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A virtual reality study on postretrieval extinction of smoking memory reconsolidation in smokers

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ABSTRACT

Exposure to smoking-related stimuli may induce the reconsolidation of smoking-related memories in smokers. Research has proposed that extinction applied after the retrieval of a smoking memory may inhibit reconsolidation and prevent craving. The aim of this study was to test the effect of postretrieval extinction (PRE) on the reconsolidation of smoking memory by using a virtual reality (VR) simulation in smokers. On the day 1 session, the study exposed 46 smokers to a neutral and then to a smoking VR scenario under a fixed-block protocol. On day 2, the study randomized participants into three groups (G) and exposed them to a 15-s VR immersion in smoking (G1, G3) or neutral (G2) scenario for memory retrieval. After 15 min, the study exposed G1 and G2 to a VR PRE during the temporal window of memory vulnerability, whereas the study exposed G3 to extinction immediately after retrieval. On day 3, the study exposed all groups to neutral and smoking scenarios similar to day 1. All groups significantly increased craving for cigarettes after exposure to the smoking scenario on day 1 ($p < 0.01$). On day 3, VR PRE after a 15-second VR smoking memory retrieval was able to inhibit reconsolidation in G1, but not in G3 exposed to PRE before the window of vulnerability, or in G2 not exposed to the smoking memory retrieval. These findings show the superiority of VR PRE after smoking memory retrieval compared to a standard extinction procedure.

1. Introduction

Events, stimuli, and contexts associated with emotional and motivational values are stored in memory as information that modulates conditioned responses. Conditioned memory could be modified by extinction or exposure therapy, which may reduce the conditioned response (Bouton & Bolles, 1979; Pavlov, 1927). However, exposure therapy is effective in the short-term and does not modify the original memory trace (Bouton, 1993; Milad & Quirk, 2002).

Research has hypothesized (Misanin et al., 1968; Nader et al., 2000) that previously consolidated memories may be reactivated and undergo a labile period termed *reconsolidation*. The reconsolidation period begins when the memory is rendered labile by presenting previously associated conditioned stimuli and/or context. Retrieved memory could thus be inhibited with pharmacological and behavioral manipulations (Alberini, 2005; Monfils et al., 2009; Przybyslawski et al., 1999; Riccio et al., 2009), suggesting potential therapies for disorders based on maladaptive memory such as post-traumatic stress disorder (PTSD) and substance use disorder (SUD) (Chiamulera et al., 2014; Dunbar & Taylor, 2017; Milton & Everitt, 2012; Torregrossa & Taylor, 2016).

Further research has proposed that a memory reactivation-extinction procedure might offer an improved efficacy for exposure therapy (Xue et al., 2013). The procedure is based on the reactivation of drug memory through a short exposure to a conditioned cue and/or context, which can render the memory transiently unstable. If extinction is applied after reactivation during a specific vulnerability time window (1–6 h), the

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reconsolidated memory trace can be updated with different, safer information (Auber et al., 2013). This sequential process of reactivation-extinction is termed *postretrieval extinction* (PRE). Lab studies have experimentally tested PRE for the reconsolidation of fear or drug memories in animals and humans, as models of fear (e.g., PTSD) and appetitive (e.g., SUD) memory (for a meta-analysis see Kredlow et al., 2016). Research has also tested the effects of PRE in patients under "naturalistic" conditions, i.e., when subjects acquired the original fear or appetitive memory (Walsh et al., 2018). However, data from research reports and meta-analysis are inconclusive; hence, the potential for PRE in therapeutic intervention for PTSD and SUD is still debated (Kredlow et al., 2017; Lee et al., 2017; Walsh et al., 2018).

Research has suggested that differences in type of learning history (naturalistic vs. experimental), age/strength of memory, and procedures and parameters of memory retrieval are the main *boundary conditions* for memory reactivation, destabilization, and reconsolidation (Hu et al., 2018; Kredlow et al., 2018; Walsh et al., 2018). Thus, the critical issue is how to model experimental conditions that are both complex and individualized, and that may also allow for control variables and parameters (Conklin & Tiffany, 2001). Therefore, researchers need to find laboratory methods able to investigate PRE with a level of validity in between the naturalistic and the experimental approach. A promising method to do so is virtual reality (VR), a technology that creates a state of immersion closer to the real situation and allows for controlled assessment of neuropsychological and behavioral responses, which has already been extensively reported in smoking research (Baumann, 2004; Baumann & Sayette, 2006; Garcia-Rodriguez et al., 2012; García-Rodríguez et al., 2011; Hone-Blanchet et al., 2014; Lee et al., 2003; Paris et al., 2011; Pericot-Valverde et al., 2015).

Our aim was to study the effects of PRE on the reactivation of smoking memory in healthy smokers by using VR. The primary outcome of interest was smoking craving assessment after exposure to VR simulation of a personalized smoking scenario compared to a neutral one. The PRE consisted of a 15-minute VR extinction session applied 15 min after brief 15-second smoking memory retrieval in the smoking scenario. Control groups were a no retrieval group (PRE after a 15-s VR neutral retrieval scenario) and a group with 15-minute PRE immediately after 15-second smoking retrieval (i.e., before the temporal window of memory lability; Xue et al., 2013).

2. Methods

2.1. Participants

The study recruited males and females between 18 and 65 years of age using local advertisements placed in and around the local university. Inclusion criteria included smoking at least 10 cigarettes per day during the last year and smoking tobacco cigarettes at the dedicated smoking zone of the local medical college. Exclusion criteria included personal or familial positive clinical history of seizures; positive clinical history for any neurological affection; current pregnancy; artificial cardiac pacemaker or participants suffering from heart disease; any severe chronic disease; bearing metallic clips or any other metallic device in the head-neck district, except the mouth; current therapy with psychiatric drugs; and consumption of psychoactive drugs that could interfere with the results of the study. An interview that the experimenter led during the screening session verified the absence of these criteria. Study staff provided participants with informative material about smoking cessation, and participants received reimbursement for their travel expenses. The Institutional Ethical Committees of Local National Healthcare System Unit (ULSS20, Verona, Italy) (n. 924CESC) approved the study and all experimental procedures designed according to the Declaration of Helsinki.

2.2. Instruments

2.2.1. Virtual reality tools

Oculus Rift is a virtual-reality head-mounted display developed by Oculus VR, (Menlo Park, California, USA). The Rift is designed to provide a stereoscopic vision of a 360° VR environment. Thanks to its rotational and positional tracking system, Oculus Rift allows the participant to explore the scene by moving his own head and body. The study implemented the virtual reality scenarios using the Unity cross-platform game engine.

2.2.2. EC50 Smokerlyzer

The study measured CO-expired concentration, a noninvasive method of assessing smoking status, using the EC50 Smokerlyzer (Bedfont Instruments; Kent, UK). Breath CO levels was expressed in parts per million (ppm) based on the conversion of CO to carbon dioxide (CO2) over a catalytically active electrode (Middleton et al., 2000).

2.2.3. Self-report measures

The primary outcome of interest in the study was the degree of change in the desire to smoke, defined as *craving*, assessed with the Questionnaire of Smoking Urge brief (QSUb). The QSUb is a 10-item questionnaire, derived from a modified version of the 32-item QSU to test the level of craving, which is a subjective description of one's desire to smoke. Research has shown the QSUb to be a quick test to obtain a multi-dimensional measure of craving (Cox et al., 2001; Tiffany & Drobes, 1991), and research has used it widely and validated the measure among smokers (e.g., West & Ussher, 2010).

The Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991) is a widely used and extensively validated questionnaire to test the degree of nicotine dependence via tobacco smoking. Motivation to Quit is a 4-item questionnaire evaluating the intensity of the motivation to quit smoking in the participant (Marino, 2000).

Research has extensively used the POMS for the assessment of mood and affective state. This questionnaire has 58 items and the factor structure represents six dimensions of the mood construct: tension, depression, anger, vigor, fatigue, and confusion. Participants answered questions on a 5-point Likert scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). Study staff transformed raw scores following the standard point table (Farnè et al., 1991).

The Simulator Sickness Questionnaire (SSQ; Kennedy et al., 1993) is a widely applied measurement tool. The SSQ is a self-report symptom checklist that includes 16 symptoms associated with simulator sickness. The SSQ provides a total severity score as well as scores for three subscales (nausea, oculomotor, and disorientation). The study administered the POMS, QSUB, and SSQ questionnaires were using the E-Prime 2.0 software.

2.3. Procedures

2.3.1. Screening session

Study staff fully debriefed participants about the rationale, scope, and possible consequences of the study. Participants received a document that included both information about the study and the consent form. The document was in a language understandable to the participants and after reading the informed consent document, participants gave their consent in written form. Immediately after, the experimenter collected demographic and smoking/psychological data from the participants, such as smoking history and degree of nicotine dependence (FTND, motivation to quit).

2.3.2. Experimental session day 1 (ES1: training)

After the screening session, participants started the ES1. First, research staff assessed smoking status by measuring the carbon monoxide (CO)-expired concentration (which was also measure at the beginning of the other two daily sessions) using the EC50 Smokerlyzer

(Bedfont Instruments; Kent, UK). Then, participants filled out POMS and QSUb to determine baseline-level craving.

The study exposed participants to a 3-minute VR acclimatization session (an office),and, immediately after, the study exposed participants to a 3-min neutral VR scenario (a mountain landscape), followed by a 3-min smoking-related VR scenario (VR simulation of the dedicated smoking zone of the local medical college) that contained four explicit cigarette cues (smoking cigarettes, a cigarette pack, a lighter, and a plastic glass filled with cigarette ends) (see Fig. 1). The protocol was a fixed-block procedure (neutral block, then smoking block), which research has recommended to avoid craving carry-over effects (Sayette et al., 2010). After each VR scenario, participants filled out a QSUb questionnaire, and at the end of the daily session, they filled out the POMS and SSQ (Fig. 2A).

2.3.3. Experimental session day 2 (ES2: retrieval + extinction)

Participants returned to the laboratory 24 h after the ES1 and the study allocated them into three groups (G) according to a randomization scheme for VR exposure to a 15-second smoking scenario (G1, G3), and to neutral scenario (G2). Afterward, they filled out POMS and QSUb. Participants in G1 and G2 underwent a waiting condition for 15 min. Schiller et al. (2010) and Xue et al. (2013) showed that extinction exposure has to be applied during a specific timeframe (reconsolidation window between 1 and 6 h) for the post-reactivation-extinction procedure to be effective (Schiller et al., 2010). Thus, the 15-min pause between retrieval and extinction in G1 and G2 allows for the application of extinction within the lability window. On the other hand, the study exposed participants in G3 immediately to the extinction procedure. The 15-min in total extinction procedure consists of 5 3-min VR scenarios, starting with a smoking scenario with only one smoking cue. The study progressively added smoking cues up to the fourth scenario, which contained four smoking cues. The fifth scenario was identical to the first one. Research staff assessed craving before the start of the ES2, and at the end of each extinction scenario. At the end of the session, participants filled out the POMS and SSQ (Fig. 2B).

2.3.4. Experimental session day 3 (ES3: test day)

Participants returned to laboratory 24 h after the ES2. The study exposed all participants to the 3-minute neutral scenario followed by the 3-minute smoking scenario. Study staff assessed craving levels after each scene and administered the POMS before starting ES3 and at the end of ES3. Participants filled out the SSQ at the end of ES3 (Fig. 2C).

2.4. Data analysis

We calculated the sample size for this study using G*Power software version 3.1.5.1 (Faul et al., 2009), with $\alpha = 0.05$ and power $(1\text{-}\beta) = 0.80$. The sample size that we estimated was equal to 21 participants for each group. To hold it against possible drop out we recruited a total of 66 participants. We excluded data from 20 participants from the analysis because they reported smoking fewer than 10 cigarettes per day or they did not smoke at the dedicated smoking zone of the local medical college (VR simulation for the smoking related scenario). Out of the 20 excluded participants, the study excluded 8 because they smoked fewer than 10 cigarettes a day, and 11 because they did not smoke at the dedicated smoking zone. The study excluded another participant due to both exclusion criteria. We used this postrecruitment exclusion criteria based on preliminary data that we obtained in pilot sessions during which the dedicated smoking scenario did not induce craving. For the criteria "smoking in the dedicated zone", we assumed that a personalized smoking context would exert a stronger smoking craving than a general context (Conklin et al., 2010; Conklin & Tiffany, 2001; McClernon et al., 2016).

The primary outcome of interest in the study was change in the level of craving, assessed by QSUb expressed as discrete scores. We first tested for normality of the QSUb scores by using Shapiro-Wilk test (data resulted not normal) and whether there were differences between groups in the baseline by using Kruskal-Wallis test. Then, study staff performed a series Wilcoxon tests (with Bonferroni correction) within each group to identify eventual change in QSUb score between the neutral and smoking-related scenarios on day 1 and day 3. We performed the same analysis for the QSUb score for the first and last extinction scenarios on day 2.

For this study, statistical significance is always accepted at $P < 0.05$. The study used paired Student's *t*-tests to measure changes in POMS values before and after each of the three daily experimental sessions. The study performed all the analysis using Prism 6 software statistical (GraphPad, CA, USA) and RStudio 1.1.463 (RStudio, Boston, MA).

3. Results

Table 1 reports the demographic data about the three groups of smokers. Participants in all groups showed low and low-to-moderate dependence assessed with the Fagerström Test for Nicotine Dependence. Most of the participants reported smoking between 10 and 15

Fig. 1. Example of smoking related VR scenario.
VR simulation of the dedicated smoking zone of the local medical college (left panel) containing four explicit cigarette cues (smoking cigarettes, a cigarette pack, a lighter and a plastic glass filled with cigarette ends [right panel]).

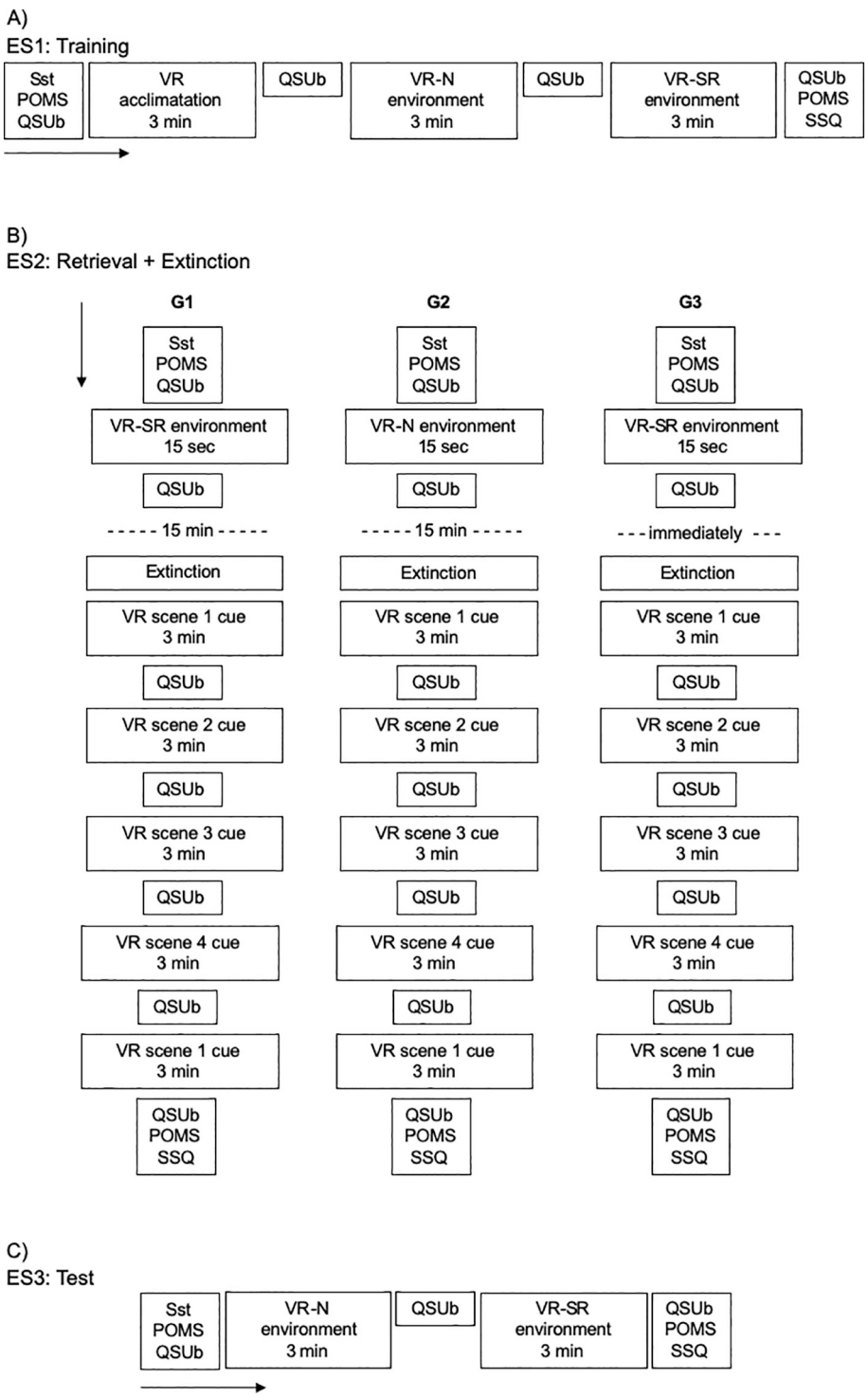

Fig. 2. Schematic representation of experimental sessions.
Note: G1: Group 1; G2: Group 2; G3: Group 3; Sst: Smoking status; POMS: Profile Of Mood State questionnaire; QSUb: Questionnaire of Smoking Urges brief; VR: Virtual Reality scene; VR-N: Virtual Reality Neutral scene; VR-SR: Virtual Reality Smoking Related scene; SSQ: Simulator Sickness Questionnaire.

cigarettes per day. Degree of nicotine dependence, number of cigarettes smoked per day, and years of smoking were equally balanced across the groups.

All groups showed a significant increase of craving at the end of the first day (day 1) training session after exposure to a 3-min VR smoking scenario compared to score values assessed after the 3-min exposure to VR neutral scenario (G1: W = 87, $p = 0.002$, $r = -0.59$, 95% CI [3.49, 9.5]; G2: W = 133 p = 0.002, $r = -0.52$, 95% CI [2.99, 11.5]; G3: W = 78, $p = 0.001$, $r = -0.55$, 95% CI [4.99, 17.5]) (Fig. 3, day 1, left panel). Groups did not significantly differ at baseline (day 1: χ^2 (2) = 1.5, $p = 0.46$; day 3: χ^2 (2) = 0.85, $p = 0.65$).

On test day (day 3), exposure to neutral and then to smoking VR scenario (similar to day 1 procedure except for the lack of initial acclimation) induced a significant increase in craving in G2 and G3, while G1—the group exposed to a 15-second smoking retrieval in the correct temporal window—showed no difference between the neutral and the

Table 1
Demographic of participants.

Characteristic	G1		G2		G3	
	N	%	N	%	N	%
Sex						
Male	6	46.15	7	38.89	6	40
Female	7	53.85	11	61.11	9	60
Age						
<25	10	76.92	16	88.89	13	86.67
26–30	2	15.38	2	11,11	2	13.33
>31	1	7.69	0	0	0	0
Highest degree awarded						
High school diploma	11	88.24	16	88.89	13	86.67
Degree	1	7.69	2	11,11	2	13.33
PhD	1	7.69	0	0	0	0
Occupation						
Student	12	92.31	18	100	15	100
Worker	1	7.69	0	0	0	0
Years of smoking						
<5	3	23.08	6	33.33	2	13.33
5–10	8	61.54	9	50	11	73.33
>10	2	15.38	3	16.67	2	13.33
Number of cigarettes/day						
10–15	12	92.31	15	83.33	13	86.67
>15	1	7.69	3	16.67	2	13.33
Fagerström score						
Low	5	38.46	9	50	6	40
Low-to-Mod	6	46.15	5	27.78	7	46.67
Moderate	2	15.38	3	16.67	1	6.67
High	0	0	1	5.56	1	6.67

Notes. G1: Group 1; G2: Group 2; G3: Group 3. The Fagerström score has been made accordingly with Heatherton et al. (1991), where *Low* dependence = 1 to 2 scores; *Low-to-Mod* dependence = 3 to 4 scores; *Moderate* dependence = 5 to 6 scores; *High* dependence = 7 or more score.

smoking scenario (G1: W = 59, $p = 0.054$, $r = -0.44$, 95% CI [0.99, 6.49]; G2: W = 105, $p = 0.004$, $r = -0.49$, 95% CI [1.5, 7.5]; G3: W = 66, $p = 0.003$, $r = -0.53$, 95% CI [4.49, 12.49]) (Fig. 3, day 3, right panel).

The analysis of craving scores on day 2, after the five extinction scenarios (Q7–Q11), showed no significant differences among groups (G1: W = 49, $p = 0.166$, r = −0.59, 95% CI [0, 7]; G2: W = 91, $p = 0.088$, $r = -0.35$, 95% CI [0.99, 8.49]; G3: W = 20, $p = 1.000$, $r = -0.12$, 95% CI [−3, 5.5]).

SSQ analysis performed to compare the total severity score of SSQ among groups, in each day evidenced no significant differences (day 1: $\chi^2 = 1.475$, $p = 0.478$; day 2: $\chi^2 = 2.42$, $p = 0.298$; day 3: $\chi^2 = 4.207$, $p = 0.122$).

Our analysis demonstrated no significant differences in POMS data when comparing the pre- and postexperimental session for each day, separately for each group (G1: day 1: T(12) = 1.433, $p = 0.533$; day 2: T (12) = 0.4459, $p = 0.664$; day 3: T(12) = 0.7252, p = 0.664; G2: day 1: T (17) = 0.4576, $p = 0.653$; day 2: T(17) = 2.597, p = 0.664; day 3: T(17) = 1.657, $p = 0.174$; G3: day 1: T(13) = 1.974, $p = 0.210$; day 2: T(13) = 0.1081, $p = 0.449$; day 3: T(13) = 0.3796, $p = 0.710$).

4. Discussion

The VR exposure to PRE after a 15-second smoking memory retrieval was able to inhibit the reconsolidation of smoking memory in healthy smokers on test day in G1 but not in the group exposed to PRE before the onset of the temporal window of memory vulnerability (G3) and in the group not exposed to the smoking memory retrieval (G2; neutral scenario retrieval). These findings suggest a superiority of PRE effects compared to a standard extinction procedure in accordance with the hypothesis of retrieval-extinction inhibition of appetitive memory reconsolidation—in this case, smoking memory.

According to the literature (Pericot-Valverde et al., 2015), we hypothesized that the VR exposure to smoking cues could produce a significant increase in smoking craving in cigarette smokers. The prediction was that the smoking-related VR scenario would evoke a significantly greater craving compared to a neutral scenario, in agreement with previous studies that used VR as a tool to elicit craving in smokers (Garcia-Rodriguez et al., 2012; Paris et al., 2011). In our study, we exposed participants to a personal spatial context (i.e., a VR simulation of the location where they used to smoke), to replicate non-VR smoking cue reactivity studies with a personalized context (Conklin et al., 2010; Conklin & Tiffany, 2001; McClernon et al., 2016). Our data confirmed the validity of the VR methodology to induce smoking craving after exposure to a VR smoking context rich in smoking cues. On day 1, all the

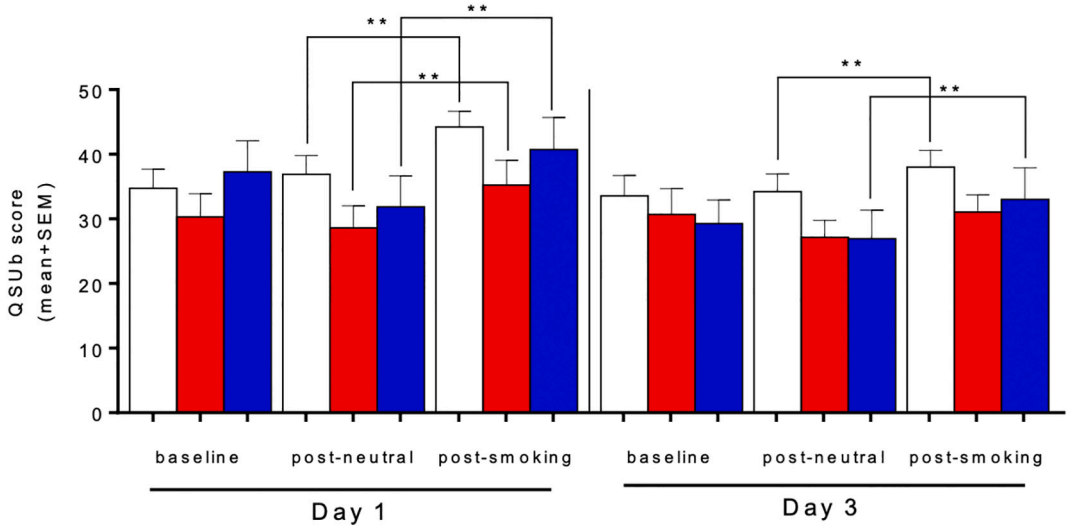

Fig. 3. Craving scores during training (day 1) and test (day 3) sessions.
Smoking craving is expressed as QSUb score (ordinates, mean + SEM) at baseline and after 3-min VR exposure to neutral and smoking scenarios. Day 1 and Day 3 sessions were identical for all groups which however were exposed on Day 2 to a 15-s VR immersion in smoking (G1, red columns; G3, blue columns) or neutral (G2, open columns) scenario for memory retrieval; G1 and G2 were then exposed to the VR post-retrieval extinction during the temporal window of memory vulnerability (15 min after) whereas G3 was exposed to extinction immediately after retrieval. Asterisks represent statistical significance vs. same group post-neutral values. ** = $P < 0.01$, Wilcoxon test. $N = 13$–18 subjects/group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

smokers reacted with significantly increased smoking cravings after immersion in the smoking scenario compared to the neutral scenario.

Our working hypothesis was that a brief retrieval of smoking memory was able to induce reconsolidation, a temporary period of memory destabilization vulnerable to inhibition by a postretrieval extinction (Auber et al., 2013; Schiller et al., 2010; Xue et al., 2013). Our predictions were that, i), a brief VR immersion in the smoking scenario (15 s) might induce reactivation of the smoking memories, and, ii), VR extinction 15-min after smoking retrieval—but not immediately after, or after immersion in the neutral scenario—would decrease smoking craving on the next test day, which our findings confirmed.

We based the extinction procedure used in our study on a graded procedure used for experimental smoking/tobacco exposure in smokers (Conklin & Tiffany, 2002; Raw & Russell, 1980), which we adapted to the VR environment. Other studies reported the use of similar cue exposure procedures in VR for smoking cessation (Culbertson et al., 2012; Giovancarli et al., 2016; Lee et al., 2003; Lee et al., 2004; Park et al., 2014; Pericot-Valverde et al., 2015; Pericot-Valverde et al., 2014; Thompson-Lake et al., 2015) and for PRE studies on spider phobia (Shiban et al., 2015). However, we point out that on day 2, under our conditions, smoking craving scores did not change during the 15-min extinction sessions, with no significant differences among groups. We should therefore more correctly define the day 2 session as an exposure session rather than an extinction one (a within-session extinction of craving that we were not able to observe).

We based the choice of a 15-s smoking memory retrieval on the PRE studies on spider phobia (Shiban et al., 2015), even though this study did not show any PRE superiority effect vs. standard exposure. Hu et al. (2018) recently investigated the time duration of threat memory reactivation, showing that only brief (1 s and 4 s), but not long (30 s), reminders made the memory vulnerable to interference. In fact, they also showed that no reminder (corresponding to our neutral scenario retrieval) was resistant to interference. However, other non-VR studies that have successfully shown the effects of PRE vs. the reconsolidation of drug memories, applied 5–10 min memory retrieval (Germeroth et al., 2017; Xue et al., 2013). We applied PRE 15 min after memory retrieval in agreement with similar literature protocols (Germeroth et al., 2017; Xue et al., 2013).

A main limitation of our study was that the study performed the test only at day 3, that is, at a single 24-hour time-point after the exposure to PRE. We may have observed a larger effect at longer time points, for instance at 1 month (Germeroth et al., 2017) or even longer (6 months; Xue et al., 2013). Another important limitation is the small sample size. We excluded subjects who smoked fewer than 10 cigarettes/day, and subjects not smoking in the dedicated smoking zone. We used this postrecruitment exclusion criteria based on preliminary data that we obtained in pilot sessions, in which the dedicated smoking scenario did not induce craving. As stated, we assumed that a personalized smoking context would exert a stronger smoking craving than a general context, in line with literature on the importance of smoking context (Conklin et al., 2010; Conklin & Tiffany, 2001; McClernon et al., 2016).

Although some literature points to evidence of PRE inhibition of fear and appetitive memory reconsolidation, there are other studies that report a lack of a PRE effect both in humans (Kindt & Soeter, 2013; Soeter & Kindt, 2011) and animals (Baker et al., 2013; Chan et al., 2010; Costanzi et al., 2011; for reviews see Auber et al., 2013; Kredlow et al., 2016 and Walsh et al., 2018). Future research should systematically investigate the boundary conditions under which memory could be reactivated, reconsolidated, and eventually inhibited. The use of the VR technology could offer a feasible methodology for further explorations of boundary conditions, in particular for a naturalistic modeling of memory retrieval.

CRediT authorship contribution statement

Thomas Zandonai: Conceptualization, Methodology, Formal analysis, Data curation, Writing - Original draft - Review & Editing. **Giulia Benvegnù:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing - Original draft- Review & Editing. **Francesco Tommasi:** Methodology, Investigation, Data curation, Writing - Review & Editing. **Elisa Ferrandi:** Methodology, Investigation, Data curation, Writing - Review & Editing. **Elettra Libener:** Methodology, Investigation, Data curation, Writing - Review & Editing. **Stefano Ferraro:** Methodology, Data curation, Writing - Review & Editing. **Bogdan Maris:** Methodology, Writing - Review & Editing. **Cristiano Chiamulera:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - Original draft- Review & Editing, Funding Acquisition, Supervision.

Declaration of competing interest

None. Authors declare have no conflict of interest.

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