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Original Investigation

Acute Stress Enhances Memory and Preference for Smoking-Related Associations in Smokers

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Abstract

Introduction: Nicotine dependence follows a chronic course that is characterized by repeated relapse, often driven by acute stress and rewarding memories of smoking retrieved from related contexts. These two triggers can also interact, with stress influencing retrieval of contextual memories. However, the roles of these processes in nicotine dependence remain unknown.

Aims and Methods: We investigated how acute stress biases memory for smoking-associated contexts among smokers ($N = 65$) using a novel laboratory paradigm. On day 1, participants formed associations between visual stimuli of items (either neutral or related to smoking) and places (background scenes). On day 2 (24 hours later), participants were exposed to an acute laboratory-based stressor (socially evaluated cold pressor test; $N = 32$) or a matched control condition ($N = 33$) prior to being tested on their memory recognition and preferences for each item and place. We distinguished the accuracy of memory into specific (ie, precisely correct) or gist (ie, lure items with similar content) categories.

Results: Results demonstrated that the stressor significantly induced physiological and subjective perceived stress responses, and that stressed smokers exhibited a memory bias in favor of smoking-related items. In addition, the stressed group displayed greater preference for both smoking-related items and places that had been paired with the smoking-related items. We also found suggestive evidence that stronger smoking-related memory biases were associated with more severe nicotine dependence (ie, years of smoking).

Conclusions: These results highlight the role of stress in biasing smokers toward remembering contexts associated with smoking, and amplifying their preference for these contexts.

Implications: The current study elucidates the role of acute stress in promoting memory biases favoring smoking-related associations among smokers. The results suggest that the retrieval of smoking-biased associative memory could be a crucial factor in stress-related nicotine seeking. This may lead to a potential intervention targeting the extinction of smoking-related context memories as a preventive strategy for stress-induced relapse.

Introduction

Addiction is widely recognized as a chronic condition with a high recurrence rate,[1] where associations between the drug-related rewards and the surrounding context contribute to the development of dependence and the tendency to relapse.[2–4] Specifically, empirical evidence supports that smokers associate rewarding memories of smoking with cues and contexts in the early phase of addiction[5] and that this effect is persistent even after the dependence is established. As memories of smoking cigarettes bind with the visuospatial context, the context alone may induce reinstatement of nicotine-seeking behavior. Hence, vivid memories of past drug use are emotionally provocative and often increase risk of relapse (a.k.a., "chasing the first high"[6]).

Several theoretical models have sought to explain drug relapse through cue reactivity.[7,8] This process involves the association of a drug reward with a neutral antecedent cue; such cues are gradually conditioned to elicit a range of involuntary responses, such as craving and physiological reactions. Consistent with this model, clinical research has primarily focused on drug-associated cues and memory for individual items.[9] Similarly, therapeutic applications have mostly focused on modification or replacement of drug-related item memory.[10,11]

In addition to the cues, drug-associated contexts can induce the urge to smoke again.[6,12,13] Neutral peripheral cues and spatiotemporal contexts bind with smoking rewards and are consolidated as long-term memories afterward. Nonhuman animal models have provided evidence that neutral contexts conditioned with drug intake provoke further drug seeking.[6,13,14] Similarly, in humans, exposure to familiar contexts associated with smoking behavior triggers memory retrieval and the urge to smoke, and therefore contributes to relapse.[5] Importantly, these contexts can be retrieved with different levels of precision. Over time, fine details of contextual information can diminish while the "gist" remains

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in one's memory (ie, less precise memory, relying more on general conceptual information during retrieval[15]), which could lead to errors such as false recognition and maladaptive decisions.[16] A recent study showed that gist-level memory for alcohol-paired contexts—and not memory for individual cues—significantly predicted prospective alcohol intake in a population of individuals with alcohol use disorder.[17] Thus, it is critical to probe memory for drug-associated contexts, including the level of precision for these memories, to understand the mechanisms by which memory drives drug-seeking choices.

Stress is a primary factor that influences memory-driven drug-seeking behaviors. Notably, stress can also significantly modulate memory retrieval.[18] While acute stress has been repeatedly shown to impair retrieval,[19] this effect varies over time[20] and is particularly strong for emotionally arousing information.[21–23] This presents a challenge for memory-based models of relapse: if stress impairs memory retrieval, how can memory contribute to drug-seeking under stress? Bornstein and Pickard (2020) suggest that stress impairs retrieval of drug-inconsistent memories, but allows retrieval of drug-consistent memories, thus facilitating drug use.[6]

In the present study, we aimed to characterize the effects of acute stress on the long-term retrieval of smoking-related episodes in active smokers. For this purpose, we developed a novel paradigm to investigate recognition of associative memory and preferences after acute stress. During encoding, smokers formed unique associations per item and place pair of visual stimuli by vividly imagining themselves using the item in the place. They recognized the specific item that had been associated with the visuospatial context (ie, place) after a 24-hour delay to ensure consolidation, which is required for long-term memory formation. Lastly, participants' preferences for smoking-related items and paired places were assessed. We hypothesized that stressed smokers would recognize smoking-related items better than neutral items, but in less detail, compared with the control group.[24] We further hypothesized that acute stress would induce greater preference for smoking-related items and places. Finally, we ran exploratory analyses to determine whether memory biases were associated with real-life smoking behaviors (as in Goldfarb et al. 2020[17]).

Methods

Participants

Written advertisements were posted online via student society websites to recruit regular smokers who smoked more than five cigarettes a day and were willing to stop smoking but not currently actively reducing their consumption and were aged 18 and above. This was to target a group of people who would be more likely to experience relapse-like symptoms after acute stress. Participants were invited to visit for a screening session and asked to abstain from alcohol, caffeine, or nicotine for 12 hours prior to the experiment. All procedures were approved by the Institutional Review Board of Seoul National University.

Screening: Clinical Measures

Participants completed semi-structured interviews of the Structured Clinical Interview for DSM-5 (SCID-V[25]) and baseline measurements during the screening session to assess substance use disorders with respect to other stimulants, opioids, and alcohol. Individuals with problematic use of any of the substances within the past 6 months were excluded. Participants were also excluded if they had been using medication that affected the hypothalamic-pituitary-adrenal axis in the past 6 months, including oral contraceptives.[20]

Exhaled carbon monoxide (CO) was measured using the Micro Smokerlyzer TM + (Bedfont Scientific Ltd, Rochester, UK). Participants with exhaled carbon monoxide levels ≥ 17 ppm were excluded after the screening session. Participants also responded to self-report questionnaires designed to assess baseline mood using the Positive and Negative Affect Scale,[26] stress with the Perceived Stress Scale,[27] nicotine dependence with the Fagerstrom Tolerance Questionnaire for Nicotine Dependence (FTND),[28] and smoking behaviors such as years of smoking history.

After the screening, participants proceeded with encoding and recognition sessions on two consecutive days. All sessions took place between 12:00 PM and 5:00 PM to account for the diurnal rhythm of cortisol,[29] which is a hormone that rises as a response to acute stress. Saliva samples for cortisol assay and subjective stress levels were collected at 4-time points as a stress manipulation check. A timeline is shown in Figure 1A.

Day 1: Encoding

The encoding and recognition tasks were based on recent work by Goldfarb et al.,[17] with modifications to the design that enabled the evaluation of associations and preferences. During the encoding task on day 1, 42 pairs of trial-unique item and place stimuli were shown on a screen (5 seconds each; image location varying randomly across trials) (Figure 1B). Participants were asked to form vivid associations per item and place pair by imagining using or carrying the item in the place and were informed that their memories would be tested the following day. They reported the levels of arousal and the valence they felt while encoding each pair using the universal pictorial assessment,[30] and how much they desired to smoke (3 seconds each). All tasks were developed using a custom-made graphical interface using Psychopy v3.0.

Day 2: Memory and Preference

Returning to the lab after 24 hours, participants first acclimated to the environment (10 minutes), and were randomly assigned to either the stress or control group. Immediately after the stress or control manipulation, participants engaged in recognition and preference tasks as described below.

Acute Stress Induction and Measurement

The socially evaluated cold pressor task was used to induce an acute stress response immediately prior to recognition.[31] During the task, participants immersed their non-dominant hand in a bath of ice-cold (3–4°C, for the stress group) or warm (33–34°C, for the control group) water, continuously for 3 minutes. An experimenter firmly told them to keep their hand in the water until they were told to remove it. In addition to this physiological stress induction and prompt to perform, the socially evaluated cold pressor task adds a social-evaluative stress component by the experimenter monitoring the participants both in-person and with a web camera on the monitor. This is known to increase the cortisol response in the stress condition.[32] Here, we had experimenters wear lab coats and talk to the stress group in an authoritative manner. Participants in the stress group were also explicitly asked

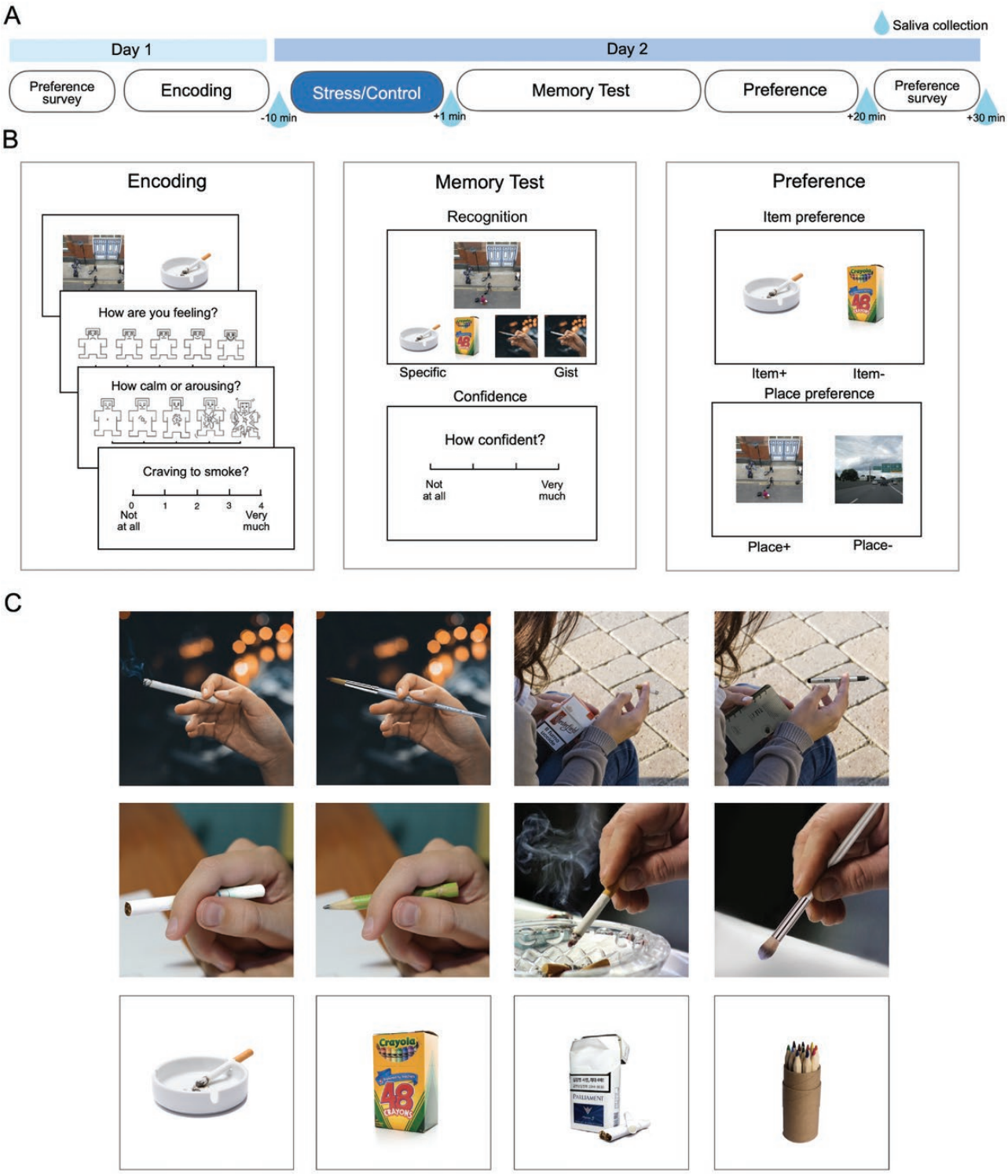

Figure 1. Experiment design and encoding result. (A) Procedure overview (B) Example screens displayed during the tasks (C) Example stimuli.

to face the web cameras, which added a socially evaluative component.

Throughout the session on day 2, we collected saliva samples to assess cortisol levels and evaluated subjective stress levels at 4-time points as a manipulation check (Figure 1A). Saliva samples were obtained by having participants place a cotton swab in the mouth at 4-time points: 10 minutes prior to, and 1, 20, and 30 minutes after the stress offset. Immediately after each saliva sample, participants rated their perceived stress levels with nine different questions including how distressed, sad, or angry they felt (0 = not at all, 100 = very much).[33]

Recognition

On day 2, participants underwent a recognition task to assess context memory (Figure 1B). On each trial, participants viewed a place (ie, background scene). Along with the place, 4 items (two smoking-related and two neutral) were presented.

These included: The item previously shown with the place (specific memory); a different item from that same category (gist memory); and 2 items from the incorrect category. All items had been shown during encoding and were thus equally familiar. Participants were asked to select the exact item they had associated with the place stimulus on day 1. Then, they rated confidence in their answer using a 4-point Likert scale (1 = not confident at all, 4 = very confident). By cueing participants with the place, this task aimed to emulate real-life situations in which drug-associated contexts promote relapse via retrieval of the drug event (eg, remembering that they had imagined using a cigarette in that place on the previous day).

Preference

After memory recognition, participants completed a binary choice task, in which they were presented with two images and instructed to select one image that they preferred (Figure 1B). The task consisted of two blocks, during which "item" or "place" stimuli were presented in each block in random order across participants. During the item block, participants were asked to choose between a pair of familiar item stimuli (N = 21 trials). Similarly, in the place block, participants chose their preferred place from two familiar place images that had been associated with items from different categories on day 1 (N = 21 trials). Although this was not explicitly stated, this task allowed the assessment of preference for places that had been paired with smoking-related versus neutral items. At the end of the experiment, participants completed a survey and rated their preference for each background scene image (1 = not preferred at all, 4 = very preferred) used in the behavioral tasks.

Visual Stimuli

We constructed two sets of visual stimuli (*item* and *place* sets) for the behavioral tasks (Figure 1C). The *item* set comprised two stimulus categories: Cigarettes (N = 21) and neutral items (N = 21). All images were retrieved from public sources,[34–36] with items separated into subcategories of: Items against a white background (eg, a cigarette pack), people interacting with items (eg, a cigarette in the hand), and supplementary items typically encountered when smoking (eg, an ashtray). For neutral items, we selected writing tools due to their perceptual similarity to cigarettes (ie, hand-held size, thin, cylindrical) and intra-category similarity (ie, pens are similar to each other).

The *place* set included scene images from standardized databases.[37] Similar to the items, it comprised different categories of places including beaches, cities, and fields. Following a validation experiment, we created a final set of items (N = 42) and placed (N = 42) images (Supplementary Figure 1). During the main experiment, all stimuli were presented at the same resolution (500 × 500 px) and the same size (11.5 × 11.5 cm).

Analytic Approach

The goal of the main analyses was to determine the effects of acute stress on memories and preferences for smoking-related items and places. All statistical analyses were performed using R 4.0.3.

We used two-way ANOVA and follow-up independent and paired t-tests for within-group analyses as appropriate. We used ANOVA to test Category effects (smoking vs. neutral object) on affective responses (ie, arousal, craving to smoke, and valence) during memory formation in encoding task. Differences between stress and control groups (in demographic characteristics and subjective responses to the stressor task) were computed using chi-squared tests and independent-sample t-tests as appropriate. To confirm that the stress manipulation was successful, we ran ANOVA that included time, group, and their interaction as predictors. Salivary cortisol concentrations (controlled for baseline levels) were analyzed by one-way ANOVA for group comparison; then the area under the curve with respect to ground was computed (AUCg[38]). For memory, recognition responses rated as "not confident at all" were excluded from the analysis (control group: N = 8.55, stress group: N = 7.48 trials per subject) to remove random guesses. We used an independent-sample t-test to confirm that the number of excluded trials did not significantly differ between groups. All main analyses were repeated including these trials rated as "not confident at all," where the main results were held across all trials (Supplementary Table S1).

Within the confident trials, associative memory performance was quantified as the proportion of trials that indicated each memory type (specific and gist). Specific memory was computed from trials in which participants correctly retrieved the exact item associated with the place. Gist memory was quantified as trials for which the incorrect item from the same category was selected. One-sample t-test was used to compare specific memory scores with the chance level (25%) of choice and ANOVA was used to compare memory performance, with group, Category, and their interaction included in the model. For the preference task, the proportion of times each category was chosen over the other was computed as the preference for each category and later included in the former memory model as a covariate. For exploratory analyses testing associations between memory and baseline smoking behavior, we used a linear model in which memory for each type and stimulus category were included as variables to explain the years of smoking.

Results

Participant Demographics

Seventy-two healthy individuals participated in the screening session. Of these, some were excluded due to the indication of more than two symptoms of alcohol dependency during the SCID (N = 4); not understanding task instructions (N = 1); or failing to complete the experiment (N = 2). In total, 65 participants between the ages of 18 and 36 were included in the final analysis. The control group included 33 participants, while the stress group included 32 participants. The two groups did not differ with respect to demographic factors, smoking behavior, or baseline cortisol concentration (Table 1 and Supplementary Table S2).

Affective Responses During Encoding

During the encoding session, the participants rated the smoking *item and place* pairs as more emotionally salient compared to the neutral *item and place* pairs. Specifically, smoking pairs were rated as more arousing (Category; $F(1,128) = 7.88$, $p = .006$, $\eta^2 = 0.06$) and as inducing a stronger desire to smoke (Category; $F(1,128) = 11.76$, $p < .001$, $\eta^2 = 0.08$), compared with neutral pairs. Similarly, smoking-related pairs were rated as significantly more positive (M = 3.13,

Table 1. Demographic Information and Baseline Intake Measures

Variables	Control ($N = 33$)		Stress ($N = 32$)			
	M	*SD*	*M*	SD	*t*	*p*
Age	24.97	3.94	23.72	2.84	1.47	.850
Sex (% male)	14.58	10.71	13.97	7.44	0.27	.791
Urge to quit	0.76	1.21	0.67	1.00	0.32	.748
Years of smoking	17.61	6.93	18.06	4.87	−0.31	.759
FTND	2.18	1.88	2.28	2.04	−0.20	.839
Baseline COHB (%)	1.22	0.37	1.32	0.44	−1.03	.360
Baseline cortisol (*μg/dL*)	0.16	0.07	0.20	0.09	1.75	.086

Variables	Control ($N = 33$)		Stress ($N = 32$)			
	N	%	N	%	χ^2	p
Daily smokes	-	-	-	-	4.32	0.229
<5 smokes	3	9.09	2	6.25		
5-10 smokes	16	48.48	13	40.62		
10-20 smokes	12	36.36	16	50.00		
>20 smokes	2	6.06	1	3.12		

SD = 0.42) than the neutral pairs ($M = 3.00$, SD = 0.42; $F(1, 128) = 4.08$, $p = .045$, $\eta^2 = 0.03$). This result was as expected because the encoding occurred prior to stress exposure. Consistently, no group difference was observed in all affective responses (group; arousal: $F(1, 63) = 0.15$, $p = .698$, $\eta^2 = 0.002$, valence: $F(1,63) = 0.38$, $p = .542$, $\eta^2 = 0.01$, craving: $F(1, 63) = 1.14$, $p = .291$, $\eta^2 = 0.102$; group × category; arousal: $F(1,126) = 0.23$, $p > .250$, $\eta^2 = 0.02$, craving: $F(1,126) = 1.99$, $p = .161$, $\eta^2 = 0.0$, valence: $F(1,126) = 0.01$, $p > .250$, $\eta^2 = 0.00$).

Acute Stress Manipulation

Subjective Stress Response

The stress group reported a significantly higher level of perceived stress compared with the control group (group: $F(1, 252) = 7.87$, $p = .005$, $\eta^2 = 0.03$; group × timepoint: $F(3, 252) = 1.77$, $p = .15$). The difference was significant immediately after completion of the stressor task (+1 min: $F(1, 63) = 12.18$, $p < .001$, $\eta^2 = 0.16$) but not during the subsequent time-points (+20 min: $F(1, 63) = 1.20$, $p > .25$, $\eta^2 = 0.02$; +30 min: $F(1, 63) = 1.21$, $p > .25$, $\eta^2 = 0.02$) (Figure 2A).

Physiological Stress Response

Prior to the stress induction, groups did not differ in baseline cortisol levels (10 minutes prior to stress offset; Table 1). Salivary cortisol levels in the stress group gradually increased after stress offset (group: $F(1, 252) = 108.89$, $p < .001$, $\eta^2 = 0.21$; group × timepoint: $F(3, 252) = 31.24$, $p < .001$, $\eta^2 = 0.18$). These levels relative to the baseline also significantly differed from levels in the control group at 20 minutes and 30 minutes after stress offset (+1 min: $F(1, 57) = 2.50$, $p = .12$, $\eta^2 = 0.04$; +20 min: $F(1, 57) = 63.11$, $p < .001$, $\eta^2 = 0.50$; +30 min: $F(1, 57) = 46.96$, $p < .001$, $\eta^2 = 0.43$) (Figure 2B). These results are consistent with previous findings of a 15- to 20-minute delay in salivary cortisol increase after a stressful event.[31] The AUCg also significantly differed between groups ($t(32) = -5.76$, $p < .001$). The behavioral tasks took place between the second and the third time points (Figure 2, shaded regions), during which salivary cortisol was ramping up.

Retrieval

Specific Memory

Memory for the smoking-related associations was significantly above chance (25%) in both groups (stress: 41.4%, $t(31) = 10.23$, $p < .001$; control: 45.2%, $t(32) = 14.80$, $p < .001$), as was memory for neutral associations (stress: 29.8%, $t(31) = 10.23$, $p < .001$; control: 36.5%, $t(32) = 12.96$, $p < .001$).

Participants in both groups were more precise in recognizing smoking-related items compared to neutral items when presented with the associated place (Figure 3A; $F(1, 126) = 12.48$, $p < .001$, $\eta^2 = 0.09$). Furthermore, there was a marginal main effect of group, with stress leading to worse specific memory ($F(1, 126) = 3.39$, $p = .068$, $\eta^2 = 0.02$).

Gist Memory

Next, we analyzed gist-level responses to test for stress or category effects on less-detailed memory. As with specific memory, there was a main effect of image category, with higher gist recognition for smoking-related items ($F(1,126) = 5.03$, $p = .027$, $\eta^2 = 0.04$). Although there were no significant differences in gist memory between the groups ($F(1, 126) = 2.21$, $p = .14$, $\eta^2 = 0.02$), we observed a significant interaction between group and stimulus category ($F(1, 126) = 5.19$, $p = .037$, $\eta^2 = 0.04$) (Figure 3B). When we performed post hoc analysis within the stress group, participants displayed greater gist memory for the smoking-associated stimuli than neural stimuli ($t(31) = -3.1$, $p = .004$). In other words, smokers exposed to stress were more likely to choose the wrong item from the correct category, particularly for the smoking stimuli. This was not evident for smokers in the control condition.

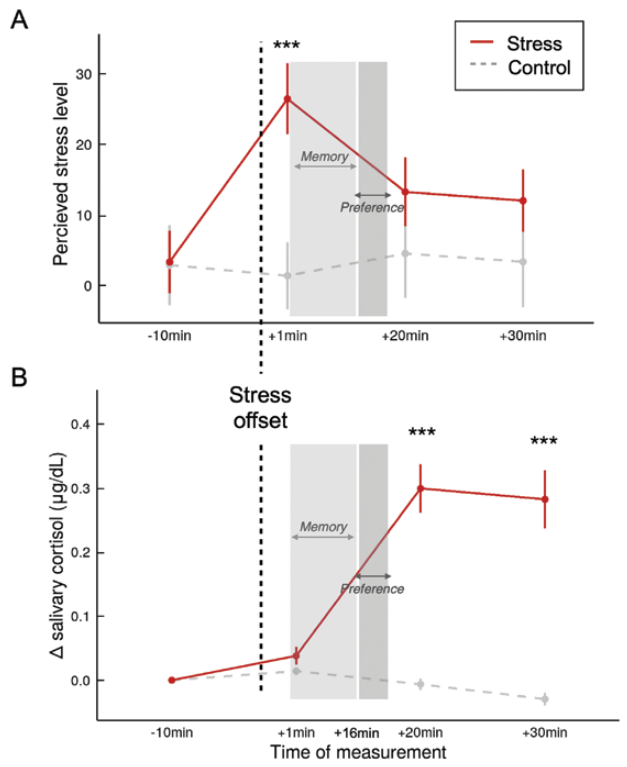

Figure 2. Stress inducement measurements. (A) Perceived stress level across time points. (B) Change in salivary cortisol level across time points. Each delta value was computed by subtracting the baseline cortisol level from the subsequent time points' cortisol level. Error bars = 1 ± SE, ***$p < .001$.

Preference

Preference for Item Stimuli

Following the memory tests, we assessed whether stress modulated preferences for smoking-related and neutral items. When participants could only select one item, the control and stress groups showed distinct preference patterns (group × category: $F(1, 126) = 4.28$, $p = .04$, $\eta^2 = 0.03$; category: $F(1, 126) = 0.70$, $p > .25$, $\eta^2 = 0.005$). The stress group preferred smoking-related items over neutral items ($t(62) = 2.15$, $p = .035$) while the control group did not, instead showing a nonsignificant preference for neutral items ($t(64) = 0.83$, $p > .25$).

Preference for Place Stimuli

In addition to these biases toward items, we explored how preferences for related contexts (represented by place stimuli) differed between groups due to acute stress. Notably, these places were initially neutral images that had not been favored or disliked before the experiment and were associated with smoking-related or neutral items during encoding.

Across groups, participants were more likely to select places that had been associated with smoking-related items compared to neutral items ($F(1, 126) = 6.14$, $p = .015$, $\eta 2 = 0.04$). However, this tendency did not differ between groups (group × category: $F(1, 126) = 0.75$, $p > .25$, $\eta^2 = 0.01$) (Figure 3C).

Relationships Between Preference and Memory

The results above demonstrate that smokers exposed to stress prior to retrieval had both stronger "gist" and "specific" memories for smoking-related items compared to neutral items when prompted by the paired context, as well as a stronger bias toward preferring smoking-related items. To further investigate acute stress effects on memory, we additionally tested whether memory performance was related to choices in the preference task. Importantly, even after accounting for preference, the significant group by-category interaction explaining gist memory was maintained ($F(1, 125) = 4.91$, $p = .029$, $\eta^2 = 0.04$), as well as the main effect of category ($F(1, 125) = 5.00$, $p = .027$, $\eta^2 = 0.04$), indicating that stress influenced memory processes beyond shifting preferences.

Bridging Real-Life Smoking With Memory

We next took an exploratory step to link our laboratory assessments of memory to real-life severity of nicotine dependence. Specifically, we tested whether specific and gist-level memory performance differed based on years of smoking, collapsed across groups.

We found a negative association with specific memory, with stronger specific memory among individuals who had not smoked for as long ($F(1, 122) = 6.83$, $p = .010$, $\eta^2 = 0.05$). On the other hand, gist memory was marginally stronger for those with longer history of smoking ($F(1, 122) = 3.84$, $p = .052$, $\eta^2 = 0.03$). This effect persisted when daily amount of smoking was added to the model (Specific memory: $F(1, 121) = 6.77$, $p = .010$, $\eta^2 = 0.05$; Gist memory: $F(1, 121) = 3.81$, $p = .053$, $\eta^2 = 0.03$).

Discussion

Our study revealed a novel bias in memory and preference for smoking-associated stimuli among smokers under acute stress. Using a between-subjects design, we demonstrated that stress induced a bias toward an enhancement of generalized (ie, gist-level) memory for smoking-related associations alongside an impairment in precise (ie, specific) memory. The stress group also preferred smoking-related items to neutral items, unlike the control group. Additionally, we observed a marginal link between gist memory and the level of smoking dependence. Put together, acute stress-induced both memory and preference biases for smoking-related items in smokers.

The current findings are in line with past literature on the effects of nicotine and drug-related cues on memory. Overlaps in brain regions purportedly responsible for cognitive bias towards smoking-related items and contexts emphasize the contribution of episodic memory in the development of further drug dependence.[39] Furthermore, our finding of stronger gist memory for smoking-related associations is consistent with a recent study, which reported that stronger gist memory for alcohol-paired contexts was associated with higher drinking in the future.[17] Nicotine's effect on increased gist memory has been noted in realistic spatial contexts, as Ruiz et al. (2020)[40] found that smokers who smoked more, or more recently, recognized the gist of the context better.

At the same time, acute stress prior to or during retrieval has often been reported to impair episodic memory (for a review, see24). Our findings extend previous work demonstrating that acute stress causes loss of fine details in memory retrieval.[41,42] The "dual-mode" model assuming a fast-acting mode of memory encoding and relatively slower mode of memory storage predicts that pre-retrieval stress would disturb adaptive shifts between modes and thus impair

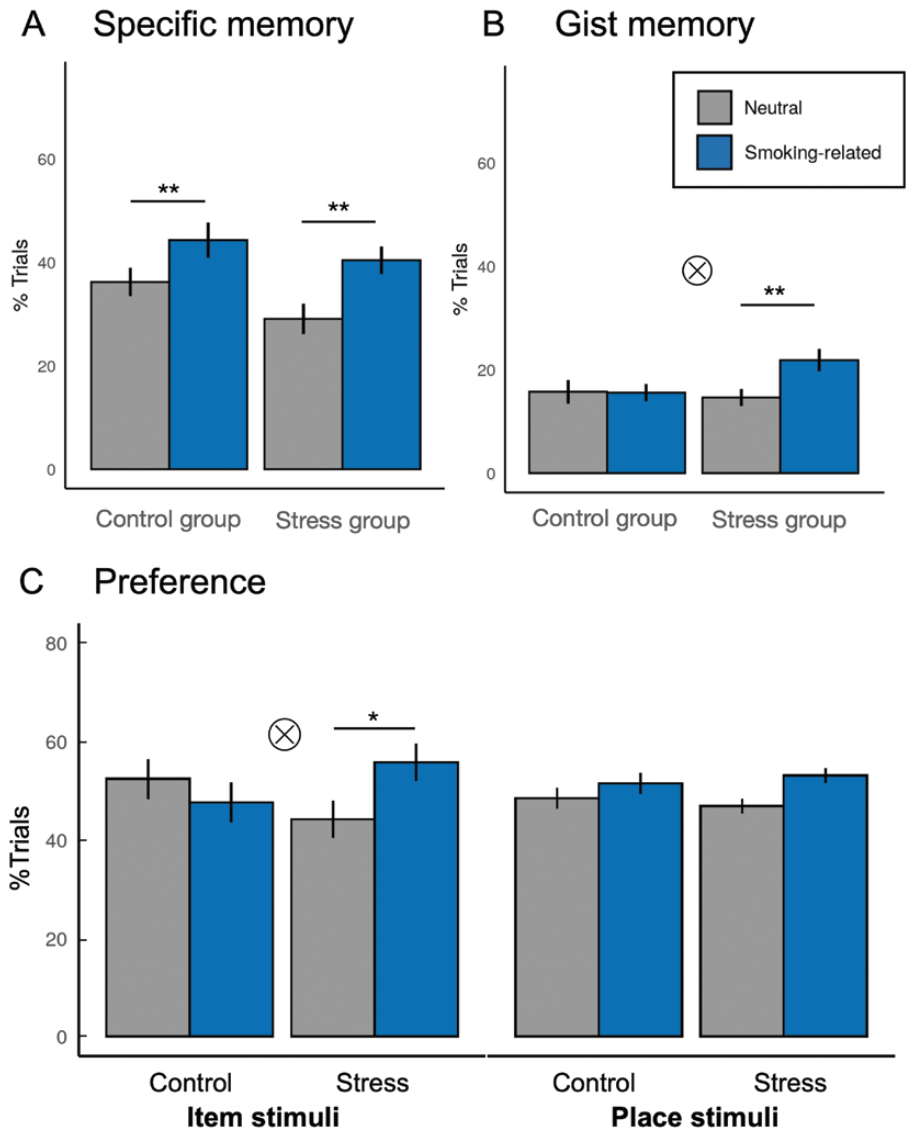

Figure 3. Behavioral task results. (A) Specific memory performance. (B) Gist memory performance. (C) Preference choice task results for item and place conditions (left), compared by stimulus category within each group. The *y*-axes indicate ratio of trials that fall into each subgroup of memory performance (ie, specific and gist), out of the total retrieval trials that were not rated as "not confident at all." Error bars = 1 ± SE, $*p < .05$, $**p < .01$. ⊗ indicates significant interaction effect.

retrieval.[43,44] Consistent with these negative stress effects, smokers exposed to pre-retrieval stress in the current study had worse memory for detailed associations.

However, stress led to stronger, albeit less detailed, memories particularly associated with smoking. This suggests that acute stress promotes retrieval of smoking-related experiences, or a heightened tendency to assign smoking-related values to contexts, perhaps indicating a mechanism by which stress promotes relapse. While past studies mainly targeted false recognition memory, our design enabled us to successfully distinguish levels of precision in associative memory while controlling for the familiarity of each stimulus.[45] This novel stress-induced memory bias was persistent after accounting for participants' stress-induced preference for smoking-related items and places.

In addition to memory biases, we identified a significant interaction between group and stimulus categories in preference for items, meaning that the stress group preferred smoking-related items more than the control group. This pattern may be associated with the role of stress in increasing the cost of self-control and leading one to pre-commit.[46] Considering that our recruited smokers all reported that they were willing to quit, this pattern may indicate an intentional avoidance of smoking-related items in the control group that was disrupted under acute stress.

Smokers in both groups preferred places associated with smoking-related items. Along with the gist memory bias, this pattern possibly implies a generalization of the rewarding values of drug-related items to associated neutral places.[47] Unlike items (which have intrinsic smoking-related value), preferring places would be driven by remembering their association with smoking-related items during learning. Similarly, in non-human studies, conditioned place preference (in which contexts are associated with addictive drugs) has been extensively investigated as a model for addiction-related behavior. Stress has been shown to enhance the rewarding effects of substances and associated places in these models,[45,48] but few studies have reported such findings with human participants.

Our work takes an important step toward translating this work to substance use in humans and elucidating the role of context memory in drug seeking.

In conclusion, the current study identifies the role of acute stress in promoting memory biases and preference toward smoking-related associations with a novel behavioral paradigm. The findings suggest that the management of associative memory retrieval, especially in spatial contexts, may play a key role in stress-related nicotine seeking. Based on the current results, treatment for nicotine dependence and its stress-induced relapse could target episodic memory of contexts. For example, recent work revealed that prolonged extinction training on cue-elicited memory can attenuate the cue-induced desire to smoke,[10] yet these clinical applications to date have not addressed contextual memory. Considering the impact that stress and vivid memory of drug use pose on actual drug-seeking behavior, revealing the contribution of drug-related context memory would provide important insights for relapse prevention. To this end, future studies could track prospective smoking behaviors to better understand the mechanism of actual relapse.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Author Contributions

Jeung-Hyun Lee (Conceptualization [Lead], Data curation [Lead], Formal analysis [Lead], Investigation [Lead], Methodology [Lead], Project administration [Lead], Visualization [Lead], Writing—original draft [Lead], Writing—review & editing [Equal]), Sanghoon Kang (Conceptualization [Equal], Validation [Equal]), Silvia Maier (Methodology [Supporting], Writing—review & editing [Supporting]), Sang Ah Lee (Conceptualization [Supporting], Writing—review & editing [Supporting]), Elizabeth Goldfarb (Conceptualization [Supporting], Formal analysis [Supporting], Supervision [Supporting], Writing—review & editing [Equal]), and Woo-Young Ahn (Conceptualization [Equal], Funding acquisition [Lead], Project administration [Equal], Resources [Lead], Supervision [Equal], Writing—review & editing [Equal]).

Declaration of Interests

The authors have no conflicts of interest to declare.

Data Availability

The raw behavioral data and limited biometric data for this study are available upon request.

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