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Emotional Stimuli and Context Moderate Effects of Nicotine on Specific, But Not Global Affects

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Abstract

We tested the hypothesis that the effects of nicotine on affect are moderated by the presence or absence of emotionally positive and negative stimuli and by attentional choice to avoid attending to emotionally negative stimuli. Thirty-two habitual smokers were assigned to tasks allowing attentional freedom to look back and forth at two simultaneously presented pictures, while another 32 habitual smokers viewed single pictures without attentional choice. Picture contents in both tasks were one of four combinations: emotionally negative + neutral, negative + positive, positive + neutral, or neutral + neutral. Participants wore a nicotine patch on one day and placebo patch on another day. Nicotine reduced anxiety most when negative pictures were presented in combination with neutral pictures, but had no effects on anxiety when negative pictures were presented in combination with positive pictures and when negative pictures were not presented. In contrast, nicotine only reduced depressive affect when the participant had attentional choice between positive and negative pictures. Nicotine also enhanced PANAS positive affect and reduced PANAS negative affect, but these effects were not moderated by task manipulations. Overall, the findings support the view that nicotine's ability to reduce specific negative affects is moderated by emotional context and attentional freedom. Nicotine tended to enhance eye-gaze orientation to emotional pictures versus neutral pictures in women, but had no significant effect on eye-gaze in men.

Keywords

nicotine; anxiety; depression; attention; STAR model

While most tobacco smokers report that one of their primary motivations for tobacco smoking is to reduce stress-induced negative affect (Gilbert, Sharpe, Ramanaiah, Detwiler, & Anderson, 2000; Spielberger, 1986), many laboratory studies have failed to detect effects of the acute administration of nicotine on subjective distress and negative mood even in abstinent smokers, though well-controlled studies have repeatedly shown increases in negative affect subsequent to smoking cessation (Hughes, Higgins, & Hatsukami, 1990; Kalman, 2002; Kassel, Stroud, & Paronis, 2003;). In an effort to explain this failure of nicotine to reduce stress-induced negative affect in many acute administration studies, Gilbert (Gilbert, 1995, 1996, Gilbert & Welser, 1989) suggested that many of the laboratory stress-induction paradigms used in acute

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administration studies do not include the situations/contexts that allow nicotine to exert stress-reducing effects. He hypothesized that nicotine attenuates negative affect and subjective distress only in situations allowing flexible attentional allocation and associative processing and occurs more frequently in individuals with trait vulnerabilities to negative affect (e.g., high neuroticism). Thus, the model was termed the Situation by Trait Adaptive Response (STAR) model. Among other things, the STAR model proposes that nicotine reduces negative affect when the context promotes internally driven, as opposed to externally driven, attentional and associative information processing (Gilbert, 1995, pp. 199–200), something referred to as the “attentional bias hypothesis” or “nicotine priming hypothesis”. Externally driven information processing refers to conditions in which there is little variability in how a person responds to the given situation because of the strong learning or phylogenetically based unconditioned nature of the stimuli (Cooper, Croft, Dominey, Burgess, & Gruzelier, 2003). Examples of externally driven processes include responding with negative emotions to the sight of a bloody face or hearing a baby cry in pain. The STAR model hypothesizes that nicotine primes and thereby promotes more positive and less negative associations in situations allowing internally driven cognitive processing. Greater degrees of internally driven processing occur when the situational and cognitive context is ambiguous, low structure, or associated with conflicting goals. Examples of internally driven processing include the association of thoughts during daydreaming, the interpretation of ambiguous social stimuli, and choosing which of two pictures one would like to look at or think about.

The hypothesis that nicotine can reduce negative affect by priming internally driven emotional processing is based on reviews of the literature (Gilbert, 1995; Gilbert & Gilbert, 1998; Gilbert & Welser, 1989) that suggest that nicotine has less of an ability to reduce negative affect when the context demands attention to potent proximal demands and stressors. Such conditions do not allow the attentional biasing effects of nicotine to overcome externally driven attentional and affect-inducing demands. An important class of internally driven situations is when there is attentional freedom of choice to easily focus or avoid focusing attention on potentially stress-inducing internal or external stimuli. One likely explanation for the reliable increase in negative affect reported in studies of smoking cessation is that they assess the average aggregated mood across the entire day, including mood in different natural environments that contain a large degree of attentional choice and ambiguous stressors that have the potential to promote negative affect. Averaging across time and situations increases the range of stimuli to which individuals are exposed. Many, if not most of these situations in the natural environment include a mixture of threatening and benign stimuli that allow attentional freedom of choice so that nicotine can reduce negative affect by altering attentional bias away from negative and toward neutral or positive stimuli. In contrast, in controlled laboratory environments, the range of affective and non-affective stimuli to which a smoker can attend is greatly restricted, and possibly more importantly, attention is usually dictated by experimental demands, rather than the preferences and other internally driven characteristics of the smoker. Thus, according to the attentional bias hypothesis, it is not surprising that during many experimental tasks negative affect is not reduced by nicotine administration because during these tasks attentional allocation is directed by experimental demands toward highly salient strong stressor stimuli that the attentional priming effects of nicotine cannot overcome.

A failure to provide salient attentional alternatives may explain the failure of a number of studies to find negative affect-reducing effects of smoking and nicotine. For example, Fleming and Lombardo (1987) found that smoking had no effect on fear or anxiety when confronting a large, unrestrained rat during a behavioral approach test. Similarly, Gilbert and Hagen (1980) found no effects of nicotine manipulation (normal vs. very-low nicotine delivery cigarettes) on negative affect experienced during the viewing of stressful movie scenes. Hatch, Bierner, and Fisher (1983) also failed to find any effects of smoking on anxiety during an anxiety-provoking speech. Morissette, Palfai, Gulliver, Spiegel, and Barlow (2005) found that anxiety

was not reduced by nicotine patch during anxiety-imagery scripts designed to focus attention on one's induced anxiety. These and other studies show little or no attenuation of negative affect in the presence of proximal and potent stressors. In contrast, studies using conditions promoting internally driven attentional allocation (distal, ambiguous, and/or anticipatory mild stressors) tend to show that smoking or nicotine reduces negative affect.

One of the early studies using tasks that promoted internally driven processing was by Jarvik, Caskey, Rose, Herskovic, & Sadehpour, (1989), who found that smoking was associated with reduced anxiety in anticipation of mild/ambiguous stressors (anagrams task and cold-pain task). Pomerleau and Pomerleau (1987) also found that smoking, relative to sham smoking, reduced anxiety in anticipation of a mental arithmetic task. Gilbert and Spielberger (1987) found smoking to reduce negative affect during a social interaction with a stranger. While the post-hoc categorization of studies led to attentional bias model (Gilbert & Welser, 1989), only a few studies have explicitly tested propositions of this model. The first experimental work designed to explicitly test the effects of attentional alternatives of this model were by Kassel (Kassel & Shiffman, 1997; Kassel & Unrod, 2000) who found support for the view that attentional bias model's hypothesis that attention allocation may mediate nicotine's anxiolytic effects. Kassel et al., manipulated nicotine and benign alternative stimuli while participants anticipated giving a speech designed to induce anxiety. Smoking nicotine-delivery cigarettes, relative to not-smoking or to low-nicotine smoking, reduced anxiety only when smokers were asked to engage in an emotionally benign art-rating task onto which they could focus their attention. Nicotine/smoking did not reduce anxiety when participants simply waited to present the speech. Both Kassel's general attentional allocation model and our attentional bias allocation model both propose that nicotine reduces negative affect by enhancing attention to benign proximal cues (if adequately salient), thereby reducing attention to more distal (less salient) peripheral stress-related stimuli. However, our attentional bias model suggests that nicotine also biases attention and associative processes toward positive cues and away from negative cues to the degree that these cues are of equal salience. Equal salience is important because of findings summarized by Gilbert's (1995) suggesting that the lateralized affective network model of which the attentional bias model is a part also sees nicotine as promoting attention to more salient stimuli, relative to less salient stimuli. Dopaminergic activation by nicotine appears to increase incentive salience generally (reviewed by Robinson & Berridge, 1993) while also enhancing positive affect-related somewhat lateralized brain function (reviewed by Gilbert, 1995).

The attentional bias hypothesis is supported by evidence suggesting that nicotine may modulate neural systems that mediate the incentive and attention-grabbing properties of stimuli associated with reward/reinforcement (Caggiula et al., 2001, 2002; Donny et al., 2003; Gilbert & Welser, 1989; Gilbert, 1995, 1997; Robinson & Berridge, 1993). For example, the recent findings by Caggiula and colleagues (Caggiula et al., 2001, 2002; Donny et al., 2003) and by Olausson, Jentsch, and Taylor (2004) suggest that nicotine can enhance the reinforcement value of conditioned reinforcers. This enhanced reinforcement value is consistent with the hypothesis that nicotine enhances attention to stimuli associated with positive reinforcement and positive affect. If nicotine promotes attention to neutral or positive affect-associated cues, the attention-grabbing effects of such cues may inhibit negative affect-related associative processes (Gilbert, 1995). Alternatively, nicotine may directly inhibit attentional bias toward negatively valenced stimuli.

The overall, general hypothesis was that nicotine's ability to reduce specific negative affects is moderated by emotional context and attentional freedom. There were three specific hypotheses. The first hypothesis was that nicotine would reduce negative affect to a greater extent during tasks that allow the choice between viewing stressful pictures or alternative emotionally neutral or positive pictures than during situations not allowing this choice. The

second hypothesis was that in a context of periodic emotionally negative stimuli, nicotine would reduce depressive affect more in situations that allow attentional focus on emotionally positive stimuli than in situations without positive stimuli because nicotine promotes attention to emotionally positive stimuli that in turn inhibits depressive affect. The third hypothesis was that nicotine's effects on mood and attention to emotion-related stimuli would be different in women than in men. This hypothesis is based on the literature review by Perkins, Donny, and Caggiula (1999) suggesting that, relative to women, men are more sensitive to the pharmacological effects of nicotine, while women may be more sensitive to situational stimuli associated with smoking.

Method

Participants

Participants included in the final sample were 32 female and 32 male smokers with a mean age of 26.1 years (8.8 *SD*) who smoked an average of 17.1 (5.7 *SD*) cigarettes per day. Nicotine dependence was assessed with the Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), which is predictive of severity of withdrawal distress and relapse to smoking (Piasecki et al., 2000). The mean FTND score was 4.0 (2.0 *SD*), indicating a moderate degree of dependence for the typical participant.

Participants were recruited by newspaper ads and postings throughout a Midwestern university and the surrounding community. Detailed phone and in-person screening interviews were used to assess whether individuals met inclusion criteria. Exclusion criteria included smoking fewer than eight cigarettes per day for the past year and smoking cigarettes Federal Trade Commission (FTC) nicotine deliveries of less than 0.6 mg/cigarette; reported use of psychoactive drugs or medications other than caffeine, marijuana, and alcohol; excessive alcohol use (28+ drinks/week); age less than 18 or more than 47 years; non-English speaking; atypical sleep cycles; and serious medical, hearing, and visual problems. Participants were instructed not to smoke tobacco or drink alcohol for the 12 hours preceding each of the experimental sessions and not to smoke marijuana for at least 72 hours prior to the session. Only those who both reported having adhered to these abstinence requirements and who had expired breath CO concentrations of less than 10 ppm were included in the data analysis. Additionally, urine drug screens were administered to a subset of individuals who during the initial screening indicated histories of drug use. In order to maximize compliance with the drug-abstinence requirements, at the onset of the study all individuals were informed that there would be urine drug screenings.

Equipment and Materials

Picture stimuli—Picture stimuli consisted of color photographs derived from two sources, the International Affective Picture System (Lang, Bradley, & Cuthbert, 2001) and an in-house picture set. Validation processes for in-house pictures included affective valence, arousal, interest, and complexity ratings made of pictures by groups of smokers and nonsmokers. Picture pairs used for simultaneous presentation in the picture attention tasks (PATs) were selected by a careful process of matching pictures as closely as possible in terms of content, complexity, interest, color, saturation, and luminosity. We were successful in equating slides across a variety of parameters. The emotional picture stimuli have been validated in terms of their potential to elicit emotional responses and nicotine-dependent electrocortical, fMRI, and PET responses (Gilbert, Sugai, et al., 2004; Lang et al., 2001).

The pictures used in the Repeated No-Choice and Repeated Two-Choice PATs described below were identical. The only difference was that each of the pictures used in the Two-Choice PATs were presented twice, once in the left visual field and once in the right visual field, while each picture was presented twice centrally in the No-Choice PATs. Pictures were presented once in

each visual field to control for possible attentional bias to one visual field relative to the other. Thus, the length and the content of the Repeated Two-Choice and Repeated No-Choice PATs were the same.

Equipment—The pictures were presented via a Pentium-class PC with an 18-inch LCD color monitor. Picture presentation was accomplished with a SuperLab™ 2.0 software (Cedrus®, Phoenix, AZ) that sent picture onset information via a serial connection to an Arrington eye-tracking system (Arrington Research, Inc., Scottsdale, AZ) run with a Pentium-class computer. The eye-tracking system uses an infrared beam directed at the eye to provide a measure of eye-gaze direction. Gaze direction was measured 30 samples/second continuously during the picture tasks. Participants viewed the computer monitor from a distance of 150 cm while seated in a comfortable, padded chair. A forehead bar, chinrest, and infrared camera were attached to a rigid support bar that allowed adjustments to maximize participant comfort.

Experimental Tasks

Our negative affect manipulation involved the systematic manipulation of two variables hypothesized by the STAR model and its attentional bias hypothesis to be important moderators of the affect-modulating effects of nicotine. These moderators included attentional choice (two-choice vs. no-choice), and presence or absence of emotionally positive alternative stimuli.

Repeated Two-Choice Picture-Attention Task (RTC-PAT)—Using the eye tracking system, the RTC-PAT provided computerized, continuous measures of visual gaze temporal patterns associated with presentation of two pictures (Fig 1). Two pictures were presented simultaneously for 3000 ms one with inner edge slightly (0.48°) to the left of the central fixation location and one with inner edge and equal distance to the right of center. Each picture of the picture pair was 15 cm $\times$ 15 cm and subtended a visual angle of 5.73° . Immediately after picture offset the computer monitor presented the word “BLINK” for 600 ms, followed by a 2000 ms duration fixation cross, that was replaced by the a second 3000 ms presentation of the same dual picture. Each RTC-PAT consisted of 48 such repeated dual picture presentations, each of which consisted of the above sequence (fixation, first presentation of dual picture, fixation, second presentation of the dual picture), followed by a similar sequence with different dual pictures beginning 2 seconds later). There were four versions of the RTC-PAT: emotionally neutral pictures paired with emotionally negative pictures, emotionally neutral pictures paired with emotionally positive pictures, emotionally negative pictures paired with emotionally positive pictures, and emotionally neutral pictures paired with other emotionally neutral pictures. Participants were told that they were free to change their gaze from one picture to the other and to look at a given picture for as long as desired, but that they should keep viewing the pictures and keep their eyes open throughout the 3-second dual-picture presentation.

Repeated No-Choice Picture-Attention Task (RNC-PAT)—The RNC-PATs (Fig 1) were identical to the RTC-PATs described immediately above with the exception that one central picture, rather than two peripheral pictures at a time, was presented on the computer monitor. The number and sequence of picture trials were also identical to that described in the preceding paragraph for the RTC-PAT. The participant's task was to look at the picture for the full three seconds of its presentation. Eye-gaze was tracked using the ViewPoint® Eye Tracking System to assure that gaze was directed at each picture for its entire presentation and to make viewing conditions identical to those used in the RTC-PAT. Like the RTC-PAT, the RNC-PAT took about 12 minutes to complete.

Neutral buffer tasks and affect-recovery ratings—After each of the emotion-induction tasks, participants performed a buffer task designed to promote the dissipation of the negative

affect by requiring judgments and/or rapid responses. Buffer task performance will be presented elsewhere.

Mood ratings—Immediately after the completion of each PAT and each buffer task, the computer monitor screen presented the Expanded Feeling State Questionnaire-E (FSQ-E). The FSQ-E consists of items from the FSQ (Gilbert, Meliska, Williams, & Jensen, 1992), including the 20-item Positive and Negative Affect Schedule (PANAS, Watson, Clark, & Tellegen, 1988), the two-item Nicotine Overdose Scale (sick/nauseous and lightheaded/dizzy), and the Specific Affect Measure (SPAM). The SPAM consists of three specific negative emotions not as fully assessed in the PANAS, yet considered important in differentiating the effects of nicotine. These specific emotions are Anger-Irritability (angry, annoyed, irritated, resentful), Anxiety (anxious, nervous, tense, worried), and Depressed (discouraged, gloomy, sad, unhappy). Each item was presented alone on the computer monitor and the participant indicated the degree to which the item corresponded to her or his mood by clicking one of 11 square buttons labeled (“0” to “10”) with labels “Not at all” to “Extremely”. During these ratings each of the SPAM affects was presented as a single item with its component affects listed in parentheses.

Picture ratings—At the conclusion of each experimental session, participants rated the pictures they saw during the PATs that day. Pictures were presented individually, in random order, for 3000 ms and then 11 square response buttons appeared at the bottom of the computer monitor while the picture continued to be presented at the top of the screen. The participant used the computer mouse to press the response button to indicate her or his emotional response to the picture. Each picture was rated in terms of how the participant responded to the picture. Responses evaluated were: interest, emotional valence, arousal, and wanting to smoke. Valence was assessed on 9-point scale bipolar scales based on IAPS ratings going from 1 = *extremely positive*, to 9 = *extremely negative*. Picture ratings from the sample showed the expected pattern, with mean valence ratings of 7.26, 4.96, and, 3.3 for the negative, neutral, and positive pictures, respectively. Rating for interest were 4.81, 2.04, and 3.79, for negative, neutral, and positive pictures, respectively, using a scale from 1 = *not at all interesting* to 10 = *extremely interesting*.

Design

Prior to the practice session, individuals were randomly assigned to the two-choice or the no-choice condition. This assignment determined whether the participant performed the no-choice or the two-choice tasks during the two experimental sessions. During both of the experimental sessions each participant completed four different versions of the RTC-PAT or the RNC-PAT: negative:neutral, positive:neutral, negative:positive, and neutral:neutral. Half of the participants wore a nicotine patch on the first session and a placebo patch on the second session, while the other half had the reverse order of patches. The study was double blind concerning the nicotine versus placebo status of the patches. Assignment to the different tasks and task orders were random and counterbalanced for gender.

Procedure

Participants attended an orientation/practice session and two experimental sessions. Each participant sat alone in a small experimental room that was electronically connected to a central control room. The control room contained a server computer for control of experimental tasks, and video display units for monitoring each participant's computer and behavior. Participants earned monetary compensation for completion of the study.

Orientation/practice session—During the first orientation session each participant was given detailed information about the nature of the study, and the consent form was reviewed

and signed. Breath samples were obtained to verify habitual smoking, and a blood sample was taken. Participants also worked on a battery of questionnaires. The remainder of the 4.5-hour orientation session was spent practicing the PATs. Participants also practiced buffer tasks, and completed the computerized mood ratings used in the subsequent two experimental sessions.

Experimental Sessions—Experimental sessions began between noon and 1:30 p.m. and lasted about three hours. A minimum of one day and generally a maximum of seven days separated the practice sessions and each of the two experimental sessions. Upon arrival at the laboratory, the participant's breath carbon monoxide (CO) concentration was monitored. The patches were placed on the upper arm of smokers approximately four hours prior to the beginning of the picture attention tasks. The nicotine patch was a 14 mg Nicoderm® transdermal patch; the placebo patch was an identical appearing patch provided by GlaxoSmithKline. In order to minimize the ability of participants to differentiate active and placebo patches by skin sensations (itching or irritation) we used a cover bandage with a small amount (.05cc) of capsaicin .075% cream (Capzasin-HP7, Chattem, Inc) applied to the Teflon-coated surface of the cover bandage, covering an area 5 mm wide immediately next to each of the edges of the bandage. Pilot testing demonstrated that this procedure reduced the ability of subjects to detect differences between the active and placebo patch when applied.

Assessment of smoking abstinence—Compliance with instructions for overnight smoking abstinence and smoking status were monitored using expired breath CO concentrations and self-report. CO was measured with a Vitalograph BreathCO (Lenexa, KS). CO had to be less than one third of late afternoon-assessed CO concentration or 10 ppm at the time of patch placement. In addition, when returning to the lab four hours later to begin the experimental session, the CO concentration had to be less than that at patch placement.

Analytic Procedures

Statistical analyses—All ANOVA probabilities were based on the Greenhouse-Geisser (1959) correction for sphericity of repeated measures. Non-corrected degrees of freedom are reported for purpose of clarity. Follow-up analyses of simple effects were performed on significant interactions. Analyses were performed with SPSS 15.0 software (SPSS Inc., Chicago, IL).

Eye-gaze processing—In preparation for statistical analyses, the eye-tracking data from each 3000 ms picture presentation epoch produced a sequence of 90 digitized values corresponding to the direction of eye gaze at time increments of 33 ms (30 samples/s). For each of the dual picture presentations involving negative pictures, an in-house Microsoft Excelc program assigned a value of 1.0 to direct gazes at the center of the negative pictures irrespective of visual field of presentation and assigned a value of -1.0 to gazing at the center of the alternative (neutral or positive) picture. For each of the positive:neutral dual picture analyses, positive pictures gazes directly at the center of the positive picture were assigned a numeric value of 1.0, while gazes at the center of the neutral picture were assigned values of -1.0. All data processing was done blind to the nicotine condition and gender. Epochs with extensive blink or other artifacts were rejected. Epochs containing several or fewer blink artifacts were easily identified by extreme (outside gaze range) values and were automatically corrected using interpolation algorithms. The gaze pattern for each picture was baseline corrected using the median value of the last 20 fixations immediately prior to dual picture onset.

Results

Patch Blindness Assessment

The Patch Guess and Attribution Questionnaire (developed by the first author) was administered at the conclusion of each session. This questionnaire included two parts— a forced choice (“Which patch do you think you were wearing?”) and a certainty measure (percentage certainty of being on nicotine patch). In the forced choice condition, 66% of smokers on the nicotine patch correctly guessed they were on the nicotine patch, while 31% of smokers guessed they were on the nicotine patch but were actually on the placebo patch. Both of these values deviated significantly from chance guessing (50%), both $ps < .02$. On the certainty measure, smokers had a mean certainty of 61% of being on the nicotine patch when they were on the nicotine patch and a mean certainty of 36% of being on the nicotine patch when they were on the placebo patch, both $ps < .01$. These results demonstrated that the participants were somewhat but not highly accurate in guessing the patch (nicotine versus placebo) they received.

Effects of Picture Types and Choice on Affect Independent of Nicotine

As expected, there were significant main effects of picture type on SPAM specific affects and on PANAS general negative and positive affect, such that negative pictures induced more negative emotional states and less positive states, while positive pictures increased happiness/ positive affect and decreased negative emotional states. As assessed by partial η^2 (eta squared) values, the greatest effect of negative picture type on experienced affect as was a highly significant increase in SPAM Depression, $F(1,60) = 39.93$, $p < 0.001$, partial $\eta^2 = .40$. SPAM Anxiety was increased by negative pictures, $F(1,60) = 8.200$, $p = 0.006$, partial $\eta^2 = .120$. SPAM Anger-Irritability was increased by negative pictures, $F(1,60) = 8.095$, $p = 0.006$, partial $\eta^2 = .119$. PANAS Negative Affect was also significantly increased by negative pictures, $F(1,60) = 22.298$, $p < 0.001$, partial $\eta^2 = .271$. In addition, negative pictures had no effect on PANAS Positive Affect scores, $F(1,60) = 0.000$, $p = 0.986$, partial $\eta^2 = .000$.

Positive pictures had no significant main effect on any of the three SPAM negative affects (Depression, Anger, Anxiety) or on PANAS Negative Affect, $F(1,60) = 2.016$, $p = 0.161$, partial $\eta^2 = .032$. In contrast, as positive pictures increased SPAM Positive Emotion, $F(1,60) = 14.510$, $p < 0.001$, partial $\eta^2 = .195$. However, positive pictures did not significantly increase PANAS Positive Affect, $F(1,60) = 2.690$, $p = 0.106$, partial $\eta^2 = .043$.

In summary, negative pictures increased SPAM-assessed depressive affect, anxiety, and anger-irritability, and PANAS Negative Affect. Negative pictures did not significantly alter PANAS Positive Affect. These findings indicate that specific negative affects measured by the SPAM were more sensitive to the effects of viewing negative and positive pictures than were PANAS Negative and Positive Affect scores. This greater sensitivity of the SPAM specific affects to the mood-inductions justifies their use as the primary dependent affective measures.

Effects of Nicotine on Negative Affect

Nicotine reduced negative affect as assessed by the SPAM Anxiety and the PANAS, but as predicted by hypotheses 1 and 2, nicotine's effects on specific negative affects were moderated by Task type (two-choice vs. no-choice and the presence or absence of negative and positive pictures). Nicotine reduced SPAM Anxiety, as evidenced by a main effect, Nicotine, $F(1,60) = 4.903$, $p = 0.031$, partial $\eta^2 = .076$, but these effects were moderated by a Nicotine $\times$ Positive Picture $\times$ Negative Picture interaction (Fig 2), $F(1,60) = 5.784$, $p = 0.019$, partial $\eta^2 = .088$, but were not influenced by Attentional Choice. Pairwise analyses (Fig 2) showed that this three-way interaction reflected the largest nicotine-promoted reduction in Anxiety when negative pictures were presented in combination with neutral pictures ($p = 0.003$), while there was no

effect of nicotine on Anxiety when negative pictures were presented in combination with positive pictures ($p = 0.689$), or when negative pictures were not presented. Given that anxiety was not significantly greater in the negative + positive picture condition than in the neutral + neutral condition, the failure of nicotine to reduce anxiety in the negative + positive condition is not surprising given this floor effect.

Nicotine did not have an overall main effect on SPAM Depressive Affect, as evidenced by a main effect, $F(1,56) = 1.336$, $p = 0.252$, partial $\eta^2 = .022$, but consistent with hypothesis 2, there was a significant Nicotine $\times$ Positive Picture $\times$ Choice interaction, $F(1,60) = 6.044$, $p = 0.017$, partial $\eta^2 = .092$. Pairwise analyses showed that this interaction was largely driven by nicotine reducing Depressive Affect in the two-choice task in the presence of positive pictures, (Fig 3), (nicotine vs. placebo difference = .542, $p = .044$). None of the other nicotine versus placebo comparisons associated with this interaction was significant for either gender.

The prediction that nicotine would reduce SPAM Anger-Irritability only approached significance, as reflected by a main effect, Nicotine, $F(1,60) = 3.185$, $p = 0.079$, partial $\eta^2 = .050$. The effects of nicotine on SPAM Anger-Irritability did not significantly interact with any of the other independent variables.

Finally, as expected, nicotine reduced PANAS Negative Affect, Nicotine, $F(1,60) = 5.482$, $p = 0.023$, partial $\eta^2 = .084$. However, unlike the effects of nicotine on SPAM specific affects, the effects of Nicotine on PANAS Negative Affect were consistent across stimulus conditions and gender, as evidenced by the lack of significant interactions involving Nicotine.

Effects of Nicotine on PANAS Positive Affect

Nicotine increased PANAS Positive Affect, $F(1,60) = 7.963$, $p = 0.006$, partial $\eta^2 = .117$, but did not interact with other experimental manipulations.

Effects of Nicotine on Attentional (Gaze) Bias to Negative and to Positive Pictures

The analysis of the effects of nicotine on attentional bias was based on principal component factor (PCA) analysis-derived time periods. Using orthogonal rotations, the PCA resulted in three meaningful time period factors. Factor 1 corresponded to 1667 to 3000 ms post picture onset (the last 1333 ms of the dual picture exposure), factor 2 was 833–1500 ms, and factor 3 corresponded to the initial movement toward one of the pictures (267 to 733 ms after picture onset). The subsequent ANOVAs of eye-gaze bias were based on mean viewing during these time periods, and included Nicotine $\times$ Gender $\times$ Picture Repetition $\times$ Picture Pair Type (Positive:Neutral vs. Negative:Neutral). Analysis of gaze associated with factor 1 (the last 1333 ms of the dual picture presentation) revealed a Nicotine $\times$ Gender $\times$ Picture Repetition, $F(1, 30) = 5.461$, $p = 0.026$, partial $\eta^2 = .154$, interaction. Follow-up analyses showed (Fig 4) this interaction to largely reflect the fact that in women during the first of the two presentations of the dual pictures, relative to placebo, nicotine significantly enhanced gaze time toward emotional (either positive or negative) pictures paired with neutral pictures ($p = .037$). In contrast, in males nicotine had a non-significant tendency to have the opposite effect, reducing attentional bias (gaze time) to both types of emotional pictures when paired with neutral pictures during the first of the two presentations of the dual pictures ($p = 0.204$). There were no effects of Nicotine or Nicotine $\times$ Gender interaction for eye gaze during the repeated presentation of the same two pictures two seconds later (Fig 4b).

Analysis of gaze associated with factor 3 (the initial orienting toward one of the two pictures) revealed a Nicotine $\times$ Gender $\times$ Picture-Pair Type, $F(2, 60) = 3.279$, $p = 0.045$, partial $\eta^2 = .099$, interaction. Follow-up analyses once again showed that in women, relative to placebo, nicotine tended to enhance gaze time toward emotionally positive pictures paired with neutral

pictures and toward emotionally negative pictures paired with neutral pictures ($p = .067$), while in men nicotine produced a non-significant tendency to have the opposite effect, reducing attentional bias (gaze time) to both types of emotional pictures when paired with neutral pictures during the first of the two presentations of the dual pictures ($p = 0.071$). In contrast, when positive and negative pictures were paired with each other, nicotine produced no significant effects on attentional gaze bias.

Discussion

Our findings support the hypotheses that contextual stimuli and gender moderate nicotine's effects on specific negative affects and attention to emotional stimuli. Specifically, while PANAS general negative and positive affect were, respectively decreased and increased across contexts, the effects of nicotine on SPAM anxiety and SPAM depression were differentially influenced by the presence or absence of positive pictures and negative pictures. Nicotine reduced SPAM anxiety when negative pictures were presented in combination with neutral pictures, but had no effect when negative pictures were not presented or when negative pictures were combined with positive pictures. This failure of nicotine to reduce anxiety in the negative + positive picture condition likely reflects a floor effect, as anxiety induction in this condition was no greater than in the neutral + neutral picture condition. In contrast, nicotine attenuated SPAM depressive affect primarily in the presence of positive pictures. The tendency of nicotine to reduce SPAM anger-irritation did not reach statistical significance. These results also suggest that nicotine's effects may differ across different specific negative affects, though the observed differences may reflect the fact that negative pictures induced greater changes in depressive affect than anger and anxiety. Finally, while we did not find gender differences in the effects of nicotine on our measures of affect, nicotine did enhance attentional bias (gaze time) toward emotional stimuli in women, while tending to have the opposite effect in men. Below we first address possible reasons why nicotine's effects on anxiety and depressive affect were modulated by situational factors while generalized positive and negative affect were not. We then discuss the tendency of nicotine to enhance attentional bias towards emotional stimuli in women.

Why were the effects of nicotine on PANAS positive affect and on PANAS negative affect not moderated by the different affective contexts that moderated anxiety and depressive affect? One possible explanation for the failure of the PANAS scales to be moderated by the emotional pictures is that nicotine enhanced general alertness and energized individuals in a manner that resulted in decreased general negative affect and increased general positive affect as assessed by the PANAS, while being insensitive to the specific affects elicited by the emotional pictures used in the present investigation. Positive PANAS items are: attentive, interested, alert, enthusiastic, excited, inspired, proud, determined, strong, and active. It is possible that the generalized arousing effects of nicotine (Gilbert, 1979) increased PANAS generalized arousal items (attentive, alert, strong, active) and thereby enhanced positive PANAS scores independently of any specific positive affective states (e.g., enthusiastic, inspired, proud, determined) and any decreases in specific negative affects. PANAS negative affect includes the following items: distressed, upset; hostile, irritable; scared, afraid, ashamed, guilty, nervous, and jittery. There is no item overlap and minimal conceptual overlap between these PANAS negative affect items and the SPAM items for depressive affect (discouraged, gloomy, sad, unhappy), but there is some, though not high, overlap for SPAM anxiety (anxious, nervous, tense, worried) and PANAS negative items. The content of our negative pictures included scenes that likely elicited more sadness and gloom identified by the SPAM than contents reflected in PANAS negative affect items. Thus, the SPAM items appear to have been more sensitive to the specific affect inductions used in the present investigation, something they were designed to be. Our findings suggest that the content of the scales used to assess affect need to

be examined and considered in terms of the mood-induction procedures used in studies of nicotine's effects.

While gender differences in the effects of nicotine on affect were not observed, we did find gender differences in the effects of nicotine on attentional bias to emotional versus neutral pictures. Nicotine enhanced gaze toward emotional pictures in women irrespective of whether the picture was emotionally positive or negative. In contrast, nicotine did not significantly influence the attentional bias of men, though there was a nonsignificant trend for nicotine to decrease attention to emotional stimuli. These gender effects may relate to previous findings suggesting that women may be more sensitive to environmental factors associated with nicotine and tobacco use than to the effects of nicotine per se. Nicotine may enhance attention to situational emotional cues in women and thereby decrease the focus of internal pharmacological effects of nicotine. Thus, to the degree that a woman's environment is positive, it might be expected that nicotine would enhance response to and action toward the emotionally positive stimuli. This would suggest that women undergoing nicotine withdrawal might become emotionally and motivationally disengaged from emotionally positive cues that promote positive affect and activity. This nicotine-enhanced response to salient stimuli is consistent with both the STAR model and the incentive sensitization model. However, neither of these models suggests why gender should moderate these effects.

Limitations of the present investigation are important to consider. The sample size was modest, largely university based, moderately well educated, young, did not abuse alcohol or psychoactive substances, and was generally limited to moderate levels of nicotine intake and nicotine dependence. The sample size limited the statistical power to detect interactions, especially the hypothesized higher-order interactions. The fact that individuals were able to distinguish the two types of patches makes the findings open to alternative interpretations. These limitations may reduce the generalizability of our findings. Also, emotional pictures with different sorts of content, and with different degrees of potency and personal relevance could also result in different findings than we observed. Furthermore, it is not clear whether the effects of nicotine in the present study reflect absolute effects or only alleviation of withdrawal effects in nicotine-deprived smokers. The difficulty of resolving the withdrawal versus inherent effects interpretation is likely to be difficult to accomplish given that evidence suggest that the effects of quitting on some attentional processes, mood, and EEG do not recover to pre-quit levels within a month of quitting (Gilbert et al., 1998; 1999; 2002; Gilbert, McClernon et al., 2004). Finally, the effects of nicotine patch on attention and affect cannot be presumed to generalize to tobacco smoking or other forms of affect induction.

The systematic manipulation of attentional choice and contextual emotional stimuli constitutes an important first step in the characterization of when, in whom, and how nicotine alters different affective states. The use of larger sample sizes would allow a number of additional important steps to be taken. The relatively small sample size of the present study limited the power to detect interactions of attentional choice (the two-choice versus no-choice picture attention task) with picture type. Because of our sample size, we chose to only assess a priori hypotheses concerning attentional choice and gender. Larger studies could systematically characterize the relative importance of neuroticism other personality and genetic traits associated with smoking and stress. Finally, there is also a need to use different types and sets of emotional pictures to see if the presently observed tendency of nicotine to modulate affect and attentional bias is reliable across various dimensions of negative and positive stimuli, different means of nicotine administration, measures of affect, and types of smokers.

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References

- Caggiula AR, Donny EC, Chaudhri N, Perkins KA, Evans-Martin FF, Sved AF. Importance of non-pharmacological factors in nicotine self-administration. *Physiology & Behavior* 2002;77:683–687. [PubMed: 12527019]
- Caggiula AR, Donny EC, White AR, Chaudhri N, Booth S, Gharib MA, Hoffman A, Perkins KA, Sved AF. Cue dependency of nicotine self-administration and smoking. *Pharmacology, Biochemistry and Behavior* 2001;70:515–530.
- Cooper NR, Croft RJ, Dominey SJJ, Burgess AP, Gruzeliier JH. Paradox lost? Exploring the role of alpha oscillations during externally vs. internally directed attention and the implications for idling and inhibition hypotheses. *International Journal of Psychophysiology* 2003;47:65–74. [PubMed: 12543447]
- Donny E, Chaudhri N, Caggiula A, Evans-Martin F, Booth S, Gharib M, Clements L, Sved A. Operant responding for a visual reinforcer in rats is enhanced by non-contingent nicotine: Implications for nicotine self-administration and reinforcement. *Psychopharmacology* 2003;169:68–76. [PubMed: 12774186]
- Fleming SE, Lombardo TW. Effects of cigarette smoking on phobic anxiety. *Addictive Behaviors* 1987;12:195–198. [PubMed: 3630806]
- Gilbert DG. Paradoxical tranquilizing and emotion-reducing effects of nicotine. *Psychological Bulletin* 1979;86:643–661. [PubMed: 482481]
- Gilbert, DG. Smoking: Individual differences, psychopathology, and emotion. Washington, DC: Taylor & Francis; 1995.
- Gilbert DG. Depression, smoking, and nicotine: Toward a bioinformational situation by trait model. *Drug Development Research* 1996;38:267–277.
- Gilbert DG. The Situation $\times$ Trait Adaptive Response (STAR) model of drug use, effects, and craving. *Human Psychopharmacology* 1997;12:S89–S102.
- Gilbert, DG.; Gilbert, BO. The situation $\times$ trait adaptive response (STAR) model of the effects of nicotine on emotional states and information processing. In: Snel, J.; Lorist, J., editors. Caffeine, social drinking and nicotine--separate and combined effects on cognition and the brain. London: Harwood; 1998. p. 131-149.
- Gilbert DG, McClernon FJ, Rabinovich NE, Dibb WD, Plath LC, Hiyane S, Jensen RA, Meliska CJ, Gehlbach BA. 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* 1999;7:427–443. [PubMed: 10609977]
- Gilbert DG, McClernon FJ, Rabinovich N, Plath LC, Jensen RA, Meliska CJ. Effects of smoking abstinence on mood and craving in men: Influences of negative-affect-related personality traits, habitual nicotine intake, and repeated measurements. *Personality and Individual Differences* 1998;25:399–423.
- Gilbert DG, McClernon FJ, Rabinovich NE, Plath LC, Masson CL, Anderson AE, Sly KF. Mood disturbance fails to resolve across 31 days of cigarette abstinence in women. *Journal of Consulting and Clinical Psychology* 2002;70:142–152. [PubMed: 11860040]
- Gilbert DG, McClernon FJ, Rabinovich NE, Sugai C, Plath LC, Asgaard G, Zuo Y, Huggenvik JI, Botros N. Effects of quitting smoking on EEG activation and attention last for more than 31 days and are more severe with stress, dependence, DRD2 A1 allele, and depressive traits. *Nicotine and Tobacco Research* 2004;6:249–267. [PubMed: 15203798]
- Gilbert DG, Meliska CJ, Williams C, Jensen RA. Subjective correlates of smoking-induced elevations of peripheral beta-endorphin and cortisol. *Psychopharmacology* 1992;106:275–281. [PubMed: 1347955]

- Gilbert DG, Sharpe JP, Ramanaiah NV, Detwiler FRJ, Anderson AE. Development of a Situation $\times$ Trait Adaptive Response (STAR) model-based smoking motivation questionnaire. *Personality and Individual Differences* 2000;29:65–84.
- Gilbert DG, Spielberger CD. Effects of smoking on heart rate, anxiety, and feelings of success during social interaction. *Journal of Behavioral Medicine* 1987;10:629–638. [PubMed: 3437451]
- Gilbert DG, Sugai C, Zuo Y, Eau Claire N, McClernon FJ, Rabinovich NE, Markus T, Asgaard G, Radtke R. Effects of nicotine on brain responses to emotional pictures. *Nicotine and Tobacco Research* 2004;6:985–996. [PubMed: 15801571]
- Gilbert, DG.; Welser, R. Emotion, anxiety and smoking. In: Ney, T.; Gale, A., editors. *Smoking and human behavior*. Chichester: Wiley; 1989. p. 171-196.
- Greenhouse SW, Geisser S. On methods in the analysis of profile data. *Psychometrika* 1959;24:95–112.
- Hatch JP, Bierner SM, Fisher JG. The effects of smoking and cigarette nicotine content on smokers' preparation and performance of a psychosocially stressful task. *Journal of Behavioral Medicine* 1983;6:207–216. [PubMed: 6620373]
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction* 1991;86:1119–1127. [PubMed: 1932883]
- Hughes, JR.; Higgins, ST.; Hatsukami, D. Effects of abstinence from tobacco: A critical review. In: Kozlowski, LT., et al., editors. *Research Advances in Alcohol and Drug Problems*. Vol. 10. New York: Plenum; 1990. p. 317-398.
- Jarvik ME, Caskey NH, Rose JE, Herskovic JE, Sadeghpour M. Anxiolytic effects of smoking associated with four stressors. *Addictive Behaviors* 1989;14:379–386. [PubMed: 2782121]
- Kalman D. The subjective effects of nicotine: methodological issues, a review of experimental studies, and recommendations for future research. *Nicotine and Tobacco Research* 2002;4:25–70. [PubMed: 11906682]
- Kassel JD, Shiffman S. Attentional Meditation of Cigarette Smoking's Effect on Anxiety. *Health Psychology* 1997;16(4):359–368. [PubMed: 9237088]
- Kassel JD, Stroud LR, Paronis CA. Smoking, stress, and negative affect: Correlation, causation, and context across stages of smoking. *Psychological Bulletin* 2003;129:270–304. [PubMed: 12696841]
- Kassel JD, Unrod M. Smoking, anxiety, and attention: Support for the role of nicotine in attentionally mediated anxiolysis. *Journal of Abnormal Psychology* 2000;109:161–166. [PubMed: 10740949]
- Lang, PJ.; Bradley, MM.; Cuthbert, BN. *International Affective Picture System (IAPS): Technical Manual and Affective Ratings*. NIMH Center for the Study of Emotion and Attention; 2001.
- Morissette BS, Palfai TP, Gulliver SB, Spiegel DA, Barlow DH. Effects of transdermal nicotine during imaginal exposure to anxiety and smoking cues in college smokers. *Psychology of Addictive Behaviors* 2005;19:192–198. [PubMed: 16011390]
- Olausson P, Jentsch JD, Taylor JR. Nicotine enhances responding with conditioned reinforcement. *Psychopharmacology* 2004;171:173–178. [PubMed: 13680077]
- Piasecki TM, Niaura R, Shadel WG, Abrams D, Goldstein M, Fiore MC, Baker TB. Smoking withdrawal dynamics in unaided quitters. *Journal of Abnormal Psychology* 2000;109:74–86. [PubMed: 10740938]
- Pomerleau CS, Pomerleau OF. The effects of a psychological stressor on cigarette smoking and on subsequent behavioral and physiological responses. *Psychophysiology* 1987;24:278–285. [PubMed: 3602283]
- Robinson TE, Berridge KC. The neural basis of craving: an incentive-sensitization theory of addiction. *Brain Research Review* 1993;18:247–291.
- Spielberger, CD. Psychological determinants of smoking behavior. In: Tollison, RD., editor. *Smoking and society: Toward a more balanced assessment*. Lexington, MA: D. C. Heath; 1986. p. 89-134.
- 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;54:1063–1070. [PubMed: 3397865]

Figure 1.

Examples of picture sequences of the Two-Choice and No-Choice Picture Attention tasks. Individuals were assigned to view four two-choice or four no-choice picture-viewing tasks during each experimental session. During each session each participant viewed, in counterbalance order, sets of dual pictures (neutral:neutral, positive:neutral, negative:neutral, and negative:positive pictures) presented either in both left and right visual fields (Two-Choice Task) or in the center of the screen (No-Choice Tasks). A given dual picture or single picture was presented once for 3 seconds and then after a 2-second pause, for an additional 3 seconds. Mood was assessed after each of the four tasks.

Figure 2. Mean and standard errors of SPAM Anxiety scores associated with the Nicotine $\times$ Positive Picture $\times$ Negative Picture interaction. Scores are for each of the four task types. Similar letters correspond to significant placebo vs. nicotine patch differences for that picture-type combination.

Figure 3.

Mean and standard errors of SPAM depressive affect scores associated with the Nicotine $\times$ Positive Picture $\times$ Choice interaction. Relative to the placebo patch, the nicotine patch was associated with less depressive affect during the two-choice picture condition with positive alternatives, but not during the other conditions. Similar letters correspond to significant placebo vs. nicotine patch differences for that picture-type combination.

Figure 4a

Figure 4b

Figure 4.

Figure 4A and 4B. Eye-Gaze Patterns across 3000 ms duration of dual picture presentations in females (Fig 4A) and males (Fig 4B) when there was an emotional (positive or negative) combined with a neutral picture in the two-choice (dual-picture) task. Values are the percentage time viewing the emotional picture relative to the neutral alternative picture. Relative to placebo patch, nicotine was associated with enhanced time gazing at emotional pictures in women, but not in men, during the first of the two consecutive presentations of a given dual-picture presentation. Similar letters correspond to this effect of nicotine in women.