Subjective and Autonomic Responses to Smoking-Related Visual Cues

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Abstract: Nicotine, like several other abused drugs, is known to act on the reward system in the brain. Smoking-associated cues produce smoking urges and cravings accompanied by autonomic dysfunction to these cues in smokers. The present study was aimed at investigating whether cues related to smoking elicit the autonomic response in smokers. The subjective and physiological reactivity of 7 smokers and 12 nonsmokers in a supine position to smoking-related visual cues was assessed under indirect dim light using a self-assessment manikin and a specially designed pupillometer. The experimental procedure consisted of the elicitation and measurement of pupil size (PS) while the subjects viewed a smoking image and images from three valence-defined categories (i.e., pleasant, unpleasant, and neutral), based on normative affective ratings selected from the International Affective Picture System. Both groups produced significantly larger PS increases in response to pleasant or unpleasant images compared to neutral images. Smokers, viewing smoking-related visual cues but no other affective images, produced significantly larger PS's compared to nonsmokers. Moreover, smokers rated the smoking image with more pleasure and arousal than nonsmokers. These findings suggest that cues related to smoking induce not only a subjective emotional alteration, but also sympathetic activation, measured by the time-series PS data in smokers.

Key words: addiction, autonomic, emotion, nicotine, arousal.

A great many studies suggest that responses to drug-related cues maintain drug use and undermine cessation attempts [1]. Exposure to smoking-related cues has been reported to increase self-reported craving and cardiovascular reactivity compared to neutral cues, and enhanced cue reactivity predicts a decreased likelihood of successful cessation [2]. In smokers, smoking-related cues elicit smoking urges and craving, which are accompanied by an attentional bias for these cues [3]. Cue reactivity has been considered a key factor that modulates motivational goal-directed behavior associated with compulsive drug taking and relapse.

Psychophysiological variables of interest during affective picture viewing have changed skin conductance response and heart rate as reliable indicators of arousal [4]. Numerous laboratory-based cue reactivity studies have found that various drug-related cues elicited strong cravings and physiological responses among addicts, such as alcoholics and smokers [5, 6]. Based on the incentive sensitization theory, the central mechanisms of smoking-associated salient stimuli on brain activation have been investigated using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) [7]. Reactivity to smoking cues has been commonly indexed by behavioral measures as well as measures of autonomic nervous system (ANS) activity, including systolic and diastolic blood pressures, vasoconstriction, heart rate, heart rate variability, and event-related heart rate deceleration [8, 9].

Pupil size (PS) has been used as a parameter in quantitative analysis of the ANS. Several studies have been conducted to observe the PS as an indicator of sympathetic activation on painful stimuli, postural change, mental workload, and emotional stimuli [10–12]. Brief visual exposure prompted autonomic and somatic reflexes of defense and appetite that confirmed emotional engagement [13]. However, few studies have examined the autonomic response to smoking-associated cues using the pupillometer. A time-series alteration of PS to smoking-related visual cues would be a good index to detect the subtle change in ANS activity.

The purpose of the present study was to determine whether cues related to smoking evoke an alteration of the ANS in smokers using a pupillometer.
METHODS

Subjects. The subject pool of 19 participants (age, mean 24.3 ± 0.4 year; 16 males, 3 females) consisted of 7 smokers who smoked at least 5 cigarettes per day and 12 nonsmokers who had never smoked. The smokers were screened for smoking history (cigarettes per day, mean 10.6 ± 1.5, and duration of smoking career, mean 6.7 ± 1.0 years). The smokers agreed to abstain from smoking during the 3-h period prior to the experimental procedures. None of the participants had a history of psychiatric disorders, ophthalmic diseases, or other substance abuse. All subjects were prohibited from alcohol, caffeine, and medical drugs. They agreed to participate in this experiment, and written informed consent was obtained. The protocol used in this study was approved by the Kyung Hee University Institutional Review Board.

Procedures. The experiments were conducted in an air-conditioned (22 ± 2°C), soundproof dark room (illumination of 0.6 lux under indirect dim light). The physiological reactivity of 7 smokers and 12 nonsmokers in a supine position to smoking-related visual cues was assessed using a specially designed pupillometer. The experimental procedure consisted of the elicitation and measurement of PS while viewing one smoking image and six standard affective images selected from the International Affective Picture System (IAPS) [14]. The standard affective images were derived from the IAPS (IAPS catalog numbers for pictures used, Neutral: 7,010 basket, 7,090 book, 7,550 office, 2,190 man; Pleasant: 4,660 erotic couple; Unpleasant: 3,010 mutilation). The smoking-related stimulus was also selected from the IAPS (IAPS catalog numbers for pictures used, Neutral: 2,715 smoking). The four neutral images, one pleasant image, one unpleasant image, and one smoking-related image, were presented to each subject in the following block design (Fig. 1). Each block consisted of a 5-s preparation (viewing blank images), a 10-s IAPS presentation (viewing IAPS images), and a 15-s evaluation (viewing blank images). The blank images consisted of visual stimuli with the same brightness and contrast. The pictures were displayed on a 55-cm monitor, with a maximum size of 44 × 33 cm, and presented approximately 1.8 m from the participant’s eyes with a visual angle of 14° horizontally and 11° vertically. The neutral images were averaged with four neutral images. All images were presented in gray scale to remove differences resulting from color composition. Differences in brightness and contrast related to luminosity were adjusted using commercial digital editing software packages. All procedures lasted for 210 s.

Physiological measurements. Pupil images were obtained using the pupil image acquisition and storage sys-

Fig. 1. Each block consisted of 5-s preparation (viewing blank images), 10-s IAPS presentation (viewing IAPS images), and 15-s evaluation (viewing blank images). All procedures lasted for 210 s. The four neutral images (7,010 basket, 7,090 book, 7,550 office, 2,190 man), one pleasant image (4,660 erotic couple), one unpleasant image (3,010 mutilation), and one smoking-related image (2,715 smoking) were presented to each subject in each block design.
system, which was designed in the author’s lab [15]. The pupil image acquisition system consisted of an infrared camera, an illumination module, a hot mirror module, a guide rail module on the helmet, and a light-source module. The helmet-type pupil image acquisition system was designed for a less-invasive measurement of unintended autonomic response of the pupil. Pupil images were stored at 30 frames/s and were processed to estimate the PS.

**Self-assessment measurements.** Valence, arousal, and dominance ratings were obtained using a self-assessment manikin (SAM) [14]. The SAM consisted of humanlike figures that embodied the dimensions of valence, arousal, and dominance, with five figures representing nine intensity levels within each dimension. This subjective assessment method has been extensively validated and is widely used in cue reactivity research [16]. Following the physiological recording, the pupillometer was removed, and participants reviewed and used the SAM to rate each of the images. The images were presented again during 10 s with an interimage interval of 20 s to complete their ratings.

**Data analysis.** The time-series PS data were estimated from the pupil image storage system. The increase rate in PS during pleasant image presentation is shown in Fig. 2B. The mean change in PS of the smokers was similar to that of the nonsmokers. The repeated measures ANOVA showed no significant effect of interaction ($F[1,28] = 0.522, p > 0.919$), a Time effect ($F[1,28] = 0.672, p > 0.800$), or a Group effect ($F[1,28] = 0.000, p > 0.984$).

The mean change in PS during pleasant image presentation is shown in Fig. 2B. The repeated measures ANOVA showed no significant effect of interaction ($F[1,28] = 10.934, p < 0.000$). However, no significant interaction ($F[1,28] = 0.896, p > 0.564$) or Group effect

**RESULTS**

**Self-assessment measures**

For each of the SAM measures, we examined profiles on image category variable sets. We conducted three $2 \times 4$ repeated measures ANOVAs with Group as the between factor and Image (neutral, pleasant, unpleasant, and smoking) as the within factor (Table 1). Regarding valence, the results revealed a significant effect of Image ($F[3,72] = 42.391, p < 0.001$) and a significant interaction (Group $\times$ Image) effect ($F[3,72] = 3.555, p < 0.05$). The image effect confirmed the expectation that valence would change as a function of the image type. Simple effect analyses testing for valence differences between groups for each of the image types revealed only significant between-group differences for the smoking-image valence ($F[1,36] = 11.618, p < 0.01$). Valence ratings for neutral, pleasant, and unpleasant images were not significantly different between smokers and nonsmokers.

The results found that arousal and dominance ratings across the neutral, pleasant, unpleasant, and smoking images in smokers and nonsmokers followed a pattern similar to that described for the valence ratings. We found significant Image effects for arousal ($F[3,72] = 13.578, p < 0.001$) and for dominance ($F[3,72] = 14.845, p < 0.001$), but no significant interaction (Group $\times$ Image) effect for arousal ($F[3,72] = 2.713, p > 0.054$) or for dominance ($F[3,72] = 0.668, p > 0.576$). Moreover, an arousal difference ($F[1,36] = 5.610, p < 0.05$) between smokers and nonsmokers was found for the smoking image with the simple effect analysis. However, a dominance difference between smokers and nonsmokers was not found for all images using the simple effect analysis.

**Physiological measures**

For each of the PS measures, we conducted four $2 \times 15$ repeated measures ANOVAs with Group as the between factor and Time as the within factor in each image. The mean change in PS during neutral image presentation is shown in Fig. 2A. The mean change in PS of the smokers was similar to that of the nonsmokers. The repeated measures ANOVA showed no significant effect of interaction (Group $\times$ Time) ($F[1,28] = 5.22, p > 0.919$), a Time effect ($F[1,28] = 0.672, p > 0.800$), or a Group effect ($F[1,28] = 0.000, p > 0.984$).

The mean change in PS during pleasant image presentation is shown in Fig. 2B. The repeated measures ANOVA showed a significant Time effect ($F[1,28] = 10.934, p < 0.000$). However, no significant interaction (Group $\times$ Time) ($F[1,28] = 0.896, p > 0.564$) or Group effect

| Table 1. A self-assessment manikin for each visual cue. |
|---------------------------------------------------------|
| **Neutral** | **Pleasant** | **Unpleasant** | **Smoking** |
| **Non-smoker** | **Smoker** | **Non-smoker** | **Smoker** | **Non-smoker** | **Smoker** | **Non-smoker** | **Smoker** |
| Valence | 5.10 | 5.00 | 6.33 | 7.43 | 1.42 | 2.43 | 3.08 | 5.88 |
| Arousal | 3.90 | 3.89 | 6.50 | 6.43 | 7.25 | 6.57 | 4.67 | 6.71 |
| Dominance | 5.96 | 6.25 | 5.92 | 6.14 | 3.17 | 4.00 | 5.83 | 7.43 |

Means and (standard errors) of valence, arousal, and dominance to the images in smokers and nonsmokers.
The mean change in PS during unpleasant image presentation is shown in Fig. 2C. The repeated measures ANOVA showed a significant Time effect ($F_{[1,28]} = 5.418, p < 0.001$). However, no significant interaction ($\text{Group} \times \text{Time}$) ($F_{[1,28]} = 0.455, p > 0.954$) or Group effect ($F_{[1,28]} = 0.256, p > 0.620$) was observed. For the unlikely neutral image, a Time effect confirmed the expectation that the PS's of both groups would change in accordance with a response to a pleasant or unpleasant image. These autonomic responses to emotional cues of the smokers, including pleasant and unpleasant images, were similar to those of the nonsmokers.

The mean change in PS during the smoking image presentation is shown in Fig. 2D. The repeated measures ANOVA showed a significant effect of interaction ($\text{Group} \times \text{Time}$) ($F_{[1,28]} = 3.684, p < 0.001$), a Time effect ($F_{[1,28]} = 1.930, p < 0.05$), and a Group effect ($F_{[1,28]} = 7.819, p < 0.05$). In the smoking image, a Group $\times$ Time effect revealed that a time-series PS before and after image presentation was different between the smokers and the nonsmokers. The autonomic responses of smokers to a smoking image were significantly higher than those of the nonsmokers.

Correlation analysis between physiological changes and subjective responses

Exploratory correlation analysis between the change in PS (difference in PS between and during each visual cue) and each SAM rating revealed a significant positive corre-
The change in pupil size (PS) was highly correlated with arousal ratings \( (r = 0.304, p < 0.001) \), but not with valence \( (r = 0.082, p > 0.346) \) or dominance \( (r = -0.043, p > 0.620) \). Each graph shows the results of the correlation analysis of one element of the SAM ratings (A: valence, B: arousal, C: dominance) with the change in PS before and during each visual cue, including four neutral, one pleasant, one unpleasant, and one smoking image.

**DISCUSSION**

Our findings demonstrated that a smoking-related visual cue induced not only subjective emotional alteration but also autonomic responses measured by the time-series PS data in smokers. To the best of our knowledge, this is the first study to incorporate the IAPS paradigm to study cue reactivity to smoking cues using a pupillometer. Smoking-related visual cues give rise to pupil dilation responses, which are indicative of a change in the ANS. Other emotional visual cues, such as pleasant or unpleasant images, also elicited arousal responses and an increase in the PS. We further observed that the degree of pupil dilation to the visual cues was quantitatively related to the amount of the subjective arousal ratings to the cues.

In the SAM ratings, other types of images included in the present study produced differentiating reactivity in valence, arousal, and dominance, both for smokers and nonsmokers. The increase in arousal to pleasant or unpleasant images in both smokers and nonsmokers is consistent with the previous report that as pictures are rated as more pleasant or more unpleasant, arousal ratings also increase, and pictures that are rated as neutral tend to be rated low in arousal as measured by the SAM rating and skin conductance response [14]. Smokers rated the smoking-related visual cues as more pleasant and more arousing than nonsmokers in the present study. Although some argue that eliciting the smoking craving might increase a negative mood, and cue exposure studies in general tend to increase a positive mood. High chocolate cravers compared to low chocolate cravers reported more pleasure and arousal to chocolate images [17]. Food-deprived and binge-eater subjects produced startle potentiation to food cues and rated these stimuli as more pleasant compared to restrained eaters and control groups [18]. Similarly, the visual smoking cues observed in our study are quite likely to be more salient in smokers than in nonsmokers.

Pupil diameter is known to be regulated by the ANS. Two antagonistic smooth muscle systems of a continuously varying activity result in a dynamic equilibrium that is expressed as pupil diameter. Several studies have conducted to observe PS an indicator in quantitative analysis of the sympathetic change during painful stimuli, postural change, mental workload, and emotional stimuli in many domains of cognitive psychology [10–12]. However, studies relating time-series PS to emotional visual cues and smoking-related visual cues had not yet been conducted. The present study found that subjects produced a larger PS in response to pleasant or unpleasant images, but not to neutral images, regardless of smoker or nonsmoker status.

It is well known that the central modulation of sympathetic and parasympathetic activities plays a crucial role in a dynamic equilibrium of PS [19]. Increases in sympathetic activity are characteristically accompanied by a central inhibition of parasympathetic activity. This inhibition is mediated by the two pathways [20]. A noradrenergic pathway connects the locus coeruleus (LC) to the Edinger-Westphal nucleus, and the other pathway connects the A1/A5 nuclei in the brainstem to the Edinger-Westphal region by way of the hypothalamus. A recent neuroimaging study found that the coordinated action of the amygdala...
and the noradrenergic LC during retrieval might facilitate the activation of the parahippocampal region, and that the response in the LC resulting from this interaction was related to the emotional arousal during encoding, as assessed by the pupillary size [21]. In the present study, autonomic responses to emotional cues, including pleasant and unpleasant images, were congruent with the previous report that sympathetic activity measured by skin conductance response was reliably enhanced when viewing pleasant or unpleasant pictures, compared to neutral ones [14]. Furthermore, the increases in PS to the emotional visual cues were positively correlated with the subjective arousal rating in the present study. Therefore it is assumed that the enhanced pupillary response to emotional or smoking-related visual cues was associated with sympathetic activation. To examine the role of parasympathetic activity in regard to the pupil responses in this experiment, however, it will be necessary to perform a functional neuroimaging study with the multidimensional measurements of the autonomic nervous system in the future.

In smokers, viewing the smoking-related visual cue, but not other emotional visual images, significantly produced a larger increase in PS compared to nonsmokers. These enhanced autonomic responses to the smoking image were observed only in smokers. Moreover, physiological change to the smoking image in smokers measured by the pupillometer was compatible with the subjective measures that caused smokers to rate the smoking image as more pleasant and more arousing. In accordance with previous reports [8, 9], our results also showed that the smoking-related visual cue elicited autonomic responses in smokers.

In the present study, smokers and non-smokers both produced a small amount of up-and-down change of PS in response to the neutral cues (Fig. 2A). These results were similar to those of previous findings that spontaneous pupillary oscillations, characteristic of a person’s level of vigilance, expressed daytime fluctuations in the central nervous system [19]. Moreover, we may wonder if non-smokers tend to lessen the PS in response to smoking cues (Fig. 2D). However, the decrease tendency of the PS to smoking-related visual cues in nonsmokers was not significantly different from the fluctuations of the neutral cues. Thus it is conceivable that the pupils of nonsmokers responded to the smoking-related visual cues similar to the neutral cues. Furthermore, the change of the PS in response to smoking cues marked the transient (peak at about 3 s), but higher, increase in smokers. On the other hand, the change of the PS in response to pleasant or unpleasant cues marked the lasting (peak at 4 to 5 s), but lower, increase in both groups. It seems very likely that the pupillary change to the smoking image in smokers measured by the time-series PS data would be a good indicator to evaluate physiological changes in the smoking cravers.

This study was supported by the SRC program of KOSEF (Korea Science and Engineering Foundation, R11-2005-014), Republic of Korea.

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