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Towards virtual reality exposure therapy for cocaine use disorder: A feasibility study of inducing cocaine craving through virtual reality

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ABSTRACT

Background: Craving is a core symptom of cocaine use disorders (CUD). Inducing craving in exposure to substance cues is of relevant interest for numerous clinical applications. Virtual reality exposure (VRE) might be a promising candidate for improving cue-exposure paradigms but remains almost not studied for cocaine. This feasibility study's main aim is to assess whether VRE to cocaine cues is capable to induce cocaine craving compared with VRE to neutral cues.

Methods: We conducted a within-subjects controlled trial in which cocaine users performed 3 consecutive 10 mins-tasks: VRE to neutral and cocaine cues, and a relaxation-based resting procedure. The primary outcome was the change in Cocaine Craving Questionnaire-Brief (CCQ-Brief) scores between VRE to neutral and cocaine cues. Secondary outcomes included between-tasks changes in scores of cocaine craving, pleasant/unpleasant emotions as well as self-efficacy to cope with craving.

Results: We recruited 11 chronic cocaine users including mostly crack smokers (45 %), cocaine snorters (36 %) and injectors (18 %), with 73 % of participants meeting DSM-IV criteria for cocaine dependence and/or abuse. Non-parametrical sign tests indicated significant large increases of CCQ-Brief scores from neutral to cocaine cue-VRE ($S(11) = 11$, $p < 0.01$, Cliff's $\Delta = 0.65$, *95 % CI:* 0.17–0.88). Exploratory comparative analyses indicated significant changes after our post-cues VRE relaxation procedure, with cocaine craving and emotions restored to baseline.

Conclusions: VRE to cocaine cues was feasible and capable to induce cocaine craving in cocaine users. This second VRE-based cue-reactivity study in cocaine paves the way for unexplored research on VRE clinical applications for CUD.

1. Introduction

Cocaine use is associated to an annual social cost of 45,469 G $ in US and an annual prevalence of 1.6 % in France in 2017 (Cartwright, 2000; Spilka et al., 2018). Importantly, 16 % of people who use cocaine will suffer from cocaine use disorder (CUD; Wagner & Anthony, 2002). Cocaine craving is considered as a central DSM-5 CUD symptom and can be defined as an obsessive motivation to use which can be automatically elicited when exposed to cocaine cues (Flaudias et al., 2019; Gauld et al., 2023).

Inducing substance craving in exposure to these cues can thus be of relevant scientific and clinical interest in CUD addictology as it allows for investigating, monitoring, and/or learning to cope with cognitive, emotional and behavioral response inherent to craving (Kiyak et al., 2023; Tiffany & Wray, 2012). In addition, cue-reactivity research suggests the interest of providing more multi-sensorial, realistic and ecologically valid exposure environments for improving exposure to substance cues and inducing higher cravings (Niaura et al., 1998). Enhancing cue-exposure might be of promising value for clinical addictology since craving response or reactivity to smoking cues

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significantly moderates craving reduction (Unrod et al., 2014) and predicts drinking latency, dependence severity and withdrawal reinstatement in a cue- exposure therapy (CET) context (Drummond & Glautier, 1994).

Virtual reality (VR) refers to technological devices allowing relative multi-sensorial immersion to fully computer designed and interactive 3D environments (Abbas et al., 2023). On the one hand, VR might have the potential to improve cue-exposure paradigms for substance use disorders (SUDs) by involving psychological processes specific to its exposure features (for a systematic review: Hone-Blanchet et al., 2014). For instance, VR high-immersive properties enhances the feeling of being present in an exposure environment (i.e. sense of presence; Makransky et al., 2019), which encompasses its believability, realism and naturalness (i.e. ecological validity; Lessiter et al., 2001). Moreover, ecological validity in VR exposure (VRE) was found to moderate and enhance craving induction in heavy drinkers (Simon et al., 2020). Finally, while numerous studies have demonstrated that VRE to substance cues can be useful to significantly induce craving response in nicotine, alcohol, cannabis and methamphetamine users (for a systematic review: Wiebe et al., 2022), the few studies of the specific interest of VRE over non-VR exposure methods suggested comparable (Culbertson et al., 2010) to superior effects (Lee et al., 2003). On the other hand, VR allows strict control and wider adaptation of exposure environments to individual needs, such as combining specific drug-related contextual cues (e.g. handling syringes in presence of peers self-injecting cocaine), which could not be used *in vivo* for safety purposes (Mazza et al., 2021). This might be of particular interest for generalizing CET effects and preventing cue-induced craving rebound (e.g. renewal effect) in patients with CUD, for who substance-related cue-reactivity strongly predicts relapse post-treatment (Kosten et al., 2006; Shiban et al., 2013).

In addition, investigating cue-VRE effects on emotions and self-efficacy might be of relevant clinical interest for cocaine craving-focused VRE applications given complex associations that are shown to exist between these three outcomes. For instance, an ecological momentary assessment study in patients treated for SUD suggested that affect could heighten or dampen the relationships between craving, self-efficacy and substance use (Stull et al., 2023).

However, craving-focused VRE feasibility and interest in CUD remains under-investigated. Only one study, in 11 crack users, indicated that VRE to crack cocaine cues significantly induced cocaine craving and reduced positive emotions compared to neutral VRE, while no expected significant decrease of self-efficacy to cope with cocaine craving was observed (Saladin et al., 2006). In addition, since cue-induced cocaine cravings are suggested as being the most intense across substances (Carter & Tiffany, 1999) and up to 2.5 h lasting carryover effects can be expected from cue-exposure on craving and negative emotions (Lundahl & Greenwald, 2016), particular attention has to be paid to post-cue VRE acceptability for patients with CUD. In Saladin et al. (2006), although after a "cool-down" relaxing procedure, post-cue VRE craving returned similar to baseline levels, post-cue VRE positive emotions remained significantly lower. Interestingly, sympathetic drive reduction-focused relaxation techniques, such as paced breathing or progressive muscle relaxation, could serve as promising procedures for damping down acute craving and any related psycho-physiological discomfort (Limsanon & Kalayasiri, 2015; Lundahl & Greenwald, 2016).

Given these gaps in the literature, our feasibility study aims to evaluate the effect (i.e. on cocaine craving, emotions and self-efficacy) of VRE to cocaine-related versus neutral environment in cocaine users, with the primary hypothesis to test that significant and largely higher levels of cocaine craving will be reported in cocaine-related VRE. On an acceptability level, a paced-breathing relaxation procedure was offered post-VRE to help participants reduce any residual discomfort, thus its intervention effect (post-relaxation) was evaluated through exploratory comparative analyses with neutral (baseline) and cocaine-related (pre-relaxation) VRE conditions.

2. Method

2.1. Participants

Voluntary participants who used cocaine 30 days prior to the inclusion and aged 18 years or older were recruited between March 31 and July 31, 2021 in the Ithaque Association's treatment, support and prevention in addictology center (CSAPA; Strasbourg, France). Every participant received a 30€ luncheon voucher for their complete participation in the study. Exclusion criteria included current psychotic, (hypo)manic or high suicidal risk episode (MINI-5.0.; (Sheehan et al., 1998)), any medical condition at risk for safety or protocol compliance (e.g. cardiac disease or blindness), having significant motion sickness using a laboratory made VR tutorial task (SSQ total score $\geq$ 10; Gervilla et al., 2022; Kennedy et al., 1993), being involved in legal procedures at risk for incarceration or under legal guardianship, and not being able to give informed consent. This study was recorded (CTG Identifier: NCT05557149) and approved by the French Research Ethics Committee (CPP - Sud Méditerranée V Identifier: 21.02.14.82513).

2.2. Procedure

Participants attended three 90 mins meetings at the Ithaque Association's CSAPA with a graduate level psychology student specialized in cognitive-behavioral therapy (CBT). During the first meeting, patients were assessed for study eligibility. At meeting 2, participants practised paced breathing relaxation which they were to use at meeting 3. At meeting 3, participants performed 3 consecutive 10 mins tasks in the following order: Neutral VR, Cocaine VR and Relaxation procedure. Studies focusing on cue-induced craving reported elevated craving levels up to 2.5 h post-cue exposure (Lundahl & Greenwald, 2016), hence Neutral VR systematically preceded Cocaine VR to reduce potential confound of Cocaine VR carry-over effect, and task order wasn't counterbalanced to reduce the duration of the meetings with appropriate between-exposures *washouts* intervals. No interaction between the investigator and participants was allowed during VR conditions. Craving safety check and relapse prevention counselling was offered before leaving the meeting (Ehrman et al., 1998).

2.2.1. Neutral VR & cocaine VR

VR exposure was performed using Meta Quest 2 VR headset. The exposure was visually and audio immersive (360° and first-person view) as well as interactive. Participants could virtually rotate and move their head, hands as well as upper body thanks to a 6 degrees of freedom headset/hand controllers system. Participants remained seated on a 360°-rotating stool and could move around in VR thanks to a laser-guided teleportation technique. Finally, participants could see and use virtual hands to grasp and move virtual trivial (e.g. TV remote) or cocaine-related (for Cocaine VR) objects.

In Neutral VR, participants were immersed in a virtual apartment and were free to move around and to look at OASIS dataset neutral picture frames displayed on the walls (Fig. 1; 3.75 $\leq$ valence mean $\leq$ 4.25; standard deviation $\leq$ 1; (Kurdi et al., 2017)).

In Cocaine VR, participants were immersed into the same virtual apartment as in Neutral VR but were rather exposed to cocaine-related content following the ensuing scenario: peers come by and talk about cocaine while using it, then participant gets offered to and, at least once, virtually holds cocaine and paraphernalia (e.g. steel spoon, paper tubes, glass pipes or syringes), prepares and self-administrates (i.e. snorting, smoking or injecting) cocaine doses placed in front of him while seated at a table; Fig. 1). Cocaine paraphernalia, doses and self-administration were individualized depending on whether participant's main use consisted of snorting, smoking or injecting cocaine/crack. Further details regarding VR environments design are available (Gervilla et al., 2022); https://vimeo.com/568320310).

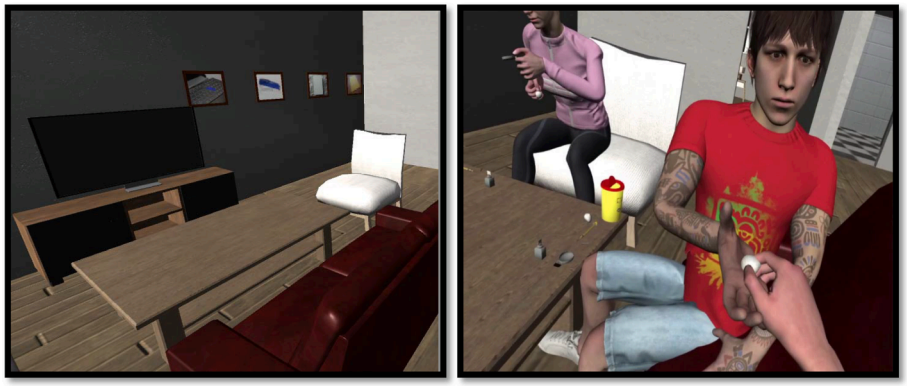

Fig. 1. First Person View in Neutral VR and Cocaine VR Conditions.

2.2.2. Relaxation

The aim of this post-VRE recovery condition was to help participants reduce any cocaine craving and craving-related psycho-physiological discomfort experienced during the Cocaine VR condition (Cerbo, 1990; Limsanon & Kalayasiri, 2015). Seated participants had to repeat cycles of nasal inhales, "as if they had to smell a flower", and buccal exhales, "as if they had to blow through a straw". Exhale periods had to last longer than inhales, shortly holding the breath between each air flows. Paced-breathing control is thought to stimulate the vagal nerve, a proponent of the parasympathetic nervous system, thus damping down any physiological sympathetic activation (Gerritsen & Band, 2018).

2.3. Primary and secondary outcomes

Immediately after each condition, levels of cocaine craving, negative and positive emotional states, as well as self-efficacy were assessed using CCQ-Brief, BMIS and DTCQ-8D scales.

2.3.1. Cocaine Craving Questionnaire – Brief (CCQ-Brief)

The CCQ–Brief is a French-validated measure of cocaine craving with satisfying psychometric properties (Karila et al., 2011). Participants rated on a 7-point Likert scale ("*Strongly disagree*" to "*Strongly agree*") the extent to which 10 cocaine craving-related statements described the way they felt.

2.3.2. Brief Mood Introspection Scale – Adapted (BMISA)

The BMIS is a measure of present unpleasant (BMISA-N) and pleasant (BMISA-P) present moods, with good psychometrical properties (Mayer & Gaschke, 1988). For this study, a laboratory-made adaptation (BMISA) of the French translated original version was used (author's permission requested; Niedenthal & Dalle, 2001); 6. Appendix A. Supplementary Material). We scored as follows: "*Definitely do not feel*" (0) to "*Definitely feel*" (3).

2.3.3. Drug Taking Confidence Questionnaire – 8D (DTCQ-8D)

The DTCQ-8D is a measure of self-efficacy to cope with craving without using, with good psychometrical properties (Sklar & Turner, 1999). For this study, a French laboratory-made translation of the original version was used (with authors' permission), in which participants rated the degree (in %) to which they would be able to resist to cocaine use urge in 8 cocaine craving-related situations.

2.4. Data analysis

For principal and secondary outcomes, statistical analyses were computed from scales raw total scores using R Statistical Software (R Core Team. (2021), 2021). Our comprehensive data working R code, including R packages and statistical hypothesis testing assumptions, are available in 6. Appendix A. Supplementary Material.

Regarding the DTCQ-8D outcomes, 1.1 to 3.4 % of answers were missing for 1 to 2 participants in 2 (#4 and #7) out of the 8 items for computing DTCQ-8D total scores. Given our small sample size ($n < 25$) and the arbitrary pattern of missing data, multiple imputations for incomplete multivariate data were performed on all missing data, using the *Amelia R* package (Burns et al., 2011; Honaker et al., 2011; McNeish, 2017). Our imputation *R* code is available in 6. A. Supplementary Material.

Descriptive statistics (n, min, max, median, q1, q3, iqr, mean, sd, se and mean ci) were computed using the *rstatix R* package (Table 1). We assume that our study sample was randomly drawn from its population. Our outcomes are of ordinal nature and collected on 3 consecutive times. Variables distributions were mostly non-normal and paired scores differences were mostly non-symmetrical around the median. Hence, Friedman and Bonferroni-corrected Sign tests were performed to test and contrast score differences between the conditions using *stats* and *rstatix R* packages (Kassambara, 2018). Our primary analyses statistical power is considered as adequate since 11 participants were recruited and that a required 13 sample size was estimated with G*Power (Faul et al., 2007) for one-tail Sign tests to detect large effect from VRE to cocaine cues in craving induction (expected Cohen's $g = 0.35$; Carter & Tiffany, 1999; Pericot-Valverde et al., 2016), with a 0.05 statistical significance threshold and a 0.85 power. Kendall's W as well as Cliff's delta effect sizes for score changes across conditions ("negligible", "small", "medium" and "large" effect for Cliff's d inferior to 0.15, 0.33, 0.47 and superior to 0.47; (Romano et al., 2006)) with 95 % CIs were computed using *irr* and *effsize R* packages.

3. Results

3.1. Characteristics of participants

Twenty patients consented to take part to the study. Nine of them met criteria for high suicidal risk episode and were not included (Sheehan et al., 1998). A total of 11 active cocaine users (*mean age* = 32 years; *sd* = 6.36; *range* = 26–48 years; males $n = 9$ [82 %]) were included in the analyses. Seven of these participants (64 %) met MINI criteria for both cocaine dependence and abuse, 1 participant (9 %) met criteria for cocaine dependance only and 3 participants (27 %) reported neither cocaine dependence nor abuse. Smoking was the most used cocaine using mode ($n = 5$ [45 %]), compared to snorting ($n = 4$ [36 %]) and injecting ($n = 2$ [18 %]). Finally, 54 % ($n = 6$) of participants were unemployed upon inclusion.

3.2. Cocaine VR versus neutral VR

Friedman's tests indicated significant differences of CCQ-Brief, BMISA-N and BMISA-P total scores only between Neutral VR, Cocaine VR and Relaxation conditions (respectively: $X2(2) = 17.07$, $p < 0.01$; *X2*

Table 1
Descriptive statistics across Neutral VR, Cocaine VR and Relaxation conditions.

		n	Min	Max	Q1	Q3	Median	Mean	sd	se
CCQ-Brief	N	11	11	67	11.5	18	14	16.4	7.79	2.35
	C	11	12	62	20	40	26	30.7	17.2	5.2
	R	11	10	44	11	21.5	13	17.9	10.1	3.04
DTCQ-8D	N	11	270	685	463	604	560	526	145	43.6
	C	11	215	640	418	575	543	486	149	45
	R	11	260	760	564	615	604	557	151	45.6
BMISA-N	N	11	0	7	0.5	4.5	2	2.64	2.54	0.77
	C	11	0	9	0.5	6.5	3	3.73	3.26	0.98
	R	11	0	7	0	2	0	1.54	2.25	0.68
BMISA-P	N	11	0	9	5.5	8.5	6	6.36	2.62	0.79
	C	11	2	9	4	6	5	5.27	2.33	0.7
	R	11	2	9	6.5	9	9	7.64	2.25	0.68

Note. CCQ-Brief = Cocaine Craving Questionnaire – Brief; DTCQ-8D = Drug Taking Confidence Questionnaire – 8D; BMISA-N = Brief Mood Introspection Scale Adapted – Negative; BMISA-P = Brief Mood Introspection Scale Adapted – Positive; N = Neutral VR; C = Cocaine VR; R = Relaxation.

(2) = 7.8, $p < 0.05$; *X2(2)* = 11.1, $p < 0.01$; Table 2).

According to Sign tests (Fig. 2; Table 2), only CCQ-Brief median total scores significantly differed between Neutral VR and Cocaine VR ($p < 0.01$, $d = 0.65$, *95 % CI* [0.17, 0.88]), with a positive and large effect size for Cocaine VR. No significant differences of BMISA-N and BMISA-P median total scores were found between Neutral VR and Cocaine VR conditions.

3.3. Post-cocaine VR relaxation versus cocaine VR or neutral VR

According to Sign tests (Fig. 2; Table 2), CCQ-Brief, BMISA-N and BMISA-P median total scores significantly differed between Relaxation and Cocaine VR conditions, with negative large, medium and positive large effect size for Relaxation on, respectively, CCQ-Brief ($p < 0.01$, $d = -0.59$, *95 % CI* [−0.85, −0.10]), BMISA-N ($p < 0.05$, $d = -0.40$, *95 % CI* [−0.74, 0.10]) and BMISA-P scores ($p < 0.05$, $d = 0.57$, *95 % CI* [0.05, 0.85]). No significant differences of CCQ-Brief, BMISA-N and BMISA-P median total scores were found between Relaxation and Neutral VR conditions.

4. Discussion

Our results indicate that immediately after VRE to cocaine-related cues, self-reported cocaine craving in cocaine users is significantly and largely higher than after VRE to neutral cues, which is in line with our primary hypothesis. This suggests that VRE to cocaine-related cues is capable to induce strong cocaine craving.

Our main findings thus corroborate those of the only published meta-analysis of VR cue-reactivity research in 541 nicotine users (N = 18 studies), which also reported a significant and large effect of VRE to nicotine cues in inducing nicotine craving ($d = +1.04$; Pericot-Valverde et al., 2016). However, given the large discrepancies of overall effects between substances in classical cue-exposure methods (ds range = +0.53 to +1.29; Carter & Tiffany, 1999), an overall effect of VRE to substance cues on craving has yet to be analyzed. Our main results are also congruent with the ones observed by Saladin et al. (2006) in 11 crack users. Their findings indicated a significant and large cocaine craving response following VRE to cocaine cues, as compared to a neutral VR condition (d > +1.14). However, several methodological limitations can be outlined compared to our study. For instance, Saladin et al. (2006) craving measures were performed with one-item rather than a multi-item assessment, which is considered best in cue-reactivity research for construct validity purposes (Glautier & Tiffany, 1995). We used a psychometrically validated and multi-item cocaine craving assessment (CCQ-Brief; Karila et al., 2011). Also, the authors did not correct their statistical significance threshold for the multiple comparisons performed, which might have inflated their T1 error rate. Finally, their VR neutral control condition consisted in viewing fish aquariums, voluntary tailored for reducing anticipatory anxiety prior to VRE. Given that viewing fish aquariums may induce relaxation (Clements et al., 2019) and the effect of relaxation in reducing substance craving (Limsanon & Kalayasiri, 2015), it is plausible that Saladin et al. (2006) control study design might have inflated their cocaine-cue VRE effect on cocaine craving. Conversely, our neutral VRE control condition consisted of watching neutral valenced picture frames, providing more internal validity to the significant and large craving inducing effect of cocaine-cue VRE we observed ($d = +0.65$). In addition, Saladin et al. (2006) study is the first and unique published study of VR-based cue-reactivity in cocaine, but in crack users only. Hence our study conducted in all types of cocaine users, i.e., crack smokers, cocaine snorters and injectors, is the first to strengthen, with reliable evidence, the pioneer assumption that VR is capable to induce cocaine craving while exposing

Table 2
Friedman test and pairwise comparisons between Neutral VR, Cocaine VR and Relaxation conditions.

	Friedman test				Sign test			Cliff's Δ and 95 % CI		
	F	df	p		S	df	p	Δ	LL	UL
CCQ-Brief	17.07	2	<.01***	C vs N	11	11	<.01***	.65	.17	.88
				R vs C	11	11	<.01***	−.59	−.85	−.1
				R vs N	6	10	1	0	−.48	.48
DTCQ-8D	5.29	2	.07	C vs N	4	10	1	−.24	−.64	.26
				R vs C	1	10	.06	.39	−.14	.75
				R vs N	4	11	1	.17	−.34	.61
BMISA-N	7.8	2	.02*	C vs N	6	7	.38	.18	−.32	.6
				R vs C	7	7	.05*	−.41	−.74	.1
				R vs N	5	8	1	−.28	−.66	.22
BMISA-P	11.1	2	<.01***	C vs N	1	6	.66	−.33	−.71	.19
				R vs C	0	8	.02*	.57	.05	.85
				R vs N	1	8	.21	.37	−.12	.72

Note. CCQ-Brief = Cocaine Craving Questionnaire – Brief; DTCQ-8 = Drug Taking Confidence Questionnaire – 8D; BMISA-N = Brief Mood Introspection Scale Adapted – Negative; BMISA-P = Brief Mood Introspection Scale Adapted – Positive; N = Neutral VR; C = Cocaine VR; R = Relaxation; *$p \leq .05$. ***$p < .01$.

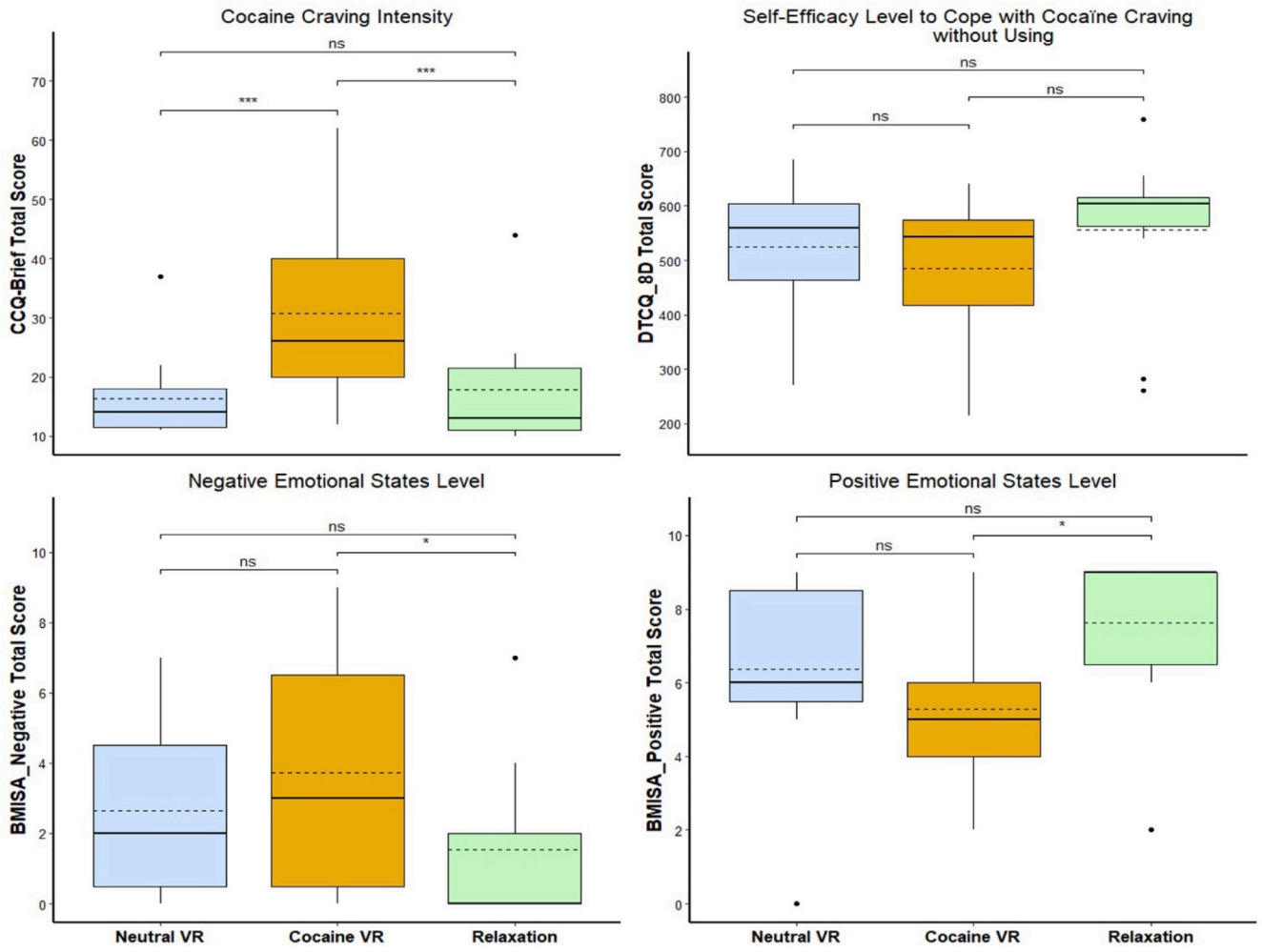

Fig. 2. Cocaine Craving, Self-Efficacy to Cope with Craving, Negative and Positive Emotional States Levels across Neutral VR, Cocaine VR and Relaxation Conditions
Note. Boxplots with mean (hatched) and median (bold) lines. CCQ-Brief = Cocaine Craving Questionnaire – Brief; DTCQ-8 = Drug Taking Confidence Questionnaire – 8D; BMISA-N = Brief Mood Introspection Scale Adapted – Negative; BMISA-P = Brief Mood Introspection Scale Adapted – Positive; ns = non-significant sign test pairwise comparison; * = $p \leq .05$; *** = $p < .01$.

to overall cocaine cues.

From a clinical perspective, these results pave the way to a broad range of VRE applications for CUDs. For instance, VRE cue-induced craving might be of relevant interest in addictology for diagnostic and prognostic purposes (Langener et al., 2021). VRE cue-induced craving is a significant proxy of drinking status (Pericot-Valverde et al., 2013), nicotine (Thompson-Lake et al., 2015) or alcohol dependence severity (Simon et al., 2020), as well as treatment response (Kotlyar et al., 2020). Moreover, VRE to cocaine-cues craving induction might contribute to the development of new psychotherapeutic options for CUDs. Traditional CBTs for SUDs demonstrate a small overall treatment efficacy in CUDs (g = 0.13; N = 13 studies; Magill & Ray, 2009). However, recent developments of VR-based CBTs for SUDs seem encouraging. For instance, memory reconsolidation-focused paradigms, which consist of modifying and reconsolidating new learning instead of maladaptive craving or cocaine using response in CUD (Marsden et al., 2018), have shown promising psychotherapeutic application when using cue-VR for methamphetamine use disorder (Wen et al., 2022). Other CET paradigms are habituation-focused, implying a decrement in cue-induced craving response after its repeated, prolonged and non-reinforced stimulation (Kandel, 1991; Tryon, 2005). Nevertheless, the latter have failed to demonstrate a significant overall treatment effect for SUDs with non-VR cue-exposure methods (N = 9 studies; Conklin & Tiffany, 2002). Interestingly, habituation focused VRET is associated with a significant post treatment reduction in smoked cigarettes/day, air expired CO2, background and VRE-induced craving, as well as an increased abstinence and readiness to quit using (Goldenhersch et al., 2020; Pericot-Valverde et al., 2014). However, VRET in these studies was either used as an add-on to an active treatment condition, or not compared to a control condition, hence its clinical benefit over classical CET or CBT is still unknown (Langener et al., 2021).

In CUD, the specific effect of VRE is debatable since inducing strong cocaine cravings in VRE may be due to the impact of cocaine use rather than to VRE properties. Neuroimaging studies suggest that chronic cocaine use results in long-term brain neuroadaptations enhancing responsiveness to cocaine cues, which might thus explain the large craving observed following cue-VRE in our ¾ cocaine dependent sample (Karoly et al., 2015; Thomas et al., 2008). Moreover, cocaine-related cues used in our study were specifically shown to induce cocaine craving in several cue-reactivity studies (Saladin et al., 2006). In addition, classical and instrumental learning models suggest that craving is conditioned to theses cues (Skinner & Aubin, 2010), but this assumption is difficult to assess unless the conditioning occurred in the laboratory (Tiffany, 1992). Finally, a meta-analysis of 41 cue-reactivity studies (Carter & Tiffany, 1999) suggested that substance cue-exposure elicits most intense self-reported cravings in CUD ($d = +1.29$) as compared to others SUDs. Taken together, the latter evidence support the hypothesis of a specific neurobiological and behavioral propensity in chronic

cocaine use that might have contributed to the large cocaine cravings observed in our Cocaine VR condition.

Another explanation to this large craving observed is related to the cue-exposure properties of our VRE condition (Hone-Blanchet et al., 2014). VRE can be interactive, multi-sensorial and imply 3D environments that can include both proximal and distal stimuli. Such exposure properties are shown to provide more realistic exposure and different cue-reactivity (Niaura et al., 1998). Indeed, ecological validity might modulate and increase substance use's effect on VR cue-induced craving in heavy users (Simon et al., 2020). In addition, sense of presence significantly predicts cue-induced craving in VRE (Ferrer-García et al., 2012). Interestingly, a meta-analysis of 115 studies indicated that immersion had a significant and medium effect on presence ($r = .316$; Cummings & Bailenson, 2016). Hence, features of our 3D interactive, complex and highly immersive VREs may have helped to enhance ecological validity, presence and consequently the large cue-induced cocaine craving observed (Simon et al., 2020). This hypothesis is corroborated by "good" and "high" levels of, respectively, presence and ecological validity levels reported by participants in our VRE conditions (Gervilla et al., 2022). However, to our knowledge, the few published studies on the topic indicated comparable to superior effect of VRE over classical exposure methods on craving induction in SUDs (Culbertson et al., 2010; Lee et al., 2003), which highlights the need for further evidence to specify the VRE interest for cue-reactivity research.

Inconsistent with our hypothesis, our exploratory and low-powered analyses indicated no significant effect of VRE to cocaine cues on self-efficacy and emotional levels. More importantly, after a relaxation based resting procedure consecutive to VRE to cocaine cues, our findings indicated a significant decrease of self-reported cocaine craving ($d = -0.59$) and negative emotional states ($d = -0.40$), as well as a significant increase of positive emotional states only ($d = +0.57$). By contrast, no significant differences were found between our relaxation procedure and neutral VRE.

These findings are congruent with evidence indicating a significant acute and long-term effect of relaxation in reducing self-reported craving, as well as psychological discomfort in SUDs (Cerbo, 1990; Limsanon & Kalayasiri, 2015). Given that median total scores of self-efficacy to cope with craving didn't significantly differ between conditions, remaining in a 543–604/800 range (DTCQ-8D; Sklar & Turner, 1999), this could be interpreted as an inherent good and stable sense of control from our sample of cocaine users over their craving or emotional difficulties, plausibly raised by their prior relaxation practices with a trained health care provider (Conrad & Roth, 2007). Secondly, while the cocaine craving reduction in the relaxation condition could be explained by a lower need to refrain from decreased unpleasant mood as observed (Skinner & Aubin, 2010), the emotional improvement observed could be due, conversely, to the diminished distressful craving experience (Tiffany & Wray, 2012). These positive changes of cocaine craving and negative/positive emotions observed might have been precipitated by a reduced sympathetic drive (Limsanon & Kalayasiri, 2015), induced by the relaxation respiratory control itself (Gerritsen & Band, 2018). However, any causal attributions regarding our relaxation procedure effect remains highly limited by the absence of a control condition. Changes observed might be due to research involvement, time and others efficacy predictors (Magill & Longabaugh, 2013). Moreover, cravings observed are supposed to be of phasic nature, i.e. with relatively short cue-dependent spikes, suggesting that changes observed during relaxation might also be due to the cessation of cue-exposure (Tiffany & Wray, 2012). Nevertheless, the fact that other similar cue-reactivity studies didn't observe a significant return of post cue-exposure craving and emotions to baseline levels after a neutral VRE or waiting condition (Saladin et al., 2006; Traylor et al., 2011) may indicate that the post cue-VRE relaxation procedure we used might be more beneficial than a simple resting time.

Taken together, although evidence suggested that, with proper clinical protections, exposure to cocaine cues doesn't increase cocaine use in outpatients with CUD (Ehrman et al., 1998), up to 2.5 h lasting carryover effects still could be expected from cue-exposure on craving and negative emotions (Lundahl & Greenwald, 2016), which thus highlights the interest of a potential effective relaxing procedure for further acceptable VRE to cocaine cues contexts.

5. Conclusion

Our study is the first to assess VR cue-reactivity not only in crack users but also in cocaine snorters and injectors, and the second in overall cocaine use. Our findings corroborate the feasibility through VR to expose to cocaine cues and its capacity to induce highly significant cocaine craving. However, the specific interest of VR to expose to cocaine cues and induce craving over non-VRE methods has yet to be investigated. Moreover, our exploratory results suggest that post-VRE to cocaine cues, a short relaxation-based resting time might be of therapeutic interest for restoring both cocaine craving and emotional states to acceptable baseline levels. Hence, our study provides new and encouraging foundations for steering future research towards VRE-based diagnostic, prognostic and therapeutic applications for CUD that remains, to date, unexplored.

CRediT authorship contribution statement

Thomas Lehoux: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Christelle Nithart Porche:** Writing – review & editing, Methodology, Conceptualization. **Antonio Capobianco:** Writing – review & editing, Supervision, Software, Resources, Methodology, Funding acquisition, Conceptualization. **Miguel Gervilla:** Software, Methodology. **Flavien Lecuyer:** Supervision, Software, Resources, Methodology. **Julien Anthouard:** Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Luisa Weiner:** Writing – review & editing, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.abrep.2024.100549.

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