked to try their best. The purpose of this manipulation was to examine whether modest incentives moderated the effect of nicotine on attention. They did not. Participants received performance feedback and payment only at the end of the session, after completing all subjective effects, decreasing the likelihood that incentive group would moderate subjective effects. Indeed, exploratory analyses suggested incentive group was unrelated to the subjective effects of nicotine, and the incentive factor is not included in the primary analyses.

²With the exception of a marginal Patch $\times$ Time $\times$ BIS interaction for High Arousal Positive Affect, Wilks Lambda $F(4,344) = 2.3$, p = .06, that appeared to be a crossed interaction without reliable simple effects, there were no significant or marginally significant findings for BIS on any subjective effect. To conserve space, further results involving BIS are not reported here.

was not statistically significant, $p = .45$. Figure 2 depicts the pattern of means conditioned at high and low BAS.

Consistent with our hypothesis that context moderates the effects of nicotine (Hypothesis 4), follow-up tests for the Patch $\times$ Time interaction revealed a significant Patch $\times$ Pre- vs. Post-Task interaction, Wilks Lambda $F(3,84) = 3.0$, $p < .05$. This interaction was driven by PANAS NA, $F(1,86) = 6.3$, $p < .02$ such that the trend for PANAS negative affect to decrease from pre- to post-task during the placebo session, mean difference = .43, $p = .09$, tended to reverse during the nicotine condition, mean difference = .41, $p = .17$. The interactions for headrush and VAS NA were nonsignificant, $F_s < 1$ (see Figure 3).

Low Arousal Negative Affect

The main effect of time, $p < .01$, was qualified by a Patch $\times$ Time interaction, Wilks Lambda $F(2,84) = 3.5$, $p < .05$. As depicted in Figure 3, follow-up tests revealed that nicotine attenuated the increase in fatigue from pre- to post-task (mean difference = 13.8, SE = 2.4), relative to placebo (mean difference = 20.2, SE = 2.4), Patch $\times$ Pre- vs. Post-Task $F(1,85) = 6.3$, $p < .02$; Patch $\times$ Baseline vs. Pre-Task $F < 1$, suggesting that contextual factors may be moderating these effects. There were no other significant differences in self-reported fatigue, $p_s > .1$.

High Arousal Positive Affect

The main effects of patch and time were significant, $p_s < .05$, but they were qualified by a Patch $\times$ Time $\times$ BAS interaction, Wilks Lambda $F(4,342) = 3.2$, $p < .02^3$. As for high arousal negative affect, the baseline vs. pre-task contrast was significant, Patch $\times$ Baseline vs. Pre-Task $\times$ BAS Wilks Lambda $F(2,85) = 5.7$, $p < .01$, but the pre- vs. post-task contrast was not, $p = .36$ (see Figure 4). Simple effects tests revealed that among high BAS individuals nicotine prevented the modest changes in positive affect observed during the placebo condition, Patch $\times$ Baseline vs. Pre-task $F(2,88) = 3.1$, $p = .05$, but this effect was marginal for low BAS individuals, $p = .09$. Among high BAS individuals, univariate tests did not reach statistical significance, PANAS PA and energized $F_s(1,89) = 3.3$ and 2.7, $p_s = .07$ and .11, respectively. Contrary to Hypothesis 2a, among low BAS individuals, there was no effect on PANAS PA, $F < 1$, but nicotine increased energy relative to placebo, Patch $\times$ Baseline vs. Pre-Task $F(1,89) = 4.1$, $p < .05$.

Low Arousal Positive Affect

VAS PA decreased from baseline to pre-task, $F(1, 85) = 16.8$, $p < .01$ and from pre- to post-task, $F(1, 85) = 30.6$, $p < .01$, mean (S.E) baseline = 69.5 (1.3), pre-task = 65.0 (1.5), post-task = 57.3 (1.8); time Wilks Lambda $F(2,84) = 28.1$, $p < .01$. However, nicotine had no impact on VAS PA, $F_s < 1$. There were no other significant effects on VAS PA, all $p_s > .11$.

Nausea

Due to missing data, nausea data are only reported on 87 participants. The main effects of patch and time were not significant, $p_s > .08$. Consistent with the prediction that context matters (Hypothesis 4), nausea increased from pre- to post-task for nicotine (mean difference = 4.9, $p < .05$), but not placebo (mean difference = 0.9, $p = .65$), the Patch $\times$ Pre- vs. Post-Task $F(1,81) = 6.3$, $p < .02$ (see Figure 3). There were no other significant effects on nausea, $p_s > .2$.

³Though males reported higher positive affect than females in general, PANAS PA males mean (SE) = 28.5 (.91) females mean (SE) = 24.3 (.94); Energized males mean (SE) = 25.9 (2.3), females mean (SE) = 18.1 (2.4), multivariate $F(2,85) = 5.8$, $p < .01$, there was no evidence in support of the prediction that men experienced greater subjective effects of nicotine, $p_s > .1$.

Discussion

The subjective effects of nicotine, particularly in nonsmokers, are often measured in small samples without consideration of moderating variables. However, theoretical and empirical findings suggest that contextual and personality factors play an important moderating role (Gilbert, 1997; Perkins, 1999). These factors may represent vulnerability or resiliency factors related to the initiation of smoking (Perkins, Coddington et al., 2008; Pomerleau, Collins, Shiffman, & Pomerleau, 1993). The present study examined both types of moderators among a relatively large sample of nonsmokers. To examine personality, scores on the Behavioral Inhibition and Behavioral Approach Scales were assessed. To examine context, subjective effects were assessed after four hours of typical daily activities and again after a boring lab task.

Given that BAS and BIS represent sensitivity to appetitive and aversive motivation, respectively, we hypothesized that participants higher in behavioral approach would endorse more positive effects of nicotine, whereas those higher in behavioral inhibition would endorse more negative subjective effects. Moderation by BAS was repeatedly observed during the 4-hour baseline to pre-task period. However, contrary to our predictions, nicotine had little effect among high-BAS participants. Rather, among Low-BAS participants, nicotine resulted in a trend towards greater increases in headrush and energy, and a diminished drop in negative affect, compared to placebo. Looking back, the finding that lower BAS scores were associated with nicotine-related increases in self-reported energy is consistent with findings that nicotine may be most reinforcing when it normalizes mood (Perkins, 1999). Nevertheless, the unexpected findings for BAS, and generally null findings for behavioral inhibition (BIS), do not converge with our expectations derived from narrow dimensions such as sensation-seeking (Perkins et al., 2000) or relatively broad dimensions such as neuroticism or impulsivity (Gilbert, Meliska, Welser, & Estes, 1994; Netter, Hennig, Huwe, & Olbrich, 1998). Moreover, what is perhaps most noticeable about the present personality effects is the small differences between nicotine and placebo – typically less than 5 points on 40- (PANAS) to 100-point (VAS) scales.

The current findings offer greater support for the hypothesis that nicotine's effects are partially dependent on context (Gilbert, 1997; Perkins, 1999). That is, the subjective effects of nicotine, at least in the absence of personality moderators, were present only from the pre- to post-task period. In the context of this boring task, nicotine increased nausea and tended to disrupt the small decrease in negative affect (PANAS NA) observed during placebo. These findings support the prediction that the effects of nicotine are generally unpleasant among nonsmokers but suggest that this will be more or less true depending on the situation. Interestingly, nicotine did exert one somewhat positive effect during the pre-post task period; the stimulant prevented an increase in fatigue.

The finding that nicotine contributed to negative affect from pre- to post-task is consistent with previous work with nonsmokers (see Kalman & Smith, 2005). Furthermore, the finding that nicotine prevented an increase in fatigue is in line with evidence that transdermal nicotine enhanced vigor among nonsmokers during a sustained attention task (Levin et al., 1998). The findings of these two studies contrasts with the meta-analytic results (Kalman & Smith, 2005), perhaps because studies in the meta-analysis were generally conducted at rest.

It is interesting that none of these effects of nicotine was apparent after the first four hours of patch administration, when participants were not in the lab but were instead engaging in 'free-range' daily activities. Although this difference in subjective effects of nicotine may be due to the differences in context, we interpret the pattern tentatively because in the present study context was confounded with duration of patch application, and four hours would be

expected to produce only about 50% of peak blood levels of nicotine. Nevertheless, the present findings appear to be broadly consistent with findings from true experimental studies of context manipulations (Gilbert, Robinson, Chamberlin, & Spielberger, 1989; Perkins, 1999) and the STAR model (Gilbert, 1995) in suggesting that future studies should continue to examine both positive and negative contextual moderators. For example, previous evidence suggests that initial experiences with smoking often occur in a social context, which may contribute to the pleasurable effects of nicotine (Mayhew, Flay, & Mott, 2000).

Another possibility for the relatively weak effects observed in all aspects of the study is the route of administration. The slow rise time of transdermal nicotine may have limited noxious effects and reduced dropout rates and discomfort to participants, but it may also have limited the magnitude of the effects of nicotine. Furthermore, initial experiences with nicotine often occur in social contexts rather than in an isolated lab setting. Perhaps manipulating the context in which nicotine is administered (i.e., in social contexts) may more accurately mimic real world smoking experiences. Particular effects of nicotine may vary as a function of route of administration. Whereas effects such as headrush may be associated with a rapid rise in nicotine levels, as obtained with nicotine nasal spray, other effects such as moderation of stressful or boring contexts may be associated with longer-lasting effects of nicotine, such as those provided by transdermal nicotine. Future research would benefit from directly comparing the magnitude of effects and covariation between transdermal nicotine and nasal nicotine among nonsmokers.

One further important limitation of the current study is the nature of the sample. Like the vast majority of the literature (see, e.g., Kalman & Smith, 2005; Trosclair, Husten, Pederson, & Dhillon, 2002), we included nonsmokers who were not completely nicotine-naïve but met the CDC definition of nonsmokers (i.e., fewer than 100 cigarettes lifetime). Pomerleau and colleagues (1998; 2009) have postulated several hypotheses to explain why some individuals who try smoking do not take up the behavior. For example, some individuals may experience an initial sensitivity to the aversive effects of nicotine which may be recalled later during subsequent exposure to nicotine (Perkins, Lerman, Coddington, & Karelitz, 2008). Others, including non-dependent smokers, may simply not experience sufficient reinforcement from nicotine to continue smoking (Perkins, Grottenthaler, & Wilson, 2009). Thus, it may be that the mild, mostly unpleasant effects of nicotine observed in non-naïve nonsmokers represent a type of protective factor, which contributed to discontinuation of smoking after modest exposure.

The potential differences between fully naïve and non-naïve nonsmokers may never be studied, given ethical concerns about giving initial dose(s) of nicotine in the laboratory. That said, the literature on subjective effects among non-naïve nonsmokers addresses a large and important population. Recent epidemiological surveys suggest that approximately 60% of 16–17 year olds report ever having smoked a cigarette (Fryar, Merino, Hirsch, & Porter, 2009), but only a small portion, approximately 8%, will go on to develop daily smoking behavior (Eaton et al., 2008). Thus, even if the results from the present study and the rest of the subjective effects literature do not generalize to completely nicotine-naïve individuals (and that is an unanswered question), the findings from the current sample and the broader subjective effects literature would still apply to a large portion of the young adult population in the United States.

In summary, the present study found evidence of modest effects of transdermal nicotine among a relatively large sample of young adult nonsmokers. In the context of a boring cognitive task, nicotine increased nausea and negative affect but reduced fatigue, relative to placebo, and these effects were not reliably influenced by personality. During the initial 4 hours of patch administration in which participants were in their natural environments

between assessments, effects of nicotine on positive and negative emotion were small and, when observed, were always moderated by individual differences in behavioral approach. The present study calls for future work on subjective effects to examine both contextual and personality moderators in large samples of smokers and nonsmokers who are exposed to nicotine through multiple routes of administration and tested for actual nicotine reinforcement (Perkins et al., 2009). Though such work will be challenging, it is critical for elucidating the role of the subjective effects of nicotine as a risk/protective factor in the initiation and escalation of smoking and nicotine dependence.

Acknowledgments

This research was funded by the Graduate Student Union Mark Diamond Research Award and the University at Buffalo College of Arts and Sciences Dissertation Fellowship Award granted to JSB. This study was completed as part of the doctoral dissertation conducted by JSB under the supervision of LWH. Completion of this manuscript was supported in part by grants R21CA111763 from the National Cancer Institute (LWH, PI) and by F31DA024532 (to RLA) from the National Institute on Drug Abuse.

References

- Acosta MC, Eissenberg T, Nichter M, Balster RL. Characterizing early cigarette use episodes in novice smokers. *Addict Behav.* 2008; 33(1):106–121. [PubMed: 17913378]
- Acton GS. Measurement of impulsivity in a hierarchical model of personality traits: implications for substance use. *Subst Use Misuse.* 2003; 38(1):67–83. [PubMed: 12602807]
- Benowitz NL. Nicotine replacement therapy. What has been accomplished--can we do better?[erratum appears in *Drugs* 1993 May;45(5)736]. *Drugs.* 1993; 45(2):157–170. [PubMed: 7681369]
- Benowitz, NL. Pharmacology of Nicotine. In: Ammerman, RT.; Ott, PJ.; Tarter, RE., editors. *Handbook of Substance Abuse: Neurobehavioral Pharmacology.* New York: Plenum Press; 1998. p. 283-297.
- Caggiula AR, Donny EC, Chaudhri N, Perkins KA, Evans-Martin FF, Sved AF. Importance of nonpharmacological factors in nicotine self-administration. *Physiol Behav.* 2002; 77(4–5):683–687. [PubMed: 12527019]
- Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishments: The BIS/BAS scales. *Journal of Personality and Social Psychology.* 1994; 67(2):319–333.
- Center for Disease Control. Cigarette smoking among adults - United States, 2000. *Morbidity and Mortality Weekly Report.* 2002; 51:642–645.
- Conklin CA, Perkins KA. Subjective and reinforcing effects of smoking during negative mood induction. *J Abnorm Psychol.* 2005; 114(1):153–164. [PubMed: 15709822]
- Eaton DK, Kann L, Kinchen S, Shanklin S, Ross J, Hawkins J, et al. Youth risk behavior surveillance--United States, 2007. *MMWR Surveill Summ.* 2008; 57(4):1–131. [PubMed: 18528314]
- Fryar CD, Merino MC, Hirsch R, Porter KS. Smoking, alcohol use, illicit drug use reported by adolescents aged 12–17 years: United States: 1999–2004. *National health statistics reports.* 2009; (15):1. [PubMed: 19634304]
- Gilbert DG. The situation x trait adaptive response (STAR) model of drug use, effects, and craving. *Human Psychopharmacology.* 1997; 12:s89–s102.
- Gilbert DG, Meliska CJ, Welser R, Estes SL. Depression, personality, and gender influence EEG, cortisol, beta-endorphin, heart rate, and subjective responses to smoking multiple cigarettes. *Personality and Individual Differences.* 1994; 16(2):247–264.
- Gilbert, DG.; Rabinovich, NE.; Rosenberger, SR. Effects of fast and slow blood-rise nicotine patches on nausea and feeling states in never-smokers; Paper presented at the Society for Research on Nicotine and Tobacco; New Orleans, LA. 2003.
- Gilbert DG, Robinson JH, Chamberlin CL, Spielberger CD. Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie. *Psychophysiology.* 1989; 26(3):311–320. [PubMed: 2756080]

- Gillin JC, Lardon M, Ruiz C, Golshan S, Salin-Pascual R. Dose-dependent effects of transdermal nicotine on early morning awakening and rapid eye movement sleep time in nonsmoking normal volunteers. *J Clin Psychopharmacol.* 1994; 14(4):264–267. [PubMed: 7962682]
- Jamner LD, Girdler SS, Shapiro D, Jarvik ME. Pain inhibition, nicotine, and gender. *Exp Clin Psychopharmacol.* 1998; 6(1):96–106. [PubMed: 9526150]
- Jamner LD, Shapiro D, Jarvik ME. Nicotine reduces the frequency of anger reports in smokers and nonsmokers with high but not low hostility: an ambulatory study. *Exp Clin Psychopharmacol.* 1999; 7(4):454–463. [PubMed: 10609980]
- Kalman D. The subjective effects of nicotine: methodological issues, a review of experimental studies, and recommendations for future research. *Nicotine & Tobacco Research.* 2002; 4(1):25–70. [PubMed: 11906682]
- Kalman D, Smith SS. Does nicotine do what we think it does? A meta-analytic review of the subjective effects of nicotine in nasal spray and intravenous studies with smokers and nonsmokers. *Nicotine Tob Res.* 2005; 7(3):317–333. [PubMed: 16085500]
- Kassel JD, Stroud LR, Paronis CA. Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. *Psychol Bull.* 2003; 129(2):270–304. [PubMed: 12696841]
- Levin ED, Conners CK, Silva D, Hinton SC, Meck WH, March J, et al. Transdermal nicotine effects on attention. *Psychopharmacology.* 1998; 140:135–141. [PubMed: 9860103]
- Mayhew KP, Flay BR, Mott JA. Stages in the development of adolescent smoking. *Drug Alcohol Depend.* 2000; 59(Suppl 1):S61–S81. [PubMed: 10773438]
- McCrae RR, Costa PT Jr, Bosse R. Anxiety, extraversion and smoking. *The British journal of social and clinical psychology.* 1978; 17(3):269. [PubMed: 687883]
- Netter P, Hennig J, Huwe S, Olbrich R. Personality related effects of nicotine, mode of application, and expectancies on performance, emotional states, and desire for smoking. *Psychopharmacology.* 1998; 135(1):52–62. [PubMed: 9489934]
- Perkins KA. Individual variability in responses to nicotine. *Behav Genet.* 1995; 25(2):119–132. [PubMed: 7733854]
- Perkins KA. Baseline-dependency of nicotine effects: a review. *Behav Pharmacol.* 1999; 10(6–7):597–615. [PubMed: 10780501]
- Perkins KA, Coddington SB, Karelitz JL, Jetton C, Scott JA, Wilson AS, et al. Variability in initial nicotine sensitivity due to sex history of other drug, and use parental smoking. *Drug Alcohol Depend.* 2008
- Perkins KA, Fonte C, Sanders M, Meeker J, Wilson A. Threshold doses for nicotine discrimination in smokers and non-smokers. *Psychopharmacology (Berl).* 2001; 155(2):163–170. [PubMed: 11401005]
- Perkins KA, Gerlach D, Broge M, Grobe JE, Wilson A. Greater sensitivity to subjective effects of nicotine in nonsmokers high in sensation seeking. *Exp Clin Psychopharmacol.* 2000; 8(4):462–471. [PubMed: 11127418]
- Perkins KA, Grottenthaler A, Wilson AS. Lack of reinforcement enhancing effects of nicotine in non-dependent smokers. *Psychopharmacology.* 2009; 205:635–645. [PubMed: 19488740]
- Perkins KA, Jacobs L, Sanders M, Caggiula AR. Sex differences in the subjective and reinforcing effects of cigarette nicotine dose. *Psychopharmacology.* 2002; 163:194–201. [PubMed: 12202966]
- Perkins KA, Lerman C, Coddington S, Karelitz JL. Association of retrospective early smoking experiences with prospective sensitivity to nicotine via nasal spray in nonsmokers. *Nicotine Tob Res.* 2008; 10(8):1335–1345. [PubMed: 18686181]
- Perkins KA, Sanders M, D'Amico D, Wilson A. Nicotine discrimination and self-administration in humans as a function of smoking status. *Psychopharmacology (Berl).* 1997; 131(4):361–370. [PubMed: 9226738]
- Perkins, KA.; Stitzer, M. Behavioral Pharmacology of Nicotine. In: Ammerman, RT.; Ott, PJ.; Tarter, RE., editors. *Handbook of Substance Abuse: Neurobehavioral Pharmacology.* New York: Plenum Press; 1998. p. 299–317.
- Pomerleau, Collins AC, Shiffman S, Pomerleau CS. Why some people smoke and others do not: new perspectives. *J Consult Clin Psychol.* 1993; 61(5):723–731. [PubMed: 8245270]

- Pomerleau OF, Pomerleau CS, Namenek RJ. Early experiences with tobacco among women smokers, ex-smokers, and never-smokers. *Addiction*. 1998; 93(4):595–599. [PubMed: 9684398]
- Pomerleau OF, Pomerleau CS, Snedecor SM, Finkenauer R, Mehringer AM, Langenecker SA, et al. Substance use, trait measures, and subjective response to nicotine in never-smokers stratified on parental smoking history and sex. *Nicotine Tob Res*. 2009:ntp099.
- Tabachnick BG, Fidell LS, Osterlind SJ. *Using multivariate statistics*. 2001
- Terracciano A, Costa PT. Smoking and the Five-Factor Model of personality. *Addiction*. 2004; 99(4): 472–481. [PubMed: 15049747]
- Trosclair A, Husten C, Pederson L, Dhillon I. Cigarette smoking among adultsóUnited States, 2000. *Morbidity and Mortality Weekly Report*. 2002; 51(29):642–645. [PubMed: 12186222]
- Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*. 1988; 54(6): 1063–1070. [PubMed: 3397865]

Figure 1.
Subjective effects of nicotine along two dimensions of affective space.

Figure 2.
Moderation by BAS on High Arousal Negative Affect

Figure 3.
Pre-to-post Task changes in negative affect

Figure 4.
Moderation by BAS on High Arousal Positive Affect