A virtual reality counterconditioning procedure to reduce methamphetamine cue-induced craving

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ABSTRACT

The present work developed a virtual reality (VR) counterconditioning procedure (VRCP), and investigated its efficacy in treatment of cue-induced craving in individuals with methamphetamine (METH) dependence. In study 1, thirty-one patients diagnosed with METH dependence received VRCP, while twenty-nine METH-dependent patients in waiting-list group did not. In study 2, the VRCP was computerized as a VR treatment system. Six-hundred and twelve abstinent individuals with a history of METH dependence received the computerized VRCP, while two-hundred seventy-six abstinent individuals with a history of METH dependence in waiting-list group did not. Patients with METH dependence who received VRCP showed a significantly larger decrease on the score of METH-craving and METH-liking from baseline to follow-up assessments, compared to those who did not received VRCP. Participants received VRCP showed a significantly larger decrease in HRV indexes on time domain and non-linear domain from baseline to follow-up assessments during exposure to VR cues, compared to those in waiting-list group. These findings indicate that the counterconditioning procedure under VR environment may be a useful strategy in suppressing cue-induced reactivity for patients with METH dependence.

1. Introduction

Methamphetamine (METH) dependence is a worldwide public health concern. In China, the proportion of illicit METH users has been dramatically increasing in the past more than ten years (Sun et al., 2014; CFDA, 2016). As to 2016, nearly four of five new initiates of illicit drug users were the users of METH (CFDA, 2016). There is a pressing demand for research to develop effective interventions for patients with METH dependence.

For METH dependence, craving is one of the most important symptoms and servers to maintain this addictive behavior (e.g., Hartz et al., 2001; Galloway and Singleton, 2009). During abstinence from METH, craving is always elicited by the METH-related cues, and thus contributes to relapse (e.g., Hormes, 2017). This, termed as "cue-induced craving", is therefore always regarded as a primary target in relapse prevention.

Recently, virtual reality (VR) has been widely introduced in addiction research. It has been well documented that exposure to VR cues could elicit more reliable craving responses than traditional methods (such as, pictures, videos, and etc.) (e.g., Lee et al., 2005, 2009;

Culbertson et al., 2010; García-Rodríguez et al., 2012, 2013; Son et al., 2015). Therefore, it could be conceivable that VR technology may facilitate the efficacy of the traditional psychosocial interventions for substance use disorders (SUD) (Hone-Blanchet et al., 2014). Most of these studies, based in classical conditioning theory, adopted a VR cue-exposure therapy (CET) to suppress the cue-drug association (Lee et al., 2004, 2007; Moon and Lee, 2009; Choi et al., 2011; Pericot-Valverde et al., 2012; Park et al., 2014). However, although VR has been appreciated for its high ecological validity, most of these studies indicated that exposure to VR cues did not show promise as a treatment for drug craving (see review by Hone-Blanchet et al., 2014).

These findings, in conjunction with the previous observations with traditional CET designs (Conklin and Tiffany, 2002; Kaplan et al., 2011), suggest that an extinction procedure may be insufficient in suppressing the drug craving. Indeed, as proposed by Hone-Blanchet et al. (2014), the emotional component inherent to the drug-related cues might challenge the efficacy of CET in SUD. In this sense, a counterconditioning approach seems to be a more logical strategy over an extinction procedure (i.e., CET). Unlike the extinction procedure, the counterconditioning approach would not only decrease the

unconditioned expectancy, but also change the affective valence of conditioned stimulus by evaluative learning (i.e., paring new unconditioned stimulus with an opposite valence with previous conditioned stimulus). Previous studies have suggested that counterconditioning might have a stronger suppressive effect than extinction on the relapse of memories (van Gucht et al., 2010; Tunstall et al., 2012; Newall et al., 2017). More importantly, the efficacy of a counterconditioning approach with VR technology has been demonstrated in SUD (Lee et al., 2009; Son et al., 2015). In Lee et al.'s work (Lee et al., 2009; Son et al., 2015), they developed a "virtual reality therapy" (VRT) procedure for alcohol dependent patients, by pairing alcohol-related cues with aversive stimuli. Their results suggest that VRT had a superior effect in attenuating alcohol craving than cognitive therapy, with a corresponding increase in frontal alpha activity (Lee et al., 2009) and a decrease in basal ganglia metabolism (Son et al., 2015).

To some extent, these finding are encouraged by the fact that there is no medication proven to be effective as a treatment for METH dependence (Newton et al., 2005; Vocci and Appel, 2007; Karila et al., 2010; Cao et al., 2016). In our previous work (Wang et al., 2018), we have developed a METH-related virtual social environment for cue-induced craving assessment. Our findings indicate that exposure METH dependent patients to this VR METH-cue model could elicit a reliable craving, with a corresponding increase in heart rate variability (HRV). Here, as a continuous work, we developed a virtual reality counterconditioning procedure (VRCP) and investigated its efficacy for METH dependence. We hypothesized that a well-designed VRCP would be associated with a reduction of cue-induced reactivity.

2. Participants and methods

2.1. Participants recruitment and procedure

The current work was approved by the ethics committees of the Seventh Hospital of Hangzhou and is in accordance with the Helsinki Declaration of 1975 (revision 1983). Data was gathered in 2016 and 2017. All participants were over 18 years of age with normal (or corrected normal) vision and hearing. The written and informed consent was obtained. see (Table 1).

The flowchart of the present work is shown in Fig. 1. In 2016, sixty-one male patients with METH-dependence were included in study 1. All patients were interviewed by an experienced clinical psychiatrist and met with the following inclusion criteria: (a) met criteria for METH dependence according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV; (b) no evidence of current or previous central nervous system (CNS) disease, (c) no history of cardiovascular diseases; and (d) no other DSM-IV Axis I disorders. They were randomly assigned into the intervention group (n = 31) or waiting-list group (n = 30) using a computer-generated list of random numbers (with ratio 1:1). The patients in the intervention group received the VRCP, while those in waiting-list group did not. The electrocardiogram (ECG) signals (i.e., resting-state ECG, cue-induced ECG at baseline and follow-up assessments) and the subjective scores on a visual analogue scale (VAS) (i.e., METH-craving, METH-liking, and METH-using) were collected for all patients.

In 2017, the VRCP were computerized as a VR treatment system and

thus could be easily implemented in the clinical settings. One thousand and eight abstinent individuals with a history of METH dependence were recruited from four detoxification centers (study 2). All participants were met with the following inclusion criteria: (a) at least two times of METH illicit use (verified by urinalysis); (b) no medical record of central nervous system (CNS) disease, (c) no medical record of cardiovascular diseases; and (d) no medical record of other DSM-IV Axis I disorders. They were assigned into intervention group (n = 693) and waiting-list group (n = 315) using block randomization (with ratio: 2:1) according to treatment units. The participants in intervention group received the computerized VRCP, while those in waiting-list group did not. The ECG signals (i.e., resting-state ECG, cue-induced ECG at baseline and follow-up assessments) were collected in study 2.

In total, there were 60 completed data of the VAS scores (data from study 1: intervention group = 31; waiting-list group = 29) and 948 valid data of ECG signals (data from study 1 and study 2: intervention group = 643, waiting-list group = 305), which were used in final statistical analyses.

2.2. The development of the VR videos for VRCP

To accurately select the aversive stimuli for VRCP, we first conducted a detailed interview among 87 patients with METH dependence to understand what they are most afraid of METH-use. As a result, six most commonly reported aversive scenarios related to METH-use were identified, including being arrested by polices, experiencing severe hallucinations, infection and skin ulcers, contracting sexually transmitted disease, caducity and tooth loss, and sudden death. After that, six VR videos were scripted and filmed by the professional actors/actresses with special effects makeup in necessity. Finally, these videos were edited with special effects. All the audio tracks were processed using Nuendo to create 5.1 analog sound channels with head-operated gyroscope positioning. The videos were rendered onto a spheroid to create a subject-centric immersive experience, and the viewing angle was pre-determined for those specific scenes requiring close-ups.

In total, six VR videos were used in the VRCP. The first part of these six videos was exactly same, which depicts a short story of men/women who are using METH together with various METH-related cues (i.e., Scene1: auditory cues with social interaction; Scene 2: drugs and drug-related paraphernalia; Scene 3: METH-use social context). In the second part of the videos, participants viewed that characters in the videos experience a distinct adverse consequence caused by METH use, respectively. Each film lasts about five minutes. An example of a video used in the VRCP is shown in Fig. 2.

2.3. Intervention procedure

The participants in intervention group received six VRCP sessions plus treatment-as-usual (i.e., physical exercises and supportive psychotherapy as usual) during the study period. The participants in waiting-list only received treatment-as-usual. The VRCP session was run 2 times/week. In each session, participants were required to watch one of the VR videos for VRCP. In the study 1, participants received the VRCP with the assistance of an experimenter, while participants in the study 2 received the computerized VRCP following the computer

Table 1
Demographic information of sample.

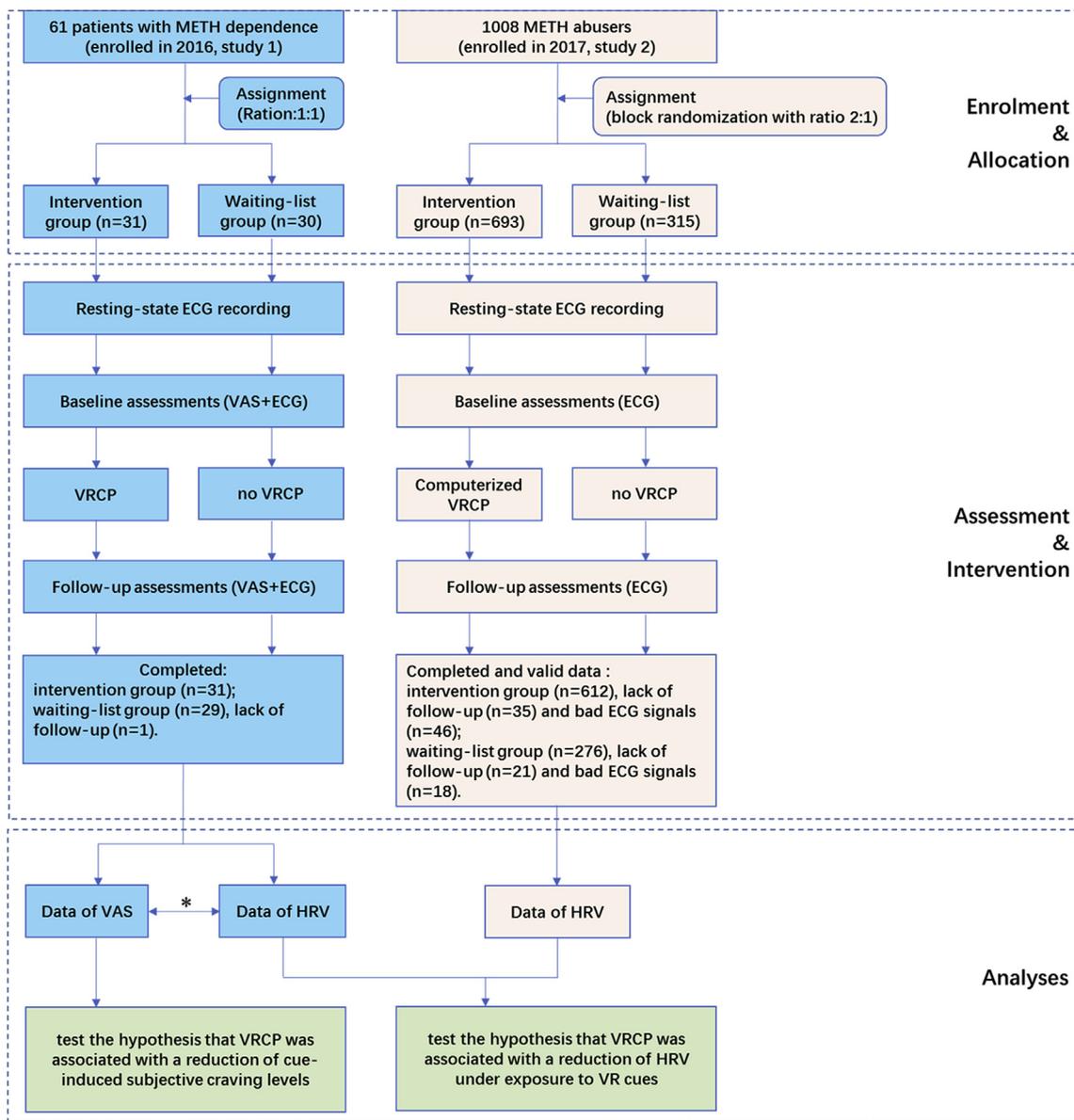|	Female/male	Age	years of METH-use	Mix-use/METH-only
Study 1 (n = 60)				
Intervention group	all males	35.03 ± 7.53	8.13 ± 3.72	10/21
Waiting-list group	all males	32.55 ± 6.64	6.45 ± 3.38	3/26
Study 2 (n = 888)				
Intervention group	103/509	33.95 ± 7.64	no data	no data
Waiting-list group	69/207	33.38 ± 7.77	no data	no data

Fig. 1. Flowchart of the present work.
(Note: * a positive correlation between VAS score on METH-craving and HRV indexes has been identified in Wang et al., 2018).
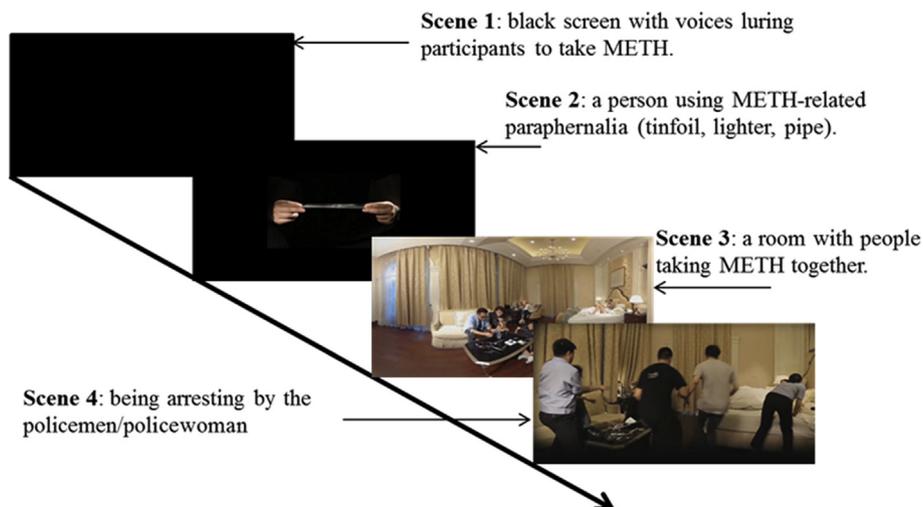

Scene 1: black screen with voices luring participants to take METH.

Scene 2: a person using METH-related paraphernalia (tinfoil, lighter, pipe).

Scene 3: a room with people taking METH together.

Scene 4: being arresting by the policemen/policewoman

Fig. 2. An example of a video used in the VRCP (being arrested by polices).

program (VR treatment system, version 2.0, Hangzhou Seventh Science and Technology Co., Ltd).

2.4. Assessment procedure

Prior to the first session of VRCP, the participants were first introduced to the equipment (i.e., heart rate recording device, VR helmet, and headphone). After participants felt comfortable with all the settings, an 8-min period of resting state continuous ECG signals (i.e., resting-state condition ECG) was recorded with a sampling rate of 1000 Hz (similar hereinafter). Then, participants were exposed to a VR METH-cue model, with concurrent recording of ECG signals (i.e., cue-induced ECG at baseline). In this VR METH-cue model, participants were required to watch an 8-min VR video, which simulates a real METH-related social context including various METH-related cues. The detail of the METH-cues VR video and its validity for craving assessment can be found in our previous work (Wang et al., 2018). One hour after the last VRCP session or three weeks after baseline assessments, participants in intervention group and those in waiting-list group were exposed to the VR METH-cue model again. The concurrent ECG signals under exposure to VR cues were recorded (i.e., cue-induced ECG at follow-up).

In addition, immediately after the VR video was finished, patients in study 1 were asked to answer three questions in turn on a visual analogue scale (VAS), by choosing the most suitable option for each question. The first question was regarding METH-craving: "How much do you crave METH/ice right now?" (ranging from 0 to 10, "0" indicated "no carving at all" and "10" indicated "extremely strong craving"). The second question was regarding METH-liking: "To what extent do you find the METH/ice pleasant/unpleasant?" (ranging from 0 to 10, "0" indicated "very unpleasant", "5" indicated "neither unpleasant nor pleasant", and "10" indicated "very pleasant"). The third question was regarding the possibility of METH-using: "If you have access to METH/ice right now, how likely would you be to use it?" (ranging from 0 to 10, "0" indicated "certainly not" and "10" indicated "certainly"). The three questions were presented for all participants in the same order.

2.5. Statistical methods

HRV indexes were computed for each participant on each condition using the HRV Analysis Software package (Tarvainen et al., 2014), including time domain (i.e., SDNN, RMSSD, and pNN50), frequency domain (i.e., nLF, nHF, and LF/HF; using autoregressive estimates), and non-linear domain (i.e., SD1 and SD2).

For better understanding the observed results, we first performed partial correlation analyses between each VAS score and each HRV index in baseline assessments for all patients from study 1, after controlling for corresponding HRV index on resting-state condition.

One-way analysis of variance (ANOVA) was performed for index age and years of METH-take between groups. A chi-square test or a continuity correction chi-square test was performed for the ratio of female/ male (study 2) and the ratio of mix-use/METH-only (study 1) between groups, respectively. Because the VAS scores were not normally distributed (all $p \leq 0.035$, by Shapiro-Wilk tests), we first used Wobbrock's aligned rank transform (Wobbrock et al., 2011) for the VAS scores. Then, a repeated measures ANOVA was conducted for the ranks for each VAS score, with time (baseline vs. follow-up) as within-group factor and group (intervention group vs. waiting-list group) as between-group factor.

A repeated measures ANCOVA was conducted for each HRV index, with time (baseline vs. follow-up) as within-group factor and group (intervention group vs. waiting-list group) as between-group factor, with controlling for HRV index on resting-state condition and gender. Further post-hoc multiple comparisons were conducted by Bonferroni correction.

3. Results

3.1. Demographic information

In study 1, no significant difference between groups was found for index age [$F(1, 58) = 1.824$, $p = 0.182$] and years of METH-use [$F(1, 58) = 3.342$, $p = 0.073$]. The intervention group had a higher ratio of Mix-use/METH-only than the waiting-list group, but the difference did not reach statistical significance ($\chi^2 = 3.046$, $p = 0.081$).

In study 2, no significant difference between groups was found for index age [$F(1, 886) = 1.074$, $p = 0.300$]. The waiting-list group in study 2 had a significantly higher ratio of female/male than the intervention group ($\chi^2 = 8.130$, $p = 0.004$).

3.2. Partial correlation

Partial correlation results showed that there was a significantly positive correlation between VAS score on METH-craving and SDNN ($r = 0.557$, $p < 0.001$) and SD2 ($r = 0.559$, $p < 0.001$). The partial correlations between VAS score on METH-craving and RMSSD ($r = 0.251$, $p = 0.055$) and SD1 ($r = 0.252$, $p = 0.054$) approached significance. No significant partial correlations were found between VAS score on METH-craving and pNN50 ($r = 0.214$, $p = 0.103$), nLF ($r = 0.218$, $p = 0.097$), nHF ($r = -0.217$, $p = 0.099$), and LF/HF ($r = 0.176$, $p = 0.182$).

There was a significantly positive correlation between VAS score on METH-liking and SDNN ($r = 0.541$, $p < 0.001$), RMSSD ($r = 0.267$, $p = 0.041$), SD1 ($r = 0.267$, $p = 0.041$), and SD2 ($r = 0.530$, $p < 0.001$). No significant partial correlations were found between VAS score on METH-liking and pNN50 ($r = 0.219$, $p = 0.095$), nLF ($r = 0.163$, $p = 0.218$), nHF ($r = -0.161$, $p = 0.222$), and LF/HF ($r = 0.146$, $p = 0.271$).

No significant partial correlations were found between VAS score on METH-using and each HRV index (all $p \geq 0.300$).
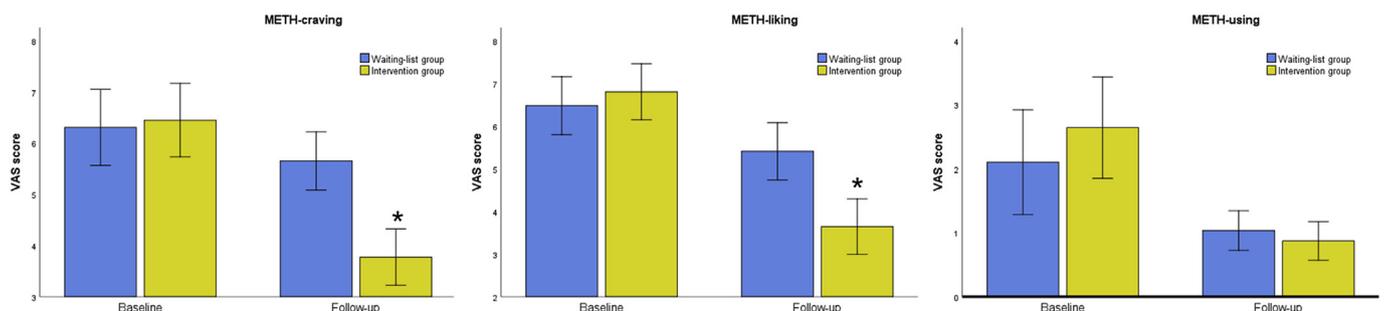

Fig. 3. Outcomes of VAS scores (Error bar: 95% CI; * indicates $p < 0.001$).

3.3. VAS scores

Outcomes of VAS scores in study 1 are shown in Fig. 3. For METH-craving, there was a significant main effect of group [$F(1, 58) = 4.755$, $p = 0.031$] and time [$F(1, 58) = 38.230$, $p < 0.001$] and a significant interaction between group and time [$F(1, 58) = 11.636$, $p = 0.001$]. Patients in intervention group showed a significantly lower score on METH-craving than those in waiting-list group at follow-up ($p < 0.001$), while no significant difference was found between groups at baseline ($p = 0.785$).

For METH-liking, there was a significant main effect of time [$F(1, 58) = 42.418$, $p < 0.001$] and a significant interaction between group and time [$F(1, 58) = 10.152$, $p = 0.002$]. No significant main effect of group [$F(1, 58) = 2.805$, $p = 0.097$] was found. Patients in intervention group showed a significantly lower score on METH-liking than those in waiting-list group at follow-up ($p < 0.001$), while no significant difference was found between groups at baseline ($p = 0.496$).

For the VAS score on METH-using, there was a significant main effect of time [$F(1, 58) = 24.332$, $p < 0.001$], reflected by a significantly larger decrease from baseline to follow-up in both group. No significant main effect of group [$F(1, 58) = 0.908$, $p = 0.343$] and no significant interaction between group and time [$F(1, 58) = 3.484$, $p = 0.064$] were found.

3.4. HRV indexes

3.4.1. Time domain

Outcomes of HRV indexes in the present work are shown in Fig. 4. Repeated measures ANCOVA results showed that there was a significant main effect of time and group for SDNN [$F(1, 945) = 7.447$, $p = 0.006$; $F(1, 945) = 4.861$, $p = 0.028$, respectively] and RMSSD [$F(1, 945) = 4.052$, $p = 0.044$; $F(1, 945) = 8.618$, $p = 0.003$, respectively]. There was a significant main effect of group for pNN50 [$F(1, 945) = 4.586$, $p = 0.032$], but with no significant main effect of time [$F(1, 945) = 1.982$, $p = 0.159$]. In addition, there was a significant interaction between group and time for SDNN [$F(1, 945) = 11.954$, $p = 0.001$], RMSSD [$F(1, 945) = 13.618$, $p < 0.001$], and pNN50 [$F(1, 945) = 7.719$, $p = 0.006$]. Patients in intervention group showed a significantly lower SDNN, RMSSD, and pNN50 than those in waiting-list group at follow-up (all $p < 0.001$, after controlling for those in resting-state condition and gender, similar hereinafter), while no significant difference was found between groups at baseline (all $p \geq 0.560$).

3.4.2. Frequency domain

Repeated measures ANCOVA results showed that there was a significant main effect of time and group for nLF [$F(1, 945) = 12.465$, $p < 0.001$; $F(1, 945) = 4.304$, $p = 0.038$, respectively] and nHF [$F(1, 945) = 7.054$, $p = 0.008$; $F(1, 945) = 4.308$, $p = 0.038$, respectively]. No significant main effect of time [$F(1, 945) = 0.469$, $p = 0.493$] and group [$F(1, 945) = 1.605$ $p = 0.206$] was found for LF/HF. No significant interaction between group and time was found for nLF [$F(1,$
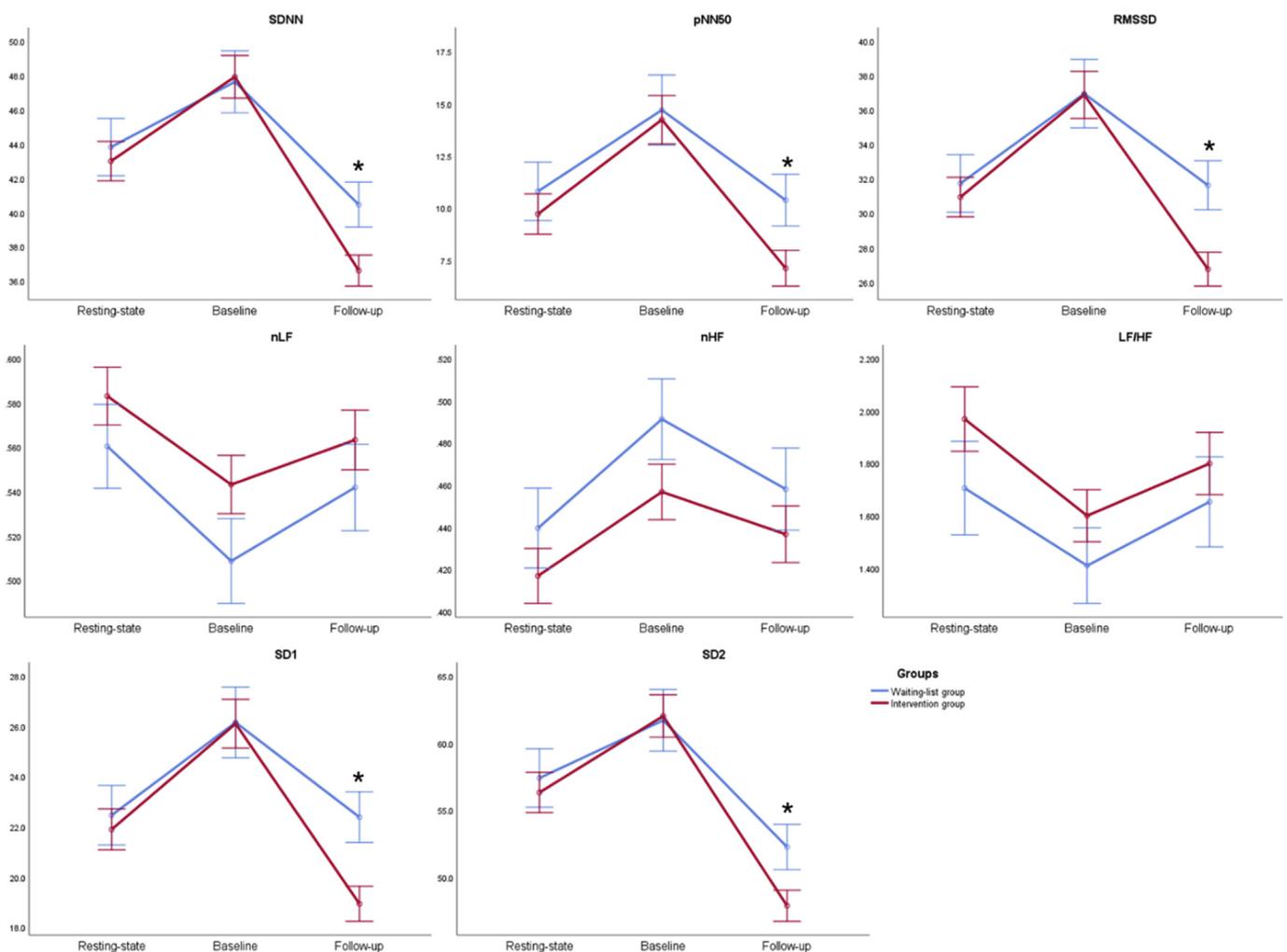

Fig. 4. Outcomes of HRV indexes (Error bar: 95% CI; * indicates $p < 0.001$, after controlling for those in resting-state condition).

945) = 1.284, $p = 0.257$], nHF [$F(1, 945) = 1.286, p = 0.257$], and LF/HF [$F(1, 945) = 0.517, p = 0.472$].

3.4.3. Non-linear domain

Repeated measures ANCOVA results showed that there was a significant main effect of time for SD1 [$F(1, 945) = 4.034, p = 0.045$] and SD2 [$F(1, 945) = 8.083, p = 0.005$]. There was a significant main effect of group for SD1 [$F(1, 945) = 8.613, p = 0.003$]. The main effect of group for SD2 approached statistical significance [$F(1, 945) = 3.654, p = 0.056$]. In addition, there was a significant interaction between group and time for SD1 [$F(1, 945) = 13.632, p < 0.001$] and SD2 [$F(1, 945) = 9.582, p = 0.002$]. Patients in intervention group showed a significantly lower SD1 and SD2 than those in waiting-list group at follow-up (all $p < 0.001$), while no significant difference was found between groups at baseline (all $p \geq 0.599$).

4. Discussion

In the present study, we first developed a counterconditioning procedure in VR environment for individuals with METH dependence and investigated its efficacy in a relatively large sample. Our results showed that participants who received VRCP exhibited a significantly larger decrease in the VAS score on METH-craving and METH-liking from baseline to follow-up assessments, relative to those in waiting-list group. Additionally, the participants received VRCP showed a significantly larger decrease in HRV indexes on time domain and non-linear domain from baseline to follow-up assessments when exposure to VR cues, compared to those in waiting-list group. Our findings indicate that the VRCP procedure may be a useful strategy in suppressing cue-induced reactivity for patients with METH dependence.

According to previous studies on evaluative conditioning (EC), to a large extent, contingency awareness may play a critical role in EC (Hofmann et al., 2010). In this sense, the aversive stimulus used in the counterconditioning procedure should be contingent to the undesirable behavior. To accurately find the fitting aversive stimulus, we first conducted a detailed interview among patients with METH dependence to understand what they were most afraid with respect to METH-use. As a result, six aversive consequences were identified and were paired with a same METH-use context. Consistent with our expectation, these videos used in VRCP has been shown robust enough to change the affective valence of METH-cues. The patients who received VRCP reported a significantly larger decrease on the VAS score in METH-liking from baseline to follow-up, relative to those in waiting-list group.

Consistent with Lee et al. (2009), our results show that patients who received VRCP exhibited a significant decrease in the VAS score on METH craving compared to those in waiting-list group. This finding suggests that a VR counterconditioning procedure may be also effective in attenuating subjective craving for the patients with METH dependence. However, we did not find an additive effect of VRCP on the VAS score of METH-using. We speculate that the lack of effect of VRCP may be explained by two factors. The VAS score on METH-using may be sensitive to change (at least subjectively) for these patients. Further, a floor effect on VAS score of METH-using may be, in part, responsible for the relatively small differences between groups.

In addition to significantly reduced subjective VAS scores, our results also showed that the VRCP was associated with a larger decrease in HRV indexes on time domain and non-linear domain when exposure to VR cues. The participants who received VRCP exhibited a larger decrease in HRV indexes on time domain and non-linear domain from baseline to follow-up, relative to those in waiting-list group. These are consistent with the findings from partial correlation analyses, showing that a larger HRV on time domain and non-linear domain were associated with a higher VAS score on both METH-liking and METH-craving. Again, similar to our previous findings (Wang et al., 2018), we did not find significant correlations between VAS scores and HRV indexes on frequency domain. Also, no additive effect of VRCP was found

on these HRV indexes. We speculate that this may be explained by the complex nature of the HRV indexes on frequency domain. Evidences have shown that many physiological parameters (e.g., the respiratory rhythm) could influence the value of nLF and nHF (Billman, 2013; Billman et al., 2015; Shaffer and Ginsberg, 2017). These confounders might have masked the activation effects of VR cues. And, thus no beneficial effect of VRCP on these HRV indexes was found in our study.

Regarding the efficacy of VRCP, the most probable interpretation is that the aversive counterconditioning might attenuate the learned association between cues and drug reward. Previous human functional magnetic resonance imaging study has reported that counterconditioning of conditioned fear responses was associated with reduced amygdala and hippocampus activation following reinstatement (Bulganin et al., 2014). More specifically, it has been documented that aversive counterconditioning could reduce reward signaling by enhanced connectivity with hippocampus and insula (Kaag et al., 2016). Further study with a comparative research design is required to assess the neural correlates with VRCP.

It should be noted that, although positive results have been found, interpretation and application of these findings should be taken with caution. First, it is noteworthy that negative reinforcement is also a key motive for drug use (e.g., Baker et al., 2004; Koob and Le Moal, 2005; Koob, 2013). That is say, quite a number of patients take METH to alleviate or escape from their aversive internal states (such as withdrawal, anxiety, depression, stress and etc.). In this sense, VRCP may be insufficient for these patients. Secondly, evidence has also indicated that the suppressive effect of aversive counterconditioning is temporary, and the cue-drug association can later recover (e.g., Tunstall et al., 2012). Recent studies have reported that counterconditioning following memory retrieval (i.e., conducted shortly after memory retrieval) might induce a long-lasting prevention of relapse to drug seeking (e.g., Das et al., 2015; Goltseker et al., 2017; Elsey et al., 2018). In addition, repetitive transcranial magnetic stimulation (rTMS) (e.g., Gorelick et al., 2014; Liu et al., 2019; Liang et al., 2018) and transcranial direct current stimulation (tDCS) (e.g., Jansen et al., 2013; Kroczek et al., 2016) as a noninvasive method of brain stimulation have also been reported effective in treatment of substance dependence. Thus, we can expect that a combination of rTMS/tDCS together with counterconditioning procedure following memory retrieval would lead to more effective relief of craving.

An important limitation of this study is that the assessments were conducted at post-treatment. Thus, it is not known whether the observed effects were stable or not. A second limitation is that only three VAS questions were used. A craving scale with more items might be optimal and could provide more useful information. Third, no information is available on their depressive symptoms, anxiety, impulsivity, dosage of METH, and motivation for drug-taking. Therefore, it is unclear whether or not the two groups differed in these variables at baseline. And, it is limited our further understanding of factors which may influence the efficacy of VRCP. Therefore, long-term follow-up study with detailed clinical assessments is warranted.

In sum, positive but still preliminary results have been obtained in the present work, suggesting that a counterconditioning intervention under VR environment may be a useful strategy in suppressing cue-induced reactivity for patients with METH dependence.

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgment

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.06.007.

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