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Methamphetamine Craving Induced in an Online Virtual Reality Environment

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Abstract

The main aim of this study was to assess self-reported craving and physiological reactivity in a methamphetamine virtual reality (METH-VR) cue model created using Second Life, a freely available online gaming platform. Seventeen, non-treatment seeking, individuals that abuse methamphetamine (METH) completed this one-day, outpatient, within-subjects study. Participants completed four test sessions: 1) METH-VR 2) neutral-VR 3) METH-video 4) neutral-video in a counterbalanced (latin square) fashion. The participants provided subjective ratings of urges to use METH, mood, and physical state throughout each cue presentation. Measures of physiological reactivity (heart rate variability) were also collected during each cue presentation and at rest. The METH-VR condition elicited the greatest change in subjective reports of “crave METH”, “desire METH”, and “want METH” at all time points. The “high craving” participants displayed more high frequency cardiovascular activity while the “low craving” participants displayed more low frequency cardiovascular activity during the cue conditions, with the greatest difference seen during the METH-VR and METH-video cues. These findings reveal a physiological divergence between high and low craving METH abusers using heart rate variability, and demonstrate the usefulness of VR cues for eliciting subjective craving in METH abusers, as well as the effectiveness of a novel VR drug cue model created within an online virtual world.

1. Introduction

Drug craving represents a key component of addiction and serves to propagate drug-taking behavior, and to elicit relapse in abstinent individuals (Galloway and Singleton, 2009; Hartz et al., 2001; McKay et al., 1999; Rohsenow et al., 2007). Craving represents a complex condition that includes emotional and cognitive aspects along with behavioral and physiological states (Merikle, 1999; Tiffany, 1990; Tiffany and Conklin, 2000). Craving has

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been extensively studied in an effort to standardize methods of quantifying this multifaceted condition (Rosenberg, 2009). Much of this work has focused on cue-induced craving, measured by self-reports and/or physiological reactivity to environmental stimuli previously associated with drug use (Carter and Tiffany, 1999; Stewart et al., 1984). Traditionally, visual (photographs and videos), in vivo (drug and/or paraphernalia) and imagery (individualized drug scripts) cues have been used to elicit craving in the laboratory (Carter and Tiffany, 1999). However, these methods typically elicit modest subjective craving (Avants et al., 1995), do not reliably induce physiological reactivity (Dudish-Poulsen and Hatsukami, 1997; Ooteman et al., 2006) and inconsistently predict subsequent drug use (Galloway and Singleton, 2009). For these reasons, more realistic and individualized cue exposure models are required to assess craving in drug abusers.

Addiction researchers have recently created and validated tobacco (Baumann and Sayette, 2006; Bordnick et al., 2004; Bordnick et al., 2005a; Bordnick et al., 2005b; Carter et al., 2008; Lee et al., 2003; Lee et al., 2005; Traylor et al., 2008), alcohol (Bordnick et al., 2008; Cho et al., 2008), cannabis (Bordnick et al., 2009), heroin (Kuntze et al., 2001) and cocaine (Saladin et al., 2006) VR drug cue systems. These systems incorporate multimodal drug cues into computer simulated environments using real-time graphics, 3-D visual displays, movement tracking devices, surround-sound audio, and tactile stimulators to create a fully immersive experience. VR drug cue models have elicit significantly more craving than traditional methods of cue exposure (Kuntze et al., 2001; Lee et al., 2003) and have also been applied to behavioral therapies for addiction (Lee et al., 2007). One pilot study applied VR cues to a stimulant abusing population and demonstrated that VR crack-cocaine cues elicit greater craving and physiological reactivity than neutral VR cues (Saladin et al., 2006). To our knowledge, no study has been conducted to assess VR cues in METH abusers.

The current study aimed to assess the effectiveness of a newly developed METH-VR cue model, compared to METH video cues, previously validated by our group (Newton et al., 2006). The METH-VR model was created using a freely available online VR platform, and included animate, inanimate, contextual and auditory cues. METH abusing participants provided subjective ratings of urges to use METH using multi-item craving questionnaire. Physiological reactivity was monitored via an electricardiogram (ECG) and analyzed for fluctuation in heart rate, or heart rate variability (HRV), that correspond with autonomic nervous system functions (1996; Allen et al., 2007; Ori et al., 1992). We hypothesized that METH abusers would exhibit greater increases in self-reported craving and display larger fluctuations of heart rate variability during the METH-VR cue exposure compared to traditional METH cues and neutral cues.

2. Methods

2.1 Participants

Otherwise healthy, non-treatment seeking METH users were recruited through local newspaper, radio and Internet advertisements. All participants underwent an initial telephone screening and provided information on their medical, psychiatric and drug use histories. Potential participants that successfully completed the telephone screen were invited to an in-person screening that included questions regarding demographics and drug use, and a urine toxicology test. Eligible participants were also required to provide self-reports of mood and recent drug use, and a urine toxicology test on the test day. All participants received a detailed verbal and written description of the study procedures before giving written informed consent, as approved by the University of California Los Angeles Institutional Review Board.

Exclusion criteria included 1) history of any self-reported Axis I psychiatric diagnosis (other than METH or nicotine dependence), 2) vision or hearing impairments, 3) use of any

medication or medical condition that may significantly effect cardiovascular function, 4) illicit drug use (cocaine, heroin, hallucinogens, etc), other than METH, in the past 30 days. Any subject reporting recreational alcohol (≤ 1 drink per day) or marijuana (≤ 3 use per week) use, not meeting criteria for abuse/dependence, was allowed to participate, but instructed to abstain prior to testing (confirmed with self-report, urine toxicology test and alcohol breathalyzer during the in-person screen and on the test day).

2.2 Cue Presentation Procedures

Participants were permitted to smoke cigarettes ad libitum prior to the start of the study, but were required to abstain from smoking during the study (approximately 2 hours). Participants first completed questionnaires (30 min) before starting the cue sessions. This procedure standardized the time since the last cigarette (30 minutes), and allowed for modest cigarette craving (Schuh and Stitzer, 1995), while avoiding the possibility of heavy cigarette craving caused by prolonged abstinence. The cue condition presentation order was counterbalanced between participants (Latin Square). The participants viewed each cue condition for 10 min, with a ten minute break between each cue condition, in a sensory-attenuated setting on a Sharp Aquos 32″ LCD HDTV. The VR and video cues were run from a Dell Dimension DXP061 desktop containing a NVIDIA GeForce 8800 GTX graphics card and 768 MB of graphics memory. The participants navigated the VR environments using a Logitech Dual Action controller. Movement within the VR environments was limited to forward/backward walking (using the D-pad) and 360-degree head directional movements (using the right analog stick). Following completion of the last cue condition, participants were debriefed to ensure that their participation would not alter future drug taking behavior. Participants remained under supervision until their self-reported craving reached baseline levels, at which point they were discharged from the study session.

2.3 Virtual Reality Cues

Photographs of the real apartment were taken (using a 6.3 MegaPixel Digital Canon EOS camera) from multiple angles under two conditions: “METH-house” (Figure 1) and “neutral-house” (Figure 2) to capture realistic light and textures in digital form. The photographs were then visually manipulated using Adobe Photoshop ® (version 7.0) to include additional METH paraphernalia and to enhance the overall realism. The finished images were applied to a 3-D mock up of the real apartment created in Second Life (www.secondlife.com). Finally, virtual avatars and drug-use animations (e.g. smoking, injecting, snorting) were created using Second Life tools and Poser Version 6, respectively, and placed into the VR environments.

The METH-VR environment was developed on the basis of self-reports from METH abusers’ to represent a “METH-house” (i.e. a location where drug transactions and use occurs). This VR environment included animate (avatars administering METH), inanimate (drug paraphernalia), contextual (“METH-house” characteristics) and auditory (music reported by each subject to be associated with METH use) cues (Figure 1). The neutral-VR environment was modeled after a modern apartment (devoid of any drug cues) and includes neutral auditory stimuli (Latin jazz) (Figure 2). The participants were instructed to explore each VR environment freely, but were restricted from leaving by natural barriers, such as doors and walls.

2.4 Video & In Vivo Cues

The METH-video included professional actors/actresses administering METH via multiple routes (smoking, snorting, injecting) in a variety of settings with a set soundtrack. The participants were also provided with in vivo mock METH paraphernalia (e.g. glass pipe, mock syringe, medical tubing, and a small plastic bag containing a substance that appears to be METH) to examine during METH-video. The neutral-video contained footage of tropical fish

swimming in a tank and included neutral music (classical guitar). The participants were also provided with in vivo neutral objects (e.g. feather, pinecone, pencil) to examine during the neutral-video. The participants were instructed to "imagine yourself in the situation while you are watching" at the start of each video.

2.5 Subjective Response Monitoring

All subjective responses were recorded on a visual analogue scale (VAS) from 0 to 100 ("none" to "very much"). The VAS form incorporated the nine following questions: four regarding urges to use METH ("How much do you crave/desire/want METH right now?", and "If you had access to METH right now, how likely would you be to use it right away?") two questions regarding mood ("How depressed/anxious do you feel right now?") and three questions regarding physical state ("Do you feel any drug effect right now?", "How high are you right now?", and "How stimulated do you feel right now?"). Desire was specifically defined in subtext next to the question as "to want (a feeling)" and crave as "strong or intense need (an internal force)".

2.6 Heart Rate Variability Recording

Electrocardiogram (ECG) activity was recorded over 10-min intervals using two active EL126 snap leads and EL204 electrodes placed on the left pectoral and sternum with a third grounded lead/electrode placed on the left lateral rib cage. ECG data was filtered through a PSYLAB Isolation BioAmplifier and measured using a PSYLAB Stand Alone Monitor (Contact Precision Instruments, Cambridge, MA). The ECG data was recorded at 500 Hz and stored in PSYLAB Measurement acquisition software on a Latitude D600 Dell laptop.

2.7 Subjective Response Analysis

Subjective reports provided prior to (time = 0), during (time = 5), after (time = 10) and following (time = 15) each cue condition served as the dependent measure of greatest interest. Change in craving for each cue condition, rather than raw craving score, was analyzed in order to measure acute cue-induced craving, to eliminate baseline variability between participants, and to account for carry-over effects between cue conditions. The craving change score was calculated by subtracting the baseline rating (time = 0) for each cue condition from the ratings at later time points (time = 5, 10, 15). A within-subjects general linear model (GLM) for repeated measures was used to assess the effect of cue condition and time on each subjective measure independently. In the case that sphericity could not be assumed (Mauchly's Test of Sphericity), the statistics reported were adjusted via the Greenhouse-Geisser method. A one-way ANOVA, including post hoc analysis (Tukey), was used to compare cue conditions at each time point (time = 5, 10, 15). A Pearson bivariate correlation was also applied to assess the relationship between recent drug use and subjective responding. Statistical analysis was performed using SPSS 11 for Mac OS X.

2.8 Heart Rate Variability Analysis

The ECG data was transferred to QRS Tool where the inter-beat interval (IBI) was manually extracted from an 8-min segment of each 10-min recording (excluding first and last minute to reduce artifacts) (Allen et al., 2007). Successive R-waves in each QRS complex were marked using individualized amplitude thresholds and the average heart beat period as guiding factors. The IBI series was then transferred to Kubios HRV 2.0 analysis software where time-domain and frequency-domain (parametric AR modeling) analyses were conducted (1996). The three frequency bands extracted for analysis included a very low frequency band (VLF, 0–0.04 Hz), a low frequency band (LF, 0.04–0.15 Hz), and a high frequency band (HF, 0.15–0.4 Hz). The measures of interest extracted from each frequency band included 1) the relative powers of VLF, LF, and HF bands, 2) the normalized LF and HF band powers and 3) the LF/HF power

ratio. The time domain and frequency domain measures were analyzed separately using two multivariate GLMs for repeated measures to assess for an overall effect of cue condition on each set of HRV measures. A Pearson bivariate correlation was also applied to assess the relationship between recent drug use and heart rate variability. Statistical analysis was performed using SPSS 11 for Mac OS X.

2.9 High and Low Craving Participant Analysis

The participants were characterized as "high craving" and "low craving" participants using a median split on baseline "crave METH" scores. The two groups were assessed for differences in demographic and drug use characteristics, and heart rate variability measures. A one-way ANOVA was used to compare all demographic and drug use characteristics, except gender and ethnicity, which were assessed using a Chi-Square test. A multivariate GLM for repeated measures was used to assess an effect of craving group on time domain and frequency domain HRV measures separately. A one-way ANOVA was then used to assess group differences in each time domain and frequency domain HRV measure independently. Lastly, a Pearson bivariate correlation was applied to each craving group separately to assess the relationship between change in subjective responses and HRV measures during each cue condition.

3. Results

3.1 Demographics and Drug Use Characteristics

The study sample consisted of 17 (14 men, 3 women) adults (mean ± SD age 39.5 ± 8.8 yr) with, on average, a high school education (mean ± SD 12.0 ± 2.0 yr). The participants used METH for 10.9 ± 5.9 (mean ± SD) years and reported 13.2 ± 11.3 (mean ± SD) days of METH use in the month prior to participation in this study. The majority of participants smoked cigarettes (82%), drank alcohol (71%) and used marijuana (59%) in the last 30 days. At baseline, the participants reported a median score of 20 out of 100 on ratings of "crave METH" (9 "high craving" participants > 20; 8 "low craving" participants ≤ 20). No significant differences were observed between the "high craving" and "low craving" participants on demographic or drug use characteristics (Table 1).

3.2 Subjective Craving and Mood

A within-subjects GLM for repeated measures assessing change in each subjective response demonstrated a significant effect of cue condition on reports of "crave METH" ($F_{3, 13} = 8.08$, $P = 0.001$), "desire METH" ($F_{3, 14} = 6.50$, $P = 0.001$), "want METH" ($F_{3, 13} = 6.40$, $P = 0.005$), "use METH right away" ($F_{3, 14} = 7.10$, $P = 0.006$), and feeling "anxious" ($F_{3, 14} = 3.85$, $P = 0.036$), and "high" ($F_{3, 14} = 3.42$, $P = 0.049$) (Figure 3). No effect of time was observed on subjective responses.

A one-way ANOVA assessing change in subjective responses at each time point separately revealed a significant effect of cue condition during (time = 5 min), after (time = 10 min) and following (time = 15 min) cue presentation for "crave METH", "desire METH", "want METH", and "use METH right away" ($P < 0.01$ for all). A significant effect of cue condition was also observed for feeling "anxious" during and after cue presentation ($P < 0.02$ for both) and for feeling "high" following cue presentation ($P < 0.03$). Post hoc (Tukey) analysis revealed that the METH-VR cue condition elicited significantly greater increases in "crave METH", "desire METH", "want METH", and "use METH right away" compared to both neutral conditions at almost all time points (Table 2). No correlations were observed between recent drug use and subjective responding.

3.3 Heart Rate Variability

A within-subjects GLM for repeated measures revealed no effect of cue condition on time domain or frequency domain HRV measures. A multivariate GLM for repeated measures revealed a significant effect of craving group on frequency domain HRV measures ($F_{3, 14}$ = 12.37, P = 0.003). A one-way ANOVA further revealed that the "high craving" participants exhibited a significantly greater amount of relative and normalized HF power during the METH-VR ($P < 0.001$ for both), METH-video ($P < 0.001$ for both), and the neutral-video ($P < 0.02$) cues compared to the "low craving" subjects. Conversely, the "low craving" participants exhibited a significantly greater amount of relative and normalized LF power during the METH-VR ($P < 0.001$ for both), METH-video ($P < 0.01$ for both) and neutral-video ($P < 0.03$ for both) cues compared to the "high craving" participants. The "low craving" participants also displayed a significantly higher LF/HF ratio during the METH-VR and METH-video ($P < 0.003$ for both) cues, and during the neutral-VR and neutral-video cues ($P < 0.03$ for both), compared to the "high craving" participants. No significant differences were observed between the craving groups at rest (Table 3). No correlations were observed between recent drug use and time domain or frequency domain HRV measures.

A bivariate correlation revealed a positive association between LF/HF ratio and change in self-reported "crave METH" ($R_7 = 0.85$, p = 0.016), "want METH" ($R_8 = 0.85$, p = 0.015), and "use METH right away"($R_8 = 0.87$, p = 0.006), and a trend towards an association with "desire METH" ($R_8 = 0.65$, p = 0.08) during the METH-video in the "low craving" participants.

4. Discussion

METH abusers demonstrated increases in subjective craving (measured as "crave METH", "desire METH", "want METH" and "use METH right away") when presented with METH-VR cues compared to the neutral-VR or neutral-video cues. The participants reported approximately twice as much subjective craving during the METH-VR cues compared to the METH-video cues, although this finding did not reach significance. The participants also report a greater increase in "anxiety" to the METH-VR cues compared to the neutral-VR cues. These findings parallel those seen in other drug abusing populations (Baumann and Sayette, 2006; Bordnick et al., 2009; Bordnick et al., 2004; Bordnick et al., 2005a; Bordnick et al., 2008; Bordnick et al., 2005b; Carter et al., 2008; Cho et al., 2008; Kuntze et al., 2001; Lee et al., 2003; Lee et al., 2007; Lee et al., 2005; Saladin et al., 2006; Traylor et al., 2008), and demonstrate the usefulness of VR cues for eliciting subjective craving in METH abusers, as well as the effectiveness of a novel VR drug cue model created within an online virtual world.

The METH-VR system was created with the goal of enhancing realism, accessibility and adaptability while reducing complexity and cost. Existing VR drug cue models incorporate proprietary software and expensive hardware to create drug specific experiences (Bordnick et al., 2009; Bordnick et al., 2005a; Bordnick et al., 2008; Carter et al., 2008; Lee et al., 2003; Saladin et al., 2006). Recently, user-created online gaming platforms have emerged to provide a forum for creating personalized virtual environments and an alternative to private VR software packages. As seen here and in previous studies, visual presentation of VR environments elicits significant levels of craving (Baumann and Sayette, 2006). These findings do not detract from the importance of presenting an immersive environment, but rather demonstrate the viability of creating such environments using freely available online software and minimal hardware (i.e. computer and monitor). Online virtual worlds have become home to a wide range of health related activities ranging from patient education to scientific experimentation (Beard et al., 2009; Boulos et al., 2007). These user-created 3-D worlds offer a number of benefits over previous VR systems including adaptability, accessibility and cost. These systems contain a variety of tools that allow users to modify and specify all aspects of the environment, such as contextual, animate and inanimate drug cues, in real time.

Furthermore, all of this data from these environments is stored onto external servers, thus allowing the user to access their VR world through a high-speed Internet connection. Anyone can download and access these systems for free, and the cost of development remains relatively very low compared to alternative VR systems. The results reported here support future applications of virtual worlds in addiction research and present a viable opportunity to create and share standardized drug cue environments in a collaborative effort.

Contrary to previous research in alcoholics (Ingjaldsson et al., 2003), the “high craving” and “low craving” participants reported here demonstrated an inverse relationship between baseline craving and physiological reactivity. The “high craving” participants exhibited a greater parasympathetic response while the “low craving” participants exhibited a greater sympathetic response to all of the cue conditions, with the greatest difference during the METH-VR and METH-video cues (1996; Ori et al., 1992). The “low craving” participants demonstrated a mild increase in sympathetic activity from rest to all of the cue conditions, and displayed a positive association between subjective craving and sympathetic activity during the METH-video, while the “high craving” participants exhibited little change from rest. The results concerning the “low craving” participants support the traditional theory of cue reactivity, which proposes that psychological craving coincides with a sympathetic or stress response (Sinha, 2009), while the results from “high craving” participants support research suggesting that a disconnect exists between subjective craving and physiological reactivity (Dudish-Poulsen and Hatsukami, 1997; Ooteman et al., 2006). Taken together, these findings present an intriguing dichotomy between “high craving” and “low craving” METH abusers and provide insight into the effect of baseline carving on subsequent physiological cue-reactivity.

This study has some limitations. The HRV results did not reveal any differences in autonomic response between the four cue conditions. A number of factors specific to this population including cardiovascular deficits (Kaye et al., 2007; Thayer et al., 2009), a blunted or disconnected physiological response to psychological stimuli (Dudish-Poulsen and Hatsukami, 1997; Ooteman et al., 2006), or general heterogeneity may account for this lack of observable difference (Newton et al., 2009). The study design used here (i.e. one-day outpatient) limited experimenter control over the participants’ behavior prior to testing. To account for this lack of control, a number of measures (demographics and drug use history) were collected and included in the analyses to explore for associations between these factors and craving. Although on par with previous studies of VR craving (Baumann and Sayette, 2006; Bordnick et al., 2009; Bordnick et al., 2005a; Saladin et al., 2006), the number of participants included in the present study, particularly female participants, was low. Future studies with a higher number of women could provide insight into gender differences in cue reactivity. The participants included in this study had a wide variety of METH, nicotine, alcohol and cannabis use characteristics, which probably accentuated variability. However, we felt it was important to include a diversely representative sample of METH abusers to obtain results that are generalizable to the overall population of METH abusers. Due to the repetitive nature of measuring acute craving, a multi-item VAS craving questionnaire was substituted for the more comprehensive multidimensional craving questionnaire (Rosenberg, 2009). The numerical limitations of the VAS craving questionnaire (1–100) may have resulted in ceiling effects in the “high craving” participants and flooring effect in the “low craving” participants. In light of these limitations, the consistency of the results presented here only further support the central finding of this study that the METH-VR model serves as a powerful clinical tool for manipulating acute craving in METH abusers.

VR technology continues to rapidly advance with commercial demands from the gaming entertainment community. Researchers now have access to unprecedented tools for creating realistic VR environments to monitor and manipulate human behavior in the laboratory. The results presented here provide evidence for the applicability of these VR tools. Future research

and development of VR drug cue environments should focus on enhancing realism and specificity to complement the complexity of individuals with substance-use disorders. Improved VR drug cue models will allow researchers to better assess cue-induced craving, as well as drug self-administration, neurocognitive abilities and patterns of locomotor behavior (e.g. drug seeking, conditioned place preference, approach avoidance) in a realistic and interactive setting. Integrating these investigative methods into VR environments will provide insight into connectivity between factors that underlie drug craving and provide an optimum paradigm for designing and testing treatments for drug addiction.

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Figure 1.
Screenshots of the methamphetamine virtual reality (METH-VR) cue environment

Figure 2.
Screenshots of the neutral virtual reality (neutral-VR) cue environment

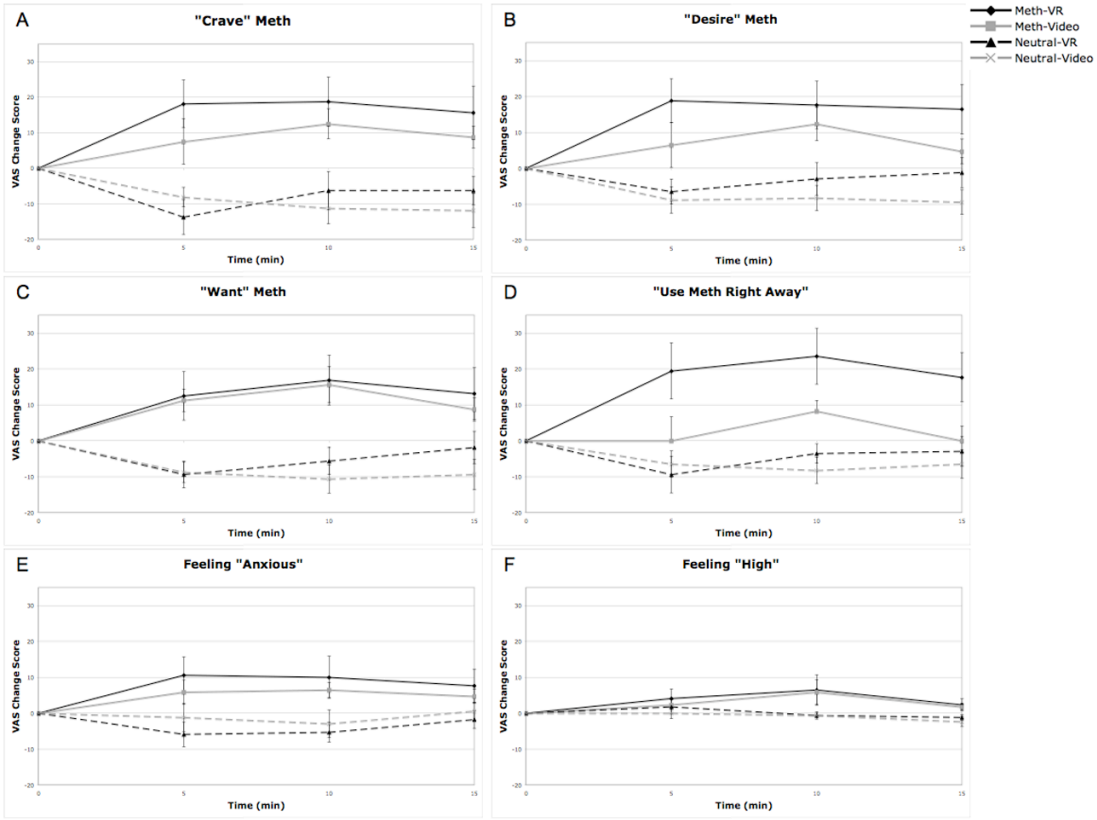

Figure 3.

Change in subjective reports of “crave METH” (A), “desire METH” (B), “want METH” (C), “use METH right away” (D), feeling “anxious” (E), and feeling “high” for all participants (N=17) during, after and following each cue condition (values represent the mean change in subjective responses (−100 – 100) ± standard error mean).

Table 1

Demographic and Drug Use Characteristics for “High Craving” and “Low Craving” Participants

	Craving Group	
	High (n = 9)	**Low** (n = 8)
Gender		
Male (%)	78	88
Female (%)	22	13
Ethnicity		
White (Not Hispanic) (%)	44	13
Hispanic or Latino (%)	33	75
African American (%)	0	13
Other (%)	22	0
Age	40.6±3.1	38.4±3.0
Education	12.6±0.5	11.4±1.0
Substance Use		
Methamphetamine (%)	100%	100%
Years Use	9.3±1.6	12.6±2.4
Days in Last 30	15.4±4.0	10.8±3.8
Nicotine (%)	78%	88%
Years Use	14.5±3.7	9.9±3.1
Cigarettes per day	11.0±4.1	11.1±4.3
Alcohol (%)	56%	88%
Days in Last 30	1.3±0.5	2.7±0.9
Cannabis (%)	44%	75%
Days in Last 30	6.6±4.1	1.9±0.6

Table 2

Self-Reported Subjective Responses During, After, and Following Each Cue Condition

		Cue Condition				Statistics (ANOVA)	
Subjective Responses		**MA-VR**	**MA-Video**	**Neutral-VR**	**Neutral-Video**	**F-stat**	***p*-value**
"Crave" Meth	*0 min*	0	0	0	0	-	-
	5 min	18.1±6.7	7.5±6.4	***−13.8±4.9*****, ^	***−8.1±2.8***	***7.18***	***0.001***
	10 min	18.8±6.9	12.5±4.2	***−6.3±5.3***	***−11.3±4.4*****, ^	***7.41***	***0.001***
	15 min	15.6±7.5	8.8±3.0	***−6.3±1.7****	***−11.9±4.8*****, ^	***6.34***	***0.001***
"Desire" Meth	*0 min*	0	0	0	0	-	-
	5 min	18.8±6.1	6.5±6.2	***−6.5±3.4***	***−8.8±3.6***	***6.47***	***0.001***
	10 min	17.6±6.6	12.4±4.6	***−2.9±4.5****	***−8.2±3.5*****, ^	***6.21***	***0.001***
	15 min	16.5±6.9	4.7±3.4	***−1.2±1.7****	***−9.4±3.4***	***5.40***	***0.002***
"Want" Meth	*0 min*	0	0	0	0	-	-
	5 min	12.5±6.7	11.3±3.1	***−9.4±3.7*****, ^^**	***−8.8±2.9*****, ^**	***7.58***	***0.001***
	10 min	16.9±6.9	15.6±5.1	***−5.6±3.8****, ^	***−10.6±3.9*****, ^**	***7.83***	***0.001***
	15 min	13.1±7.2	8.8±3.3	−1.9±1.7	***−9.4±4.2****	***4.12***	***0.010***
"Likely To Use" Meth	*0 min*	0	0	0	0	-	-
	5 min	19.4±7.8	0.0±6.7	***−9.4±5.1***	***−6.5±3.6****	***4.64***	***0.005***
	10 min	23.5±7.8	8.2±3.0	***−3.5±2.7***	***−8.2±3.7***	***8.92***	***0.001***
	15 min	17.6±6.8	0.0±4.1	***−2.9±1.7****	***−6.5±3.9***	***4.77***	***0.005***
Feeling "Anxious"	*0 min*	0	0	0	0	-	-
	5 min	10.6±5.0	5.9±3.3	***−5.9±3.4***	−1.2±3.9	***3.90***	***0.013***
	10 min	10.0±5.8	6.5±2.1	***−5.3±2.7****	−2.9±3.8	***3.47***	***0.021***
	15 min	7.6±4.7	4.7±1.9	−1.8±1.7	0.6±2.5	1.87	0.144
Feeling "Depressed"	*0 min*	0	0	0	0	-	-
	5 min	−1.2±0.8	0.0±1.5	0.0±3.6	−1.2±2.7	0.08	0.971

		Cue Condition				Statistics (ANOVA)	
Subjective Responses		**MA-VR**	**MA-Video**	**Neutral-VR**	**Neutral-Video**	**F-stat**	***p*-value**
	10 min	0.0±1.5	−1.8±1.5	−1.8±1.8	−2.4±2.4	0.39	0.761
	15 min	−0.6±0.6	2.4±2.2	0.0±1.7	−1.8±2.5	0.73	0.536
Feeling "Stimulated"	*0 min*	0	0	0	0	-	-
	5 min	12.4±6.4	7.6±5.5	−0.6±0.6	−3.5±2.1	***2.28***	***0.046***
	10 min	11.8±6.3	8.8±5.1	−6.5±5.9	0.0±1.9	2.68	0.054
	15 min	7.1±3.7	1.8±4.9	−5.3±1.7	−2.9±1.4	1.58	0.203
Feeling "High"	*0 min*	0	0	0	0	-	-
	5 min	4.1±2.6	2.4±1.4	1.8±2.0	0.0±1.5	0.79	0.503
	10 min	6.5±4.2	5.9±3.4	−0.6±0.6	−0.6±1.0	1.99	0.125
	15 min	2.4±1.6	1.8±1.0	−1.2±1.7	***−2.4±1.4****	***3.43***	***0.022***
Feeling "Drug Effect"	*0 min*	0	0	0	0	-	-
	5 min	6.5±4.0	6.5±2.1	1.8±3.1	−2.6±2.5	2.10	0.109
	10 min	8.8±6.1	5.9±2.6	0.0±0.9	0.9±1.5	1.51	0.220
	15 min	2.6±2.5	−2.4±2.5	1.2±1.7	−0.3±0.9	1.12	0.346

Values represent mean ± S.E.M.,

** p<0.01;

* p<0.05 compared to Meth-VR

^^ p<0.01;

^ p<0.05 compared to Meth-Video

Table 3

Between Group Comparisons of Heart Rate Variability Frequency Domain Measures During Each Cue Condition

	Craving Group	
	High	**Low**
MA-VR		
VLF (%)	12.3±1.6	15.9±1.5
LF (%)	***55.8±2.1*** **	***69.0±2.1*** ^^
HF (%)	***31.9±3.2*** **	***15.1±2.1*** ^^
LF/HF	***2.0±0.3*** **	***5.4±1.0*** ^^
LF (n.u.)	***64.0±3.2*** **	***82.1±2.3*** ^^
HF (n.u.)	***36.0±3.2*** **	***17.9±2.3*** ^^
MA-Video		
VLF (%)	12.4±1.7	17.9±2.4
LF (%)	***54.6±2.7*** **	***67.8±3.4*** ^^
HF (%)	***33.1±3.2*** **	***14.3±3.3*** ^^
LF/HF	***1.8±0.2*** **	***6.6±1.3*** ^^
LF (n.u.)	***62.4±3.2*** **	***82.8±3.9*** ^^
HF (n.u.)	***37.6±3.2*** **	***17.2±3.9*** ^^
Neutral-VR		
VLF (%)	14.4±1.9	17.4±2.7
LF (%)	52.2±3.8	64.2±5.1
HF (%)	33.4±5.2	18.5±5.7
LF/HF	*1.9±0.3* *	*6.7±2.1* ^
LF (n.u.)	61.7±5.0	78.1±6.3
HF (n.u.)	38.3±5.0	21.9±6.3
Neutral-Video		
VLF (%)	14.1±1.4	16.6±2.8
LF (%)	*56.1±2.9* *	*67.7±3.9* ^
HF (%)	*29.8±3.7* *	*15.7±3.9* ^
LF/HF	*2.3±0.5* *	*6.5±1.5* ^
LF (n.u.)	*65.6±4.0* *	*81.4±4.3* ^
HF (n.u.)	*34.4±4.0* *	*18.6±4.3* ^
Rest		
VLF (%)	11.1±1.6	13.2±2.4
LF (%)	54.0±2.8	62.1±3.1
HF (%)	34.9±3.9	24.6±2.6
LF/HF	1.9±0.4	2.8±0.4
LF (n.u.)	61.2±4.0	71.6±2.9

Values represent mean ± S.E.M.,

** *vs* ^^ $p<0.01$;

* *vs* ^ $p<0.05$