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A Functional Magnetic Resonance Imaging (fMRI) Study of Cue-Induced Smoking Craving in Virtual Environments

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Smokers who are exposed to smoking-related cues show cardiovascular reactivity and smoking craving compared with their responses to neutral cues, and increased cue reactivity predicts decreased likelihood of successful cessation. Several brain imaging studies suggested four candidate brain regions that might differ in gray matter volumes and densities between smokers and nonsmokers. However, in these studies, smokers were only exposed to smoking-related objects. In our pilot study utilizing a virtual reality (VR) technique, virtual environments (VEs) were more immersive and evoked smoking craving more effectively than traditionally used methods. In this study, we sought to test whether smokers could experience cue-induced smoking craving inside the MRI scanner by using the VR system. The smoking cue reactivity scenario was based in part on our preliminary task and consisted of 2D and 3D (or VE) conditions. The group mean of participants had increased activity in the prefrontal cortex (PFC), left anterior cingulate gyrus (ACC), left supplementary motor area, left uncus, right inferior temporal gyrus, right lingual gyrus, and right precuneus in the 2D condition. Areas of differential activation in the 3D condition were as follows: left superior temporal gyrus, right superior frontal gyrus, and left inferior occipital gyrus in the 3D condition. This finding is consistent with those of previous studies of nicotine craving showing PFC and ACC activation. However, in the 3D condition, the PFC including the superior frontal gyrus as well as the superior temporal gyrus, inferior occipital gyrus, and cerebellum were activated. Therefore, in the 3D condition, participants seemed to have more attention, visual balance, and coordinating movement than in the 2D condition.

KEY WORDS: smoking; craving; fMRI; virtual reality; virtual environment; cue reactivity.

During the last 10 years, smoking cessation programs have commonly combined medication, cognitive–behavioral therapy, and psychoeducation. Although many methods exist to treat nicotine dependence, one of the greatest problems is smoking relapse. Payne,

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Schare, Levis, and Colletti (1991) proposed that many smokers experience an increase in the desire to smoke when exposed to smoking-related cues. Former smokers are bombarded with smoking-related cues on a daily basis. They experience psychological and physical responses to smoking-related cues. Several studies (Maude-Griffin & Tiffany, 1996; Niaura, Abrams, Demuth, Pinto, & Monti, 1989a; Niaura, Abrams, Monti, & Pedraza, 1989b; Niaura, Abrams, Pedraza, & Monti, 1992) reported that smokers who are exposed to smoking-related cues show increased cardiovascular reactivity and smoking craving compared with their responses to neutral cues, and increased cue reactivity predicts decreased likelihood of successful cessation. A strong desire or craving to smoke seems to play an important role in the maintenance of cigarette smoking (Killen & Fortmann, 1997).

The basic theory of cue reactivity is based most commonly on a classical conditioning model of learning. From this perspective, the nicotine is the unconditioned stimulus (US), and the nicotine effects are the unconditioned responses (UR). The conditions and objects that relate to the nicotine become conditioned stimuli (CS) that evoke conditioned responses (CR) that mediate nicotine or cigarette seeking and consumption. According to this learning theory, cue-induced craving or reactivity might partly reflect CRs established by a learned association between smoking-related cues (i.e., cigarettes, lighters, ashtrays, etc.; "Chained CSs") and nicotine intake (US; Niaura et al., 1988).

Cues related to addictive drugs are commonly known to induce craving and drug use in addicts. The sight of a bare forearm may prompt a heroin user to inject, while the sight and smell of a burning cigarette will elicit a strong urge to smoke in an abstinent smoker. Several brain imaging studies of substance addicts, especially cocaine addicts, have examined the effects of substance-related stimuli on brain activation. Positron emission tomography (PET) studies (Childress et al., 1999; Grant et al., 1996) in cocaine addicts detected brain regions activated by cocaine craving using visual stimuli (videos showing cocaine-related vs. neutral content). Also, functional magnetic resonance imaging (fMRI) studies (Garavan et al., 2000; Maas et al., 1998; Wexler et al., 2001) have suggested that brain regions, like the anterior cingulate and the prefrontal cortex, are related to cocaine craving. Similarly, an fMRI study of alcoholics' craving suggested cue-induced activation of brain regions including the right amygdala/hippocampus, superior temporal gyrus, and cerebellum (Schneider et al., 2001).

However, despite extensive behavioral and physiological work on drug cue effects, relatively few studies have explored the effects of smoking cues on human brain activity. A few articles on smoking have reported that cigarette smoking history is related to large-scale structural brain abnormalities. Increased ventricular and sulcal size or atrophy have been revealed in heavy smokers (Longstreth et al., 2000, 2001). In addition to these large-scale brain abnormalities, recent fMRI and PET studies suggest four candidate brain regions that might differ in gray matter volumes and densities between smokers and nonsmokers. Functional brain imaging studies demonstrated that administration of nicotine (or cigarette smoking) or exposure to smoking-related cues activated the prefrontal cortex (PFC; Due, Huettel, Hall, & Rubin, 2002; Nakamura, Tanaka, Nomoto, Ueno, & Nakayama, 2000; Stein et al., 1998), anterior cingulate cortex (ACC; Brody et al., 2002; Stein et al., 1998), ventral striatum (Nakamura et al., 2000; Stein et al., 1998), and thalamus (Domino et al., 2000; Nakamura et al., 2000; Rose et al., 2003; Stein et al., 1998; Zubieta et al., 2001). These findings in humans are consistent with imaging studies of nonhuman primates and rodents, which demonstrate that nicotine administration results in dopamine release in the

ventral striatum (Dewey et al., 1999) and that the highest density of nicotinic acetylcholine receptors is in the thalamus (Horti et al., 1998; Musachio et al., 1997). Thus, four regions (the PFC, ACC, ventral striatum, and thalamus) are implicated repeatedly in responses to smoking and smoking cues.

However, in these studies, smokers were only exposed to smoking-related objects. Many researchers have emphasized the importance of context rather than the objects. Therefore, although they used still 2D photos and videos of objects to stimulate craving, these devices have some limits in providing the smoking-related context or situation. Recently, virtual reality (VR) technology and 3D animation techniques have been developed that provide a "presence" or a "feeling of being there" for individuals immersed in a virtual environment (VE) scenario. In our pilot study (Lee et al., 2003), utilizing this new technique, VR was shown to be more immersive and evoked smoking craving more effectively than traditionally used methods (e.g., still photos). This greater effectiveness appears to arise from the fact that VR can present a context-specific stimulus with a high degree of ecological validity.

A functional magnetic resonance imaging can be useful for in-depth studies of brain activity that may be correlated with human mental states when a person is immersed in a virtual environment. Hoffman, Richards, Coda, Richards, and Sharar (2003) demonstrated that subjects could still experience a strong illusion of presence during fMRI despite the constraints of the fMRI magnet (i.e., immobilized head and high ambient noise). Furthermore, a few researchers (Baumann et al., 2003; Mraz et al., 2003) have developed a flexible VR system platform for a variety of neurobehavioral experiments performed inside MRI scanners and have launched a research program to investigate the potential usefulness of the VR—fMRI combination.

In this study, we sought to test whether smokers could experience cue-induced smoking craving inside the MRI scanner by using the VR system, and if so, whether the magnitude of craving differed between the classical device (2D pictures) and the VE scenario. Independent of potential differences in self-reported smoking craving, we also sought to investigate whether specific brain regions would be differentially activated in smokers while viewing smoking cues compared with neutral cues.

METHODS

Participants

The participants were eight adolescent volunteers, 16–18 years of age (eight right-handed men; mean age = 17.13 years, $SD = 0.83$) who smoked at least 10 cigarettes per day. They had been recruited from a program of smoking cessation in a high school prior to this brain imaging study and were offered the equivalent of $70 to participate in the "VR-fMRI-smoking craving study." Subjects agreed to abstain from smoking during the 7-hr before the scanning session. Subjects completed a brief medical screening form and evaluation showed no lifetime history of medical, psychiatric, or other substance abuse, or medication usage thought to affect brain structure or function at the time of scanning. Handedness was determined with a standard rating scale (Oldfield, 1971), and participants abstained from alcohol use for 24 hr prior to the scans.

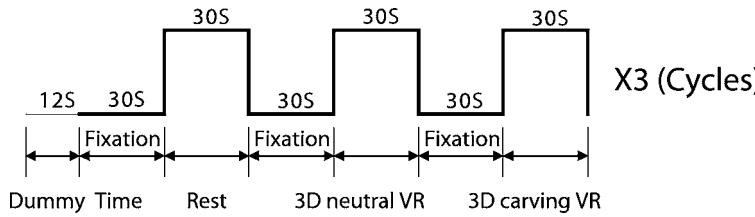


Fig. 1. A diagram of the functional magnetic resonance imaging.

Procedures

Before the experiment, subjects were asked for their demographic data, medical history, and a survey of smoking behavior (the number of cigarettes smoked per day) and were also asked to complete a modified Fagerstrom Tolerance Questionnaire (Prokhorov, Koehly, Pallonen, & Hudmon, 1996) and a self-rating on a 10-point scale of current smoking craving before and after scanning. The smoking cue reactivity scenario was based in part on our preliminary task (Lee et al., 2003) and consisted of 2D and 3D conditions (VE). All participants were repeatedly scanned under 2D and 3D conditions in which the order was counterbalanced, and they were navigated along programed routes without movement of a joystick in the 3D condition. Participants completed questionnaires (Presence Questionnaire [Witmer & Singer, 1998] and Simulator Sickness Questionnaire [Kennedy, Lane, Berbaum, & Lillienthal, 1993]) related to the virtual experience immediately after scanning. Answers were given as ratings on a five-point scale, which ranged from "not at all" to "extremely" for all questions (see Fig. 1).

VR Instrument and Scenario for Craving

The VR system consisted of a Pentium IV PC, OpenGL Accelerator VGA Card, and MR-compatible goggles (Fig. 2) with XGA resolution (1024 × 768) and 30 degrees FOV (VisuaStim XGA, Resonance Inc.). The PC with 3D Accelerator VGA Card generated real-time virtual images for the participant to navigate.

The VE was designed based on our preliminary data for smoking craving. The background environment was a bar, and objects within it included an alcoholic drink, a pack of cigarettes, a lighter, an ashtray, a glass of beer, advertising posters, and an avatar smoking a cigarette (Fig. 3). Six types of stimulus were employed: 2D and 3D smoking-related images, neutral 2D and 3D images, and 2D and 3D nonsmoking-related images. The 2D smoking-related images included posters advertising tobacco and alcohol. The 2D nonsmoking-related images were matched by the experimenters to approximate the general content (logo of company and a paper poster). The 2D and 3D neutral images were seascapes. The 3D smoking-related images were of a virtual bar, and the 3D nonsmoking-related images were of a virtual office. The virtual office was very similar to the virtual bar except for the smoking-related objects.

MRI Image Acquisition

All participants were scanned on a 1.5 T GE Signa CV/i scanner with a 70-cm-diameter short bore and a whole-body 44-cm-diameter gradient set with a maximum strength of

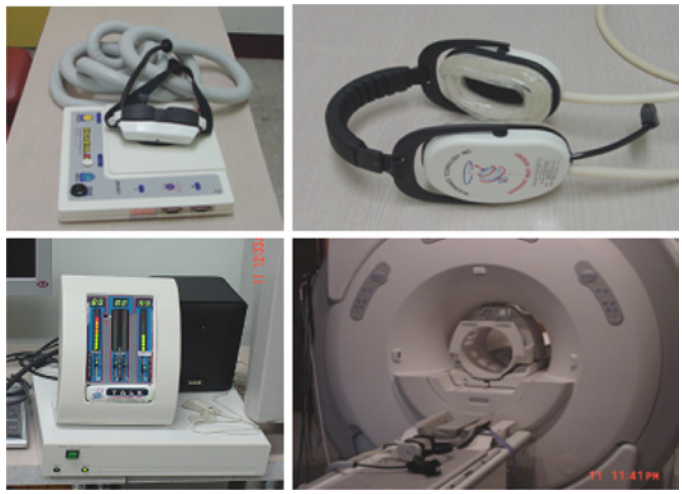


Fig. 2. An experimental device compatible for MRI.

40 mT/m gradients and a slew rate of 150 mT/m in Hanyang University Guri Hospital, Korea. The MRI scanner was used to obtain fMRI data, and participants in the magnet were able to see a visual stimulus (VE or 2D pictures) through MR-compatible goggles. A whole-head hybrid birdcage radio frequency (RF) coil was used for transmission and detection of signal. Before imaging, a global shimming procedure, using first- and second-order shims, were performed to optimize the magnetic field over the imaging volume of interest. The participants' heads were placed into a cradle and packed tightly with copious amounts of foam to reduce motion. The RF coil was subsequently placed around the subject's head. Each functional brain volume was acquired using a navigator echo corrected, interleaved multishot (four shots) echo planar imaging pulse sequence with a 64×64 matrix size and a total volume acquisition time of 3 s (echo time [TE] = 50 ms, TR = 3 s, flip angle = 90°, FOV [field of view] = 24.0 cm). During each imaging session, high-resolution (256×256), two-dimensional, T1-weighted anatomic images were acquired in the same FOV and orientation as the functional images (TE = 9.0 ms, TR = 350 ms, inversion time

Fig. 3. Representative stimuli in the 3D condition (virtual bar).

[TI] = 500 ms, gap 0 mm). The resulting acquisition produced 28 contiguous structural images each with a slice thickness of 5 mm.

Data Analysis

Activation maps were calculated using analysis of functional neuroimages (AFNI V2.5) freeware (Cox, 1996). For each task, the first five time points in all the time series data were discarded to eliminate the fMRI signal decay associated with the magnetization's reaching equilibrium. All remaining fMRI data were coregistered to the first remaining time sample to correct for the confounding effects of small head motions during task performance. Further processing included temporal and spatial smoothing (three-point median filter and a Gaussian filter with 4 mm full width at half maximum [FWHM], respectively) as well as detrending to remove constant, linear and quadratic trends from the time series data. The final brain activation maps were produced using a deconvolution routine provided in AFNI that contrasted the stimulus periods with the neutral periods.

RESULTS

The demographic data (age and daily cigarette count) and the mean score of questionnaires (the FTQ, SSQ, and PQ) are presented in Table I. Participants reported moderate levels of nicotine dependency and presence, and a low level of cybersickness.

The current smoking craving was increased after scanning compared with that before it, based on participants self-report on a 10-point craving scale. In order to observe the regions activated only by the smoking craving in functional neuroimaging, the activation images in which the images from craving and neutral stimulus were subtracted were obtained. The regions in which the differences of blood oxygen level-dependent (BOLD) signals were statistically significant at $p < .05$ were considered to be the regions of interest (ROI), and they were converted to Talairach coordinates to determine the ROI by their Brodmann area.

Participants displayed increases in brain activity when viewing the smoking-related images compared with the nonsmoking-related cues. The group mean of participants had increased activity in the PFC (superior and right middle frontal gyrus, and left orbital gyri), left anterior cingulate gyrus, left supplementary motor area (SMA), left uncus, right inferior temporal gyrus, right lingual gyrus, and right precuneus in the 2D condition (see Table II and Fig. 4). Areas of differential activation in the 3D condition were as follows: left superior temporal gyrus, right superior frontal gyrus, and left inferior occipital gyrus in the 3D condition (see Table II and Fig. 4).

Table I. Demographic and Questionnaire Data (Mean ± *SD*)

Measures	Mean ± *SD*
Age	17.00 ± 0.76
Smoking count/day	15.33 ± 4.98
FTQ	4.38 ± 2.13
Current craving before scanning	5.25 ± 1.98
Current craving after scanning	6.07 ± 2.03
SSQ	2.18 ± 1.05
PQ	5.88 ± 0.98

Table II. Brain Regions Activated by Condition

Region	Brodmann area	Talairach *x*, *y*, *z*	Volume size	Max int.
2D condition				
Right superior frontal gyrus	8	7, 47, 46	5744	4.401
Right inferior frontal gyrus	38	27, 9, −22	4016	3.866
Left supplementary motor area	6	−23, −1, 64	3256	3.185
Left anterior cingulated gyrus	32	−1, 11, 42	3216	4.494
Left orbital gyri	11	−23, 45, −10	2168	3.300
Right medial frontal gyrus	8	35, 27, 40	1952	3.289
Left uncus	20	−37, −15, −30	1440	2.785
Left superior frontal gyrus	9	−33, 49, 26	1432	3.481
Right inferior temporal cortex	20	43, −5, −24	1368	3.103
Right lingual gyrus	18	3, −85, −16	736	2.795
Right precuneus	19	43, −69, 40	552	2.604
3D condition				
Left superior temporal gyrus	41	−51, −17, 12	2640	2.821
Right superior frontal gyrus	9	15, 59, 30	672	3.098
Left inferior occipital gyrus	18	−39, −87, −2	512	3.842

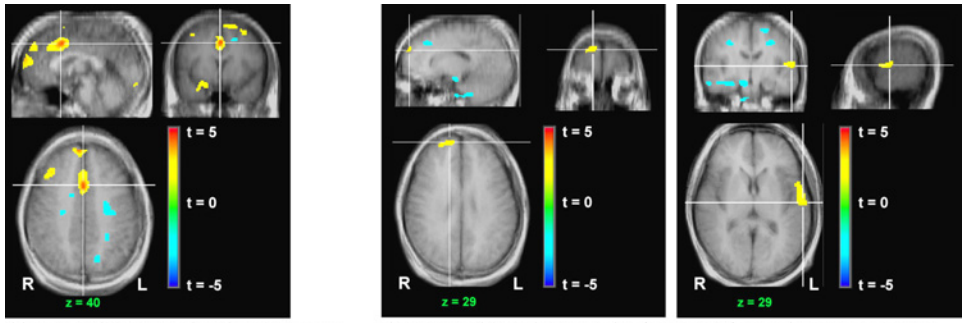
Note. Max int.: Maximum *t*-value within the cluster.

DISCUSSION

This study sought evidence to confirm the hypothesis that smokers experience greater craving in response to smoking cues than to affectively neutral cues that do not have smoking content. This study also sought differences in craving between classical cues (2D pictures) and 3D VEs.

In the 2D condition, the prefrontal cortex (PFC), anterior cingulate cortex (ACC), SMA, inferior temporal cortex, and occipital lobe are activated in smokers while viewing smoking cues. This finding is consistent with those of previous studies of nicotine craving: the PFC (Due et al., 2002; Nakamura et al., 2000; Stein et al., 1998) and ACC (Brody et al., 2002, 2004; Stein et al., 1998).

Due et al. (2002) have confirmed the participation of mesocorticolimbic regions in response to visual drug-related cues in abstinent users. In their study, visual cues related to smoking were associated with greater neural activation both in mesocorticolimbic areas,



(a) 2D condition: anterior cingulate gyrus (b) 3D condition: right superior fontal & left superior temporal gyrus

Fig. 4. Brain activation in the 2D and 3D conditions. (a) 2D condition: anterior cingulate gyrus and (b) 3D condition: right superior fontal and left superior temporal gyrus.

which have been associated with reward processing, and in areas implicated in visuospatial attention. They found significant activation in prefrontal regions and in mesolimbic regions (e.g., amygdala and hippocampus). It is important to note that all these regions showed greater activation in response to smoking-related images than to neutral ones within the smoking group, and greater relative activation in smokers than in nonsmokers. Moreover, a few researchers (Devinsky, Morrell, & Vogt, 1995; Vogt, Finch, & Olson, 1992) reported that medial frontal and anterior cingulate lobes were activated during craving, and that the anterior cingulate is considered to play an integrated role in cognitive and emotional information processing. Reiman (1997) reported that anterior cingulate and medial frontal lobes were associated with the conscious experience, attention, or behavioral responses for anxiety-inducing situations. Therefore, these studies suggest that the changes in emotion processing for smoking-related stimuli are linked to the pathophysiology of craving.

In our experiment, although results similar to those of previous studies were obtained in the 2D condition, they were obtained in the 3D condition only in part. In the 3D (or VE) condition, the PFC including the superior frontal gyrus as well as the superior temporal gyrus, inferior occipital gyrus, and cerebellum was activated. In the 3D condition, we extracted nonsmoking-related images (virtual office) from smoking-related images (virtual bar). Although the virtual bar was very similar to the virtual office, there are many smoking-related cues, and participants were required to look at the smoking-related cues that evoked their smoking craving while automatically moving on the forced routes. Therefore, in the 3D condition, participants required more attention and visual balance than in the 2D condition. This assumption is related to findings (Hegemann, Fitzek, Fitzek, & Fetter, 2004) that the superior temporal gyrus was not only involved in spatial orientation and vestibular function but was also a primary auditory area. Therefore, in our 3D condition, the activated regions including the superior temporal gyrus and cerebellum seem to be associated with activities including coordinating movement and maintaining posture and equilibrium. At present, there are a few limitations in this method of studying craving in the MRI and VEs. In the future, a study of presence, spatial navigation, and vestibular function in VEs is required, and of smoking craving in VEs with greater realism and lower movement.

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