뇌기능영상기법을 이용한 흡연욕구 가상환경 단서노출치료 효과 연구

Cue Exposure Treatment in Virtual Environments to Reduce Nicotine Craving: Using fMRI

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요약 본 연구에서는 가상현실을 이용한 단서노출치료가 흡연자의 니코틴 갈망수준을 감소시키는지를 알아보았다. 이를 위하여 8명의 흡연청소년을 대상으로 6회기의 가상환경 단서노출치료를 실시하였다. 또한 단서노출치료 실시 전과 후에 흡연관련 사진과 중립사진을 제시하는 동안 참가자들의 뇌를 기능성 자기공명영상장치(fMRI)로 측정하였다. 그 결과 단서노출실시 전에는 prefrontal cortex(PFC), Anterior cingulate gyrus(ACC) 영역을 비롯한 7개의 영역이 활성화되었고, 단서노출치료 후에는 right middle frontal gyrus, right uncus, left medial frontal gyrus, right fusiform gyrus, 그리고 right superior frontal gyrus 영역이 활성화되었다. 단서노출치료 전과 후의 비교에서는 PFC가 관찰되었다. 본 연구의 결과로 흡연자의 흡연 갈망은 감소되었으며, 가상현실단서노출치료는 흡연자들뿐 아니라 여러 물질의존자들의 치료에 유용한 방법이 될 것이라는 것을 시사한다.

핵심어: 흡연, 갈망, 단서노출치료, 가상환경, fMRI

1. Introduction

Nicotine dependence is the most common substance abuse disorder. Despite the fact that cigarette smoking is associated with health risks such as lung cancer, asthma, cardiovascular diseases, and neurological disorders, it has been estimated that each year fewer than 10% of smokers attempt to quit and that only 3% of smokers successfully do so[1]. Although the harmful effects of cigarette smoking are widely known, cessation of smoking is difficult, even for those who have a strong desire to stop smoking.

Craving is generally considered one of the reasons why substance-dependent individuals have difficulty abstaining from drugs. A strong desire or craving to smoke seems to play an important role in the maintenance of cigarette smoking[2]. The most common explanation for craving is conditioning: after repeated exposure to associations between cigarette smoking and conditions and objects related to nicotine (substance-related cues, CS), CS elicits conditioned response (CR), which induces nicotine or cigarette seeking and consumption. Thus, the cue that evokes nicotine craving is regarded as an activator of addictive behaviors.

Exposure to cues related to addictive drugs induces craving among substance-dependent individuals. Physiological reactions to cue exposure such as skin conductance, heart rate, salivation, and body temperature have been investigated[3]; brain activation studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have also been conducted. Studies have shown that the anterior cingulate cortex [4][5] and the orbitofrontal cortex [4][5] are activated by drug-related stimuli. Researches on substance addiction have shown that drug-related cues induce craving. Smokers exhibit greater cardiovascular reactivity and craving when exposed to smoking-related cues than when exposed to neutral cues [6]. Alcohol-dependent young women have a greater blood oxygen level-dependent (BOLD) response in the left anterior cingulate and orbitofrontal regions to alcohol-related than controls [7]. In a study of cocaine addicts[8], Saladin and colleagues

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found that craving was greater in a cocaine-related context than in a neutral context according to self-assessment and measurement of heart rate.

The aim of cue exposure treatment (CET) is to extinguish CR by repeated presentation of substance-related cues. In other words, the aim of CET is to break the association between nicotine intake and smoking-related cues. This process is called extinction in learning-based theory. Cue exposure has been advocated as a potentially effective method of treating addictive behaviors[9]. CET has been applied to the treatment of addictions to a variety of substances, including cigarettes, alcohol, and illegal drugs. However, reports on the efficiency of CET are conflicting. Tiffany and Conklin[10] evaluated 18 cue exposure studies conducted on nicotine, alcohol, opiate, and cocaine addicts by applying meta-analytical techniques. They found that some studies reported that CET was effective in promoting abstinence or a reduction in drug use[11][12][13] and that others reported that CET had no effect on drug use[14][15].

Several studies have shown that stimuli such as photographs, videotapes, audiotapes, or in vivo cues can provoke craving. In these studies, the most prevalent mode of presentation was in vivo cues[10], the advantage of which is that participants can manipulate the cues during exposure to them. On the other hand, the main disadvantages of this method are that the range and complexity of stimuli are somewhat limited[8] and that presentation can be dangerous. In addition, most cue presentation studies were conducted in laboratories or hospitals, which invoke the issue of whether the results of such studies are applicable outside these environments. Extinction in one context does not necessarily have an effect in another context. Because of the renewal effect, exposure to cue presentation in multiple domains increases the scope of extinction[10].

Exposure to cues in virtual environment (VE) may prevent relapses and generalize the effect of CET. The most successful treatments tend to involve multiple domains[16] and VE technology can simulate a wide range of situations. VE technology can also be used to train individuals to perform tasks in dangerous situations and hostile environments[17] or in illegal, unethical, and other situations that would be impossible to recreate in the real world. Furthermore, the degree of immersion and realism that can be attained by VE could evoke craving more effectively than traditional methods. In our previous study[18], VE was better at eliciting desire than 2D pictures. We also found that the craving for cigarettes gradually decreases during the course of a session of VE-CET, and that VE-CET is an effective treatment for smokers[19]. Nevertheless, these two studies were limited in that they were restricted to measuring the subjective responses of the participants.

Thus, the present study was designed to measure brain activation using fMRI to determine whether VE-CET is an effective method of reducing nicotine craving in smokers. We presented 2D cues and examined BOLD responses of smokers and nonsmokers before and after VE-CET.

2. Methods

2.1 Participants

Eight late-adolescent males who smoked at least 10 cigarettes per day were recruited (mean age = 17.00, SD = 0.76). All participants were right-handed and consented to abstain from smoking for 7 h and before the treatment. Participants had no medical or psychiatric disorders. None of the participants reported abuse of other substances or medication that might have affected brain structure or function at the time of scanning.

2.1 Material and Procedure

The smoking cue reactivity scenarios in the virtual environments were created based on our previous studies [18][19]. The background environment was a public bar containing various objects such as alcoholic drinks, a pack of cigarettes, a lighter, and ashtray, posters advertising alcohol and cigarette, and avatar smoking a cigarette (see Fig 1). An auditory stimulus consisting of noise and music typical of a bar was also offered. Participants navigated VE, wearing HMD. The VE-CET consisted of 6 sessions for different

themes and took 10 days to complete. In session 1 (initial navigation), participants navigated freely around the bar. Cue exposure focused on person-elicited craving in session 2, object-elicited craving in session 3, and situation-elicited craving in session 4. In session 5, participants reviewed all the stimuli presented in session 2, 3, and 4. In session 6, participants navigated freely around the virtual bar again. Each session lasted for 20 min, including navigation, interviews about feelings, and completion of a questionnaire about craving.

Fig 1. Virtual Bar

Before the first VE-CET session began and after the last session finished, brain activation was scanned using MRI scanner (1.5 T GE Signa CV/i scanner) for fMRI data. While brain activation was scanned, photographic smoking-related cues (e.g., posters advertising tobacco and alcohol) and neutral cues (e.g., a seascape) were presented. After 12 s of dummy, 30 s of fixation, and 30 s of resting, the neutral cues were shown for 30 s. Smoking-related cues were shown for 30 s after the neutral cues were shown, and there was 30 s of fixation between presenting neutral cues and smoking-related cues. This whole process for fMRI scan was cycled three times. Brain activation maps were calculated using analysis of functional neuroimages (AFNI 2.5) freeware.

3. Results

All individuals understood the instructions and successfully completed the fMRI. Participants reported moderate levels of nicotine dependency (4.38 ± 2.13) in FTQ and presence (5.88 ± 0.98) in PQ, and a low level of cyber sickness (2.18 ± 1.05) in SSQ. Although there was no significant reduction in subjective craving nor smoking count per day, craving was gradually decreased during the course of the sessions with repeated measures ANOVA (5.74 ± 1.75 for 1st session, 6.72±1.62 for 2nd session, 5.24±2.59 for 3rd session, 5.69±2.11 for 4th session, 6.02±2.21 for 5th session, and 5.26±2.33 for the last session).

In order to observe regions that were activated only by smoking craving using functional neuroimaging, activation image regions stimulated by neutral stimuli were subtracted from those obtained during craving. Regions in which differences of BOLD signals were statistically significant at $p<0.05$ were considered to be the regions of interest(ROI) and were converted to Talairach coordinates to determine the ROI using their Brodmannarea.

Prior to VE-CET, the participants displayed greater brain activity when they viewed smoking-related images than neutral cues. The ROI were prefrontal cortex (PFC) (superior frontal gyrus, right medialfrontal gyrus, left orbital gyri), left anterior cingulate gyrus (ACC), right superior temporal gyrus, left uncus, right fusiform gyrus, right lingual gyrus, and right precuneus. Table 1 shows the regions in detail.

Table 1. Brain regions identified for the contrast of smoking related cues vs. neutral cues before VE-CET

Disturbance Term	Side	Brodmann area	Talarirach			Volume Size
			x	y	z	
Superior frontal gyrus	R	8	7	47	46	5744
Superior temporal gyrus	R	38	27	9	−22	4016
Superior frontal gyrus	L	6	−23	−1	64	3256
Cingulate gyrus	L	32	−1	11	42	3216
Orbital frontal gyri	L	11	−23	4	−10	2168
Medial frontal gyrus	R	8	35	27	40	1952
Uncus	L	20	−37	−15	−30	1440
Superior frontal gyrus	L	9	−33	49	26	1432
Fusiform gyrus	R	20	43	−5	−25	1368
Lingual gyrus	R	18	3	−16	−16	736
Precuneus	R	19	43	40	40	552

After six sessions of VE-CET, regions that displayed greater brain activity when subjects viewed

smoking-related images than when they viewed neutral cues were the right middle frontal gyrus, right uncus, left medial frontal gyrus, right fusiform gyrus, and right superior frontal gyrus, as detailed shown in Table 2.

Table 2. Brain regions activated for the contrast of smoking related cues vs. neutral cues after VE-CET

Disturbance Term	Side	Brodmann area	Talarirach			Volume Size
			x	y	z	
Superior frontal gyrus	R	8	7	47	46	5744
Superior temporal gyrus	R	38	27	9	-22	4016
Superior frontal gyrus	L	6	-23	-1	64	3256
Cingulate gyrus	L	32	-1	11	42	3216
Orbital frontal gyri	L	11	-23	4	-10	2168

We compared regions that were activated before VE-CET with those activated after VE-CET to confirm the efficacy of VE-CET. Details of the activated regions are defined in Table 3. All regions showed greater activity before VE-CET than after VE-CET, especially the left inferior frontal gyrus and left superior frontal gyrus.

Table 3. Brain regions activated for the contrast of smoking related cues vs. neutral cues after VE-CET

Disturbance Term	Side	Brodmann area	Talarirach			Volume Size
			x	y	z	
Superior frontal gyrus	R	8	7	47	46	5744
Superior temporal gyrus	R	38	27	9	-22	4016

4. Discussion

In this study, we found that visual cues related to smoking were associated with greater neural activation than neutral cues. We compared the activation of brain regions before and after VE-CET to confirm the efficacy of VE-CET.

For the smokers, eleven regions of interest showed significant responses during exposure to smoking-related visual cues (see Table 1) before VE-CET. These regions are situated in the frontal (superior frontal gyrus, orbital gyri, medial frontal gyrus), limbic (cingulate gyrus, uncus), temporal (fusiform gyrus), occipital (lingual gyrus), and parietal (precuneus) lobes. David and collegues[20] observed greater activation in the ventral striatum, orbito frontal cortex, anterior cingulate cortex, and fusiform gyrus of smokers when presented with smoking-related cues than when presented with neutral cues. Due and collegues[21] reported greater neural activation in the prefrontal gyrus and fusiform gyrus and a tendency for greater brain activity in the anterior cingulate cortex in response to exposure to smoking-related cues compared with neutral cues. These results are considerably overlapped with activated regions of our own research.

According to Daglish and colleagues[22], PFC and ACC are commonly associated with addiction. ThePFC[23][24]and ACC regions[4][5] have frequently been associated with cue exposure paradigms; the ACC is known as the control circuit and the orbito frontal cortex of the PFC is known as the motivational/drive circuit[25]. These circuits receive direct dopaminergic innervation, are both part of the mesocortical dopamine circuit, and are involved with cognitive decisions to obtain rewards[26]. It is notable that according to Due and colleagues[21], smoking-related cues activate regions involved in dopamine-dependent incentive sensitization processes in multiple cortical and subcortical limbic regions.

Moreover, frontal brain regions are thought to function in the processing of visual drug cues; both the PFC and the ACC are considered components of the visuospatial attention circuit. According to Reiman[27], the anterior cingulate and medial frontal lobes are associated with the conscious experience, attention, or behavioral responses in anxiety-inducing situations. Consequently, greater activity of the ACC is associated with greater anxiety. It is plausible, therefore, that changes in the emotional processing of smoking-related stimuli are linked to the pathophysiology of craving.

Taken together, the results of our study indicate that responses to visual smoking-related cues activate brain systems involved with reward, control, memory,

and motivation before VE-CET. It has been found that drug-seeking behavior involves four integrated circuits; reward, control, memory, and motivation. Thus, the activated regions that untreated smokers in this study showed can be attributed to addiction to nicotine.

After VE-CET, five regions were activated. As shown in Table 2, VE-CET decreased overall brain activation as well as craving-related brain regions and induced change in the activated regions. After VE-CET, brain responses to craving-provoking stimuli were modified as a result of a reduction in the urge to smoke.

Comparison of activated brain regions before and after VE-CET showed that the PFC (see Fig 2), including the inferior frontal gyrus and the superior frontal gyrus, was activated by smoking-related cues. Thus, the decrease in activity of the PFC after VE-CET can be attributed to a decrease in nicotine craving and CET conducted in VE seems to be an effective method of treating nicotine craving.

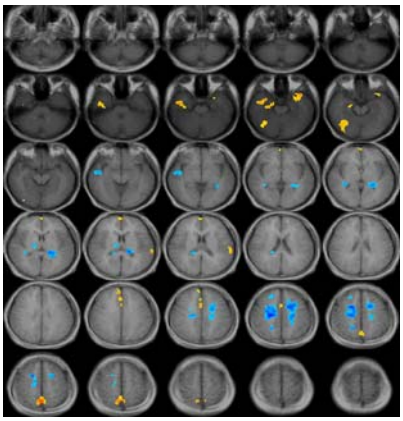

Fig 2. Representative statistical parametric maps of the contrast pre-CET vs. post-CET, indicating active brain regions. See text for full description of activated regions. Labels for the activated regions are defined in Talbe 3.

Obvious subjective craving reduction and substantial changes were not observed after VE-CET because of the relatively short treatment sessions. However, the brain activations which were detected prior to the treatment decreased and the activated regions changed after the treatment. That is brain responses were changed as a result of CET, a decrease in the smoking craving.

Much research has been conducted using the cue exposure method to elicit craving. To our knowledge, our study is the first to demonstrate the efficacy of VE-CET for reducing craving using a neuroimaging method. Our results may help elucidate neural basis of addicts such as changes in brain regions of addicts who are recovering from nicotine dependence.

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