Original investigation

Withdrawal Symptoms and Nicotine Dependence Severity Predict Virtual Reality Craving in Cigarette-Deprived Smokers

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Abstract

Introduction: Virtual reality (VR) has been shown to be effective in eliciting responses to nicotine cues in cigarette smokers. The primary aim of this study was to investigate whether cigarette-deprived smokers would exhibit increased craving and changes in heart rate when viewing cigarette related cues as compared to non-smoking cues in a VR environment, and the secondary aim was to assess the extent to which self-assessed measures of withdrawal and dependence correlated with VR craving.

Methods: Nicotine-dependent cigarette smokers were recruited for a 2 day study. On Day 1, participants smoked as usual and on Day 2 were deprived from smoking overnight. On both days, participants completed self-assessment questionnaires on withdrawal, craving, and nicotine-dependence. Participants completed a VR session during the cigarette deprivation condition only (Day 2). During this session, they were exposed to active smoking and placebo (non-smoking) cues.

Results: The data show that self-reported levels of “craving” ($p < .01$) and “thinking about cigarettes” ($p < .0001$) were significantly greater after exposure to the active cues versus non-smoking cues. Significant increases in heart rate were found for 3 of 4 active cues when compared to non-smoking cues ($p < .05$). Finally, significant positive correlations were found between self-reported craving prior to the VR session and craving induced by active VR cues ($p < .01$).

Conclusions: In this report, active VR cues elicited craving during cigarette deprivation. This is the first study to demonstrate that self-reported craving, withdrawal symptoms, and nicotine dependence severity predict cue-induced craving in the VR setting.

Introduction

An important variable contributing to smoking relapse is craving.^{1,2} Exposure to certain stimuli can trigger acute episodic craving known as cue-induced craving.³ In cigarette smokers, cue reactivity has

been shown to be a robust phenomenon and one that remains constant across both time^{4,5} and setting.⁶ A wide variety of stimuli has been used to successfully induce psychological craving and physiological reactions in nicotine studies, including photos,⁷ videos⁸ in

vivo visual cues,⁶ personalized scripts and imagery^{9,10} and tobacco advertisements.¹¹

Although craving may be induced by individual cues, the reality is that craving generally arises because of a complex association of emotional, environmental, autobiographical, and sensory information. To generate a more realistic craving state, recent studies have begun to use dynamic and complex virtual environments,^{1,12–14} which allow users to navigate through the environment and become fully immersed in it. These multifaceted three-dimensional (3D) environments are designed to recreate settings where drug use is likely to occur, employing techniques such as interaction with avatars and presenting explicit drug or drug-associated stimuli.

Virtual reality (VR) incorporates a human-computer interaction that goes beyond the simple presentation and observation of images on a computer screen by providing active participation within a 3D virtual world. Through the integration of computer graphics, spatial and audio input technologies (e.g., head and hand tracking), and scents, the participant feels immersed in the VR environment. In fact, one key distinguishing feature of VR from a multimedia experience, video game, or inactive computer graphic display is the immersion that users report. This sense of presence in virtual environments has been evaluated using the Imagery and Realism Presence Questionnaire¹⁵ in which participants have reported that they feel as if they are inside the VR environment.^{16,17}

VR environments have been shown to be more effective in increasing reactivity over traditional cue presentation methods in methamphetamine-,¹⁸ alcohol-,¹⁶ and cocaine-dependent populations,¹⁹ as well as in nicotine-dependent individuals.²⁰ The evidence is compelling for VR eliciting greater craving versus that achieved with isolated cue presentations, and also when drug versus non-drug stimuli are shown.²¹

The majority of VR studies involving cigarette smokers have used non-deprived participants.^{12,13,17,20,22,23} One exception was a study that demonstrated an effect of cue-induced VR craving in smokers who had not smoked for at least 12 hr, though this system did not use a head mounted device (HMD) to create a fully immersive environment. The only other exception was a functional magnetic resonance imaging (fMRI) study in deprived smokers that used magnetic resonance imagining compatible goggles to create a 3D environment. In this report, the investigators showed that the system induced craving more effectively than using two-dimensional environments.¹⁴

In addition, the majority of VR studies reported in the literature have not shown physiological data and those studies which have reported physiological responses to cues in VR have yielded inconsistent findings. One study using VR to compare differences in heart rate (HR) between smokers and non-smokers found no difference between the two groups,²⁴ while others have found that physiological reactivity increased after exposure to smoking cues.^{13,25}

To date, the relationship between craving responses to VR cues and well established pen-and-paper assessments of nicotine craving has not been assessed. Additionally, nicotine dependence has been shown to predict neural responses to nicotine cue stimulation during fMRI,²⁶ although there is a lack of data for how well this relates to VR. To address current gaps in the literature, the primary aim of this study was to investigate whether cigarette-deprived smokers would exhibit increased craving and HR when viewing cigarette related cues as compared to non-smoking cues in a VR environment. The secondary aim was to assess the extent to which self-assessed measures of withdrawal and dependence correlated with VR craving.

Methods

Participants

Thirty-six nicotine-dependent participants were enrolled in the study. Participants were recruited from the Houston area via fliers, newspaper, and Internet advertisements. Phone screens identified callers who were between the ages of 18–64 years, not seeking smoking cessation treatment, and who smoked ≥ 10 cigarettes a day for at least one year. Eligible subjects attended an in-person screen which served as Day 1 if the participants were deemed eligible. Exclusion criteria included: other non-tobacco substance dependence or diagnosis of any Axis I disorder according to the Mini-International Neuropsychiatric Interview.²⁷ In addition, subjects completed a multiple drug use questionnaire and were excluded if they provided a positive illicit drug urine toxicology during either study day.

After signing the informed consent, the study was carried out across two days at the MEDVAMC. On Day 1, the time since last cigarette was not controlled for, that is, the participants arrived having smoked *ad libitum*. On Day 2, subjects were deprived from cigarettes overnight, for a minimum of 12 hrs. Cigarette deprivation was defined by an exhaled breath CO ≤ 7 ppm, and was measured using Micro+ Smokerlyzer Monitor (Bedfont Scientific). This number was selected as a cut-off as it has been shown to provide high confidence intervals for abstinence without being so low that it could yield false positives.²⁸ Self-report assessments were completed immediately after consenting on Day 1, and as soon as the participant arrived on Day 2, before they completed the VR session.

HR data was recorded during the VR session, however this commenced midway through the study, therefore, only 50% ($n = 18$) of participants were included in this data analysis. This study was approved by Baylor College of Medicine and MEDVAMC institutional review boards and participants were compensated for their time.

Assessments

Wisconsin Smoking Withdrawal Scale

The Wisconsin smoking withdrawal scale (WSWS)²⁹ is a 28-item scale assessing withdrawal symptoms, and was administered on Day 1 (smoking as usual) and again on Day 2 (deprived) before the VR session. The assessment is scored using a Likert scale and gives 7 subscales; anger, anxiety, sadness, concentration, craving, sleep, and hunger, as well as an average overall score.

Shiffman-Jarvik Withdrawal Questionnaire

A short form Shiffman-Jarvik withdrawal questionnaire (SJWQ)³⁰ was also used to assess withdrawal symptoms and was administered on Day 1 and again on Day 2 before the VR session. This short scoring version of the original 25 item SJWQ uses 15 of the original questions scored with the same Likert scale from 1 to 7. Subscales are crave, physical, stimulated, psychological, and appetite, and an average overall score.

Questionnaire of Smoking Urges

The questionnaire of smoking urges (QSU)³¹ assessed craving urges and was administered on Day 1 and again on Day 2 before the VR session. The total score can be used to assess thoughts and feeling about the desire to smoke cigarettes and the relief of negative symptoms.³² The assessment is comprised of 10 questions scored using a Likert scale from 1 to 7.

Fagerström Test of Nicotine Dependence

The Fagerström test of nicotine dependence (FTND)³³ was administered on Day 1 to assess the level of nicotine dependence. The FTND consists of 10 questions with a mixture of multiple choice questions (scored 0–3) and yes/no questions (scored 0 or 1). The total score range is from 0–10.

Virtual Reality

On Day 2, cigarette-deprived smokers took part in a VR session using Virtually Better™ software. The VR was viewed through a specially designed HMD with tracker (Emagin z800, Emagin), auditory cues were received via headphones, and olfactory cues were timed to on-screen stimuli and included cigarette smoke, pizza, alcohol, and coffee. The participant sat on a chair that allowed them to turn 360 degrees to view all parts of the virtual environment. This study utilized a placebo-controlled design in which participants were exposed to a room with no smoking cues at the start (placebo 1) and end (placebo 2) of each VR session. These placebo rooms were a similar design as the active rooms, and the participant was able to move around and interact with stimuli in the environment. These rooms included non-smoking visual and auditory cues of buffalo and flamingos presented on virtual television sets in the room. The two active cue rooms were a smoking paraphernalia room (active paraphernalia) and a party room (active party). The active paraphernalia room contained sights, sounds, and smells associated with smoking cigarettes, including a lit cigarette in an ashtray, a pack of the participant's preferred brand of cigarettes, beer bottles and glasses of alcohol, and coffee. The active party room contained similar smoking cues and included interaction with avatars, with cigarettes being offered, drinks being poured and conversations being held while people lit up cigarettes. The order of active rooms was randomized. These rooms were chosen from the Virtually Better™ software as they have been previous validated for non-abstinent smokers.^{12,16}

Exposure to each VR room lasted approximately 3 min and followed a timed path where at certain points participants were visually directed for a few seconds to pay attention to non-smoking or active cues in order to standardize some of the VR exposure within the environment. This visual guiding (lasting only a few seconds) ensured that the subject viewed some of the environment rather than, for example, staring at a wall in each room. For the remainder of the time the subject was free to look around the room at whichever stimuli they desired. After navigation through each room, participants were presented with four questions via the HMD. They were asked to rate each question using a keypad. "How much did you crave cigarettes" ("crave") was rated with a visual analogue scale (VAS) from 0 through 100, where 0 was no craving and 100 was the most they have ever craved. Participants then rated on a scale of 0–10 (where 0 was low, and 10 was high) answers to the following questions; "How much did you think about cigarettes," "How much did you pay attention to the sight of cigarettes," and "How much did you pay attention to the smell of cigarettes." As there were no visual or olfactory smoking cues in the placebo rooms, these last two questions were included as manipulation checks. Due to a technical issue, one set of VR data was lost, so the final analysis of VR data is for 35 of the 36 participants.

At standardized time points when specific stimuli were observed by participants, HR was recorded using a GE Dash-3000 blood pressure machine with a pulse oximetry attachment (GE Medical Systems).

Data Analyses

Paired *t* tests were used to compare differences between Day 1 and Day 2 for breath CO, salivary cotinine levels, hours since last use, WSWs, SJWQ, and QSU. Paired *t* tests were also used to compare differences between VR ratings for active party versus active paraphernalia, active party versus placebo 1, and active paraphernalia versus placebo 1. An additional paired *t* test was conducted between placebo1 versus placebo 2 to evaluate potential "carryover effects" produced by exposure to active cues.

Simple linear regression was conducted to evaluate the relationship between crave induced by active party cues and (a) the SJWQ sub-score of crave, (b) the WSWs sub-score of crave, (c) the QSU score, and (d) nicotine dependence, assessed by the FTND.

Changes in HR were analyzed using paired *t* tests comparing a non-smoking cue within the placebo room (nature video shown on a virtual television set in the room) versus four different active cues. Two active cues were taken from the party room including an avatar lighting up a cigarette and an avatar offering a cigarette to the participant. Two active cues from the paraphernalia room included a cigarette packet on the table and a burning cigarette in an ashtray.

In all cases $p < .05$ was considered statistically significant. All analyses were conducted using Statview™ version 5.0.

Results

Demographics and Smoking Characteristics

The study sample included 36 adults (14 female and 22 male), with an average education of 13.1 ± 1.7 (mean $\pm$ SD) years who identified as Caucasian (58%), Black (36%) or both Caucasian and Black (6%). On average, subjects smoked 18.3 ± 8.6 cigarettes per day for 23.6 ± 10.7 years and had an FTND score of 6.0 ± 2.4 .

Self-reported hours since last cigarette were significantly greater on Day 2 than Day 1 (26.9 ± 7.2 vs. 1.3 ± 0.8 ; $t = -21.60$, $p < .0001$), and exhaled breath CO was significantly lower on Day 2 versus Day 1 (3.3 ± 1.8 vs. 16.0 ± 6.6 ppm; $t = 11.32$, $p < .0001$). Salivary cotinine levels were significantly lower on Day 2 versus Day 1 (161.5 ± 131.5 vs. 356.6 ± 226.9 ng/ml; $p = .0008$).

Subjective Self-Assessment Measures

Significant increases were noted between Day 2 versus Day 1 for the WSWs average score ($t(35) = -3.12$, $p = .004$) (Figure 1a), and sub-scores crave ($t(35) = -4.48$, $p < .0001$), anger ($t(35) = -2.36$, $p = .02$), concentration ($t(35) = -3.18$, $p = .003$), and hunger ($t(35) = -2.82$, $p = .008$). No significant differences were found for sadness, anxious, or sleep (p 's $> .05$).

Significant increases were noted between Day 2 versus Day 1 for average SJWQ score ($t(35) = -3.37$, $p = .002$) (Figure 1b), and sub-scores crave ($t(35) = -2.46$, $p = .02$), physical ($t(35) = -2.44$, $p = .02$), and psychological symptoms ($t(35) = -3.33$, $p = .002$). No significant differences were found for stimulated or appetite (p 's $> .05$).

Significant increases were noted between Day 2 versus Day 1 for total QSU score (50.8 ± 15.9 vs. 45.1 ± 14.4 ; $t(35) = -2.54$, $p = .016$). Factor 1, the intention to smoke, was significantly higher on Day 2 versus Day 1 (29.2 ± 8.2 vs. 26.3 ± 7.5 ; $t(35) = -2.42$, $p = .02$), and Factor 2, relief of negative affect, was found to be significantly greater on Day 2 than Day 1 (21.6 ± 9.3 vs. 18.8 ± 8.1 ; $t(35) = -2.08$, $p = .045$).

Virtual Reality

There were no gender differences in craving response to cues for any of the VR rooms (p 's $> .05$). Participants verbally reported a great

Figure 1. Effects of overnight deprivation of cigarettes on withdrawal-like symptom scores measured using the Shiffman-Jarvik withdrawal questionnaire (a) and the Wisconsin smoking withdrawal scale (b) * $p < .05$ (Day 2 vs. Day 1).

sense of immersion within the VR environment and greater craving in the active rooms. Examples include “I wanted to reach out a grab the cigarette (from the avatar)”, “It really feels like you are moving around the room but you are sitting down, it’s incredible,” and “Talking with the people who were smoking really felt real, it really made me want a cigarette”.

Self-reported levels of crave during VR were significantly greater in the active party room versus placebo room 1 ($t(34) = -3.12$, $p = .004$), but were not significantly greater in the active paraphernalia room versus placebo room 1 ($t(34) = -1.74$, $p = .09$) (Figure 2). Crave was also significantly greater in the active party room versus the active paraphernalia room ($t(34) = -2.44$, $p = .02$). There was no significant difference in craving between the placebo rooms ($t(34) = 1.00$, $p = .3$).

The sight of cigarettes was attended to significantly more in the active party room versus placebo room 1 ($t(34) = -15.64$, $p < .0001$), and significantly more in the active paraphernalia room versus placebo room 1 ($t(34) = -12.83$, $p < .0001$). There was no significant difference for sight of cigarettes between the two active rooms, and no difference between placebo rooms ($ps > .05$).

The smell of cigarettes was attended to significantly more in the active party room versus placebo room 1 ($t(34) = -4.37$, $p = .001$) and significantly more in the active paraphernalia room versus placebo room 1 ($t(34) = -3.22$, $p = .003$). There was no significant difference between smell of cigarettes between the two active rooms, and no difference between placebo rooms ($ps > .05$).

Self-reported levels of thinking about cigarettes were significantly greater in the active party room versus placebo room 1 ($t(34) = -6.26$, $p < .0001$), and significantly greater in the active paraphernalia room versus placebo room 1 ($t(34) = -5.06$, $p < .0001$). Lastly, there was a significant difference in level of thinking about cigarettes between the two placebo rooms ($t(34) = -3.07$, $p < .004$).

The following self-assessment scores were taken from the cigarette-deprived condition. There were significant positive correlations between (a) SJWQ sub-score crave and active party VR craving ($r = .57$, $p = .0004$), (b) WSWS sub-score crave and active party VR craving ($r = .56$, $p = .0005$), and (c) total QSU score and active party VR craving ($r = .58$, $p = .0003$). In order to assess the predictive value of nicotine dependence while smoking as usual and VR induced craving when deprived, each participant’s FTND score was correlated with VR craving. Notably, a significant positive correlation was found between FTND and active party VR craving ($r(33) = .58$, $p = .0003$) (Figure 3).

Cue Effects on Heart Rate

There were no statistical differences for demographic or drug use data (age, gender, education, or cigarettes per day) between those subjects with physiological data versus the entire sample ($ps > .05$) with the exception that the full sample of participants had lower FTND scores compared with the physiological subgroup ($t(34) = -2.81$, $p = .008$). In the active party room, as compared to the non-smoking cues, significant increases in HR were detected for the active cues of an avatar lighting up a cigarette (68.9 ± 10.5 vs. 67.8 ± 9.9 beats per minute (bpm); $t(15) = -2.41$, $p = .03$) and an avatar offering a cigarette to the participant (70.1 ± 8.9 vs. 67.8 ± 9.9 bpm; $t(15) = -2.67$, $p = .017$). In the active paraphernalia room, as compared to the non-smoking cue, significant increases in HR were detected for the active cue of a burning cigarette in an ashtray (70.5 ± 9.7 vs. 67.8 ± 9.9 bpm; $t(15) = -3.17$, $p = .006$), but HR did not increase when viewing the active cue of a cigarette pack on the table (68.3 ± 9.5 vs. 67.8 ± 9.9 bpm; $t(15) = -2.11$, $p = .052$). Finally, when the two placebo (non-smoking) cues were compared, HR was significantly increased in the final neutral room (70.5 ± 8.7 vs. 67.8 ± 9.9 bpm; $t(15) = -2.77$, $p = .01$).

To assess for any possible additive effects of active cues on HR, cues were recoded and analyzed in the order they were presented for each individual renaming them HR 2, HR 3, HR 4, and HR 5 (reminder that HR 1 and HR 6 were fixed assessments of HR assessments of nonsmoking cues). The data reveal no significant effects of HR for active cues HR 2 versus HR 3 (68.3 vs. 70.6 bpm; $t(1.7)$, $p = .12$), HR 3 versus HR 4 (70.6 vs. 68.9 bpm; $t(1.4)$, $p = .17$), nor HR 4 versus HR 5 (68.9 vs. 70.0 bpm; $t(1.5)$, $p = .14$).

Discussion

The data in this report show that self-reported levels of craving and thinking about cigarettes were significantly greater after exposure to active (smoking) cues versus placebo (non-smoking) cues. These results are consistent with previous VR studies that evaluated craving in cigarette smokers.^{12,13,17,20,34} In our study, the paraphernalia room increased craving to a lesser extent than the more detailed social setting that included avatar interaction in the party room. This finding supports existing literature showing that richer, more salient environments may have greater ecological validity and therefore elicit greater craving responses.³⁵

In the current study, self-assessment questionnaires revealed that participants exhibited several symptoms of withdrawal and increased craving on Day 2, although withdrawal symptoms and

Figure 2. Subjective measures in response to active party or active paraphernalia cues as compared to non-smoking cues when nicotine-dependent cigarette smokers were deprived from smoking overnight. In all cases $*p < .05$ versus placebo 1.

Figure 3. Correlation of nicotine dependence severity, measured using Fagerström test of nicotine dependence, with virtual reality craving in the active party room after cigarette deprivation.

craving for cigarettes were notably present on Day 1. Considering the time since the last cigarette smoked on Day 1 (~1 hr), this short amount of time was apparently enough to induce withdrawal symptoms and craving in nicotine-dependent smokers. To our knowledge, the current report shows for the first time that withdrawal symptoms and self-reported craving prior to the VR session are strong predictors of craving in the virtual environment. Also, nicotine dependence severity at baseline was a robust predictor of craving responses to active VR cues.

These findings may have important implications in predicting who may respond most effectively to cue exposure therapy (CET)

for smoking cessation. A review of smoking cessation outcomes based on responses to cues found results to be inconsistent; this was suggested to be due to the lack of a standardized measure of smoking urges, such as the QSU.³⁶ Interesting future studies might explore if individuals who exhibit higher craving, withdrawal and dependence, as assessed by the self-report questionnaires used in the current study, may respond more favorably to VR CET. Several reports suggest that CET may prove useful for smoking cessation. Namely, projected 3D VR cues for CET (once weekly for 4 weeks) decreased subjective craving for smoking,²¹ a separate study reported a significant reduction of craving across 5 weeks of VR cue-exposure,³⁷ and

a report from our group showed that VR CET and cognitive behavioral therapy (CBT) (twice weekly for 8 weeks) improved quit rates and reduced cigarettes smoked per day.³⁸ More recent work by our group includes a study involving compound d-cycloserine plus VR CET and CBT (three times weekly for 4 weeks) in cocaine-dependent cigarette smokers, and the data revealed significant reductions in cue-induced craving and cigarette smoking regardless of treatment group.³⁹

In the current study, significant increases in HR were detected in response to 3 out of 4 active cues. The pack of cigarettes on the table did not elicit a significant increase in HR, and this may have occurred since craving has been shown to differ for lit versus non-lit cigarettes.^{6,35} In previous studies, physiological responses have not always been shown to be positively correlated with craving intensity.^{6,21,40,41} For example, one study found an increase in HR after presentation of tobacco stimuli,¹⁰ another report found no change in skin conductance or HR after presentation of cue stimuli.³⁵ One reason for these inconsistent results could be that the cues are eliciting different responses in the observer; some creating a negative response associated with withdrawal and others acting as a positive reinforcer of the value of the drug.^{40,42,43} Another explanation could be the lack of standardization of stimuli used and the varied means of presenting cues. In the current report, we presented cues in a complex and immersive setting and included standardized cues and the results reveal significant increases in HR suggesting that VR cigarette cues are provocative stimuli for cigarette-deprived individuals. In addition, the data show that increases in HR remain elevated for a period of time after the stimuli were no longer present. The current data support that of previous work with HR measurement after active and non-smoking cues in a VR environment.²⁵

While this study contributes important new findings to the cue-induced craving literature, there are limitations that should be considered. First, we did not measure VR responses on both days and therefore do not have a within-subjects measure of VR craving when subjects had been smoking as usual. Second, on Day 1 we did not standardize the time since the last cigarette before subjects filled in the self-assessment questionnaires. Given that some subjects had not smoked in over an hour they may have been in greater withdrawal than those who smoked immediately before entering the research facility. Third, the design of the placebo rooms could be improved. For example, a better neutral-paraphernalia room might be an office with objects on a desk; this office environment could also involve avatar interaction for an active placebo room. Lastly, the sample size for the HR data suggests that these results should be interpreted with caution. In future studies, the quantity and quality of physiological data could also be improved using a remote physiological device to provide outputs for respiration and surface body temperature.⁴⁴

In conclusion, the current report shows for the first time that withdrawal symptoms and self-reported craving prior to the VR session are strong predictors of craving in a virtual environment, and that nicotine dependence severity at baseline was a robust predictor of craving responses to active VR cues. These findings may have important implications for smoking cessation therapy that employs cue exposure therapy.

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Declaration of Interests

None declared.

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