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Non-Psychoactive Cannabis Extract Disrupts Reinstatement and Reconsolidation in Cocaine-Induced Conditioned Place Preference in Mice

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Abstract

Cocaine use disorder (CUD) remains a significant global health issue, with no FDA-approved pharmacological treatments. Cannabidiol (CBD), a non-psychoactive phytocannabinoid primarily derived from Cannabis sativa L., has demonstrated promising results in preclinical research to disrupt the consolidation and retrieval of drug-associated memories, thereby reducing relapse behaviors linked to substance use disorders such as cocaine dependence. This study evaluates the effects of a non-psychoactive cannabis extract (NPCE) on the reinstatement and reconsolidation of cocaine-induced conditioned place preference (CPP) in CD1 male mice—processes that, to our knowledge, have not been previously examined. The results showed that NPCE significantly inhibited both priming -induced and stress-induced reinstatement of cocaine-induced CPP, suggesting its potential to disrupt drug-associated memories. Additionally, NPCE effectively impaired the reconsolidation of cocaine-induced CPP, suggesting an effect on memory reconfiguration lasting at least two weeks. Additionally, NPCE alone did not produce any effect on CPP acquisition. These findings underscore the potential of NPCE, in targeting memory-related mechanisms underlying cocaine addiction, specifically in the reconsolidation and reinstatement. These results indicated that NPCE may reduce relapse risk by modulating drug-reward memories, potentially through interactions with CB1 receptors and other molecular signaling pathways like serotonergic receptors. This research contributes to the growing body of evidence, which suggests that cannabinoids, particularly non-psychoactive extracts, could offer novel therapeutic options for treating CUD. Further studies are needed to explore the individual effects of other cannabinoids on cocaine dependence and to assess clinical applicability of these findings.

Keywords: non-psychoactive cannabis extract; cocaine; conditioned place preference; reconsolidation; reinstatement

1. Introduction

Cocaine, a tropane alkaloid extracted from *Erythroxylum coca*, is processed for use as a recreational drug. In illegal markets, it exists in two primary forms: cocaine base (commonly smoked after pyrolysis) and cocaine hydrochloride in powder form, typically administered via nasal insufflation ("snorting") or intravenous injection [1]. According to the 2024 World Drug Report by the United Nations Office on Drugs and Crime (UNODC), it is estimated that approximately 23 million people used cocaine in 2022. This number reflects a significant increase in global cocaine production

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and consumption compared with the previous report (2023), leading to a rise in health problems and violence associated with this drug [2]. Despite the growing number of individuals with cocaine use disorder (CUD) worldwide, the U.S. Food and Drug Administration (FDA) has not approved any specific medication for the treatment of CUD [1].

Cannabidiol (CBD), the primary non-psychoactive cannabinoid, found in the *Cannabis sativa* L. plant, has been the subject of numerous studies due to its potential therapeutic properties in the treatment of substance use disorder (SUD). This substance lacks intrinsic rewarding or hedonic properties [3], and preclinical and clinical studies have explored its impact on the consumption of various drugs, including psychostimulants, alcohol, opioids, nicotine and cannabis [4]. As a potential treatment for cocaine addiction, CBD has demonstrated significant potential in several aspects. These effects include modulation of cocaine-related reward, reduction of cocaine consumption, anxiolytic effects, promotion of neuronal proliferation, and hepatoprotective properties [5]. Preclinically, CBD has been evaluated in behavioral studies, particularly in modulating behavioral responses in the conditioned place preference (CPP) paradigm, including cocaine-induced CPP [6–10]. This paradigm is a widely used Pavlovian learning model designed to evaluate the motivational properties of substances and the memories associated with their use [11]. The procedure of CPP comprises three main phases: preconditioning (Pre-C), where the animal's baseline preference is determined; conditioning (Cond), in which the substance is paired with one chamber and the vehicle with the other; and CPP-test, during which, in a drug-free state, the time spent in each chamber is recorded. After Cond, the persistence of CPP memory and relapse-like behavior can be evaluated using post-conditioning procedures such as extinction and reinstatement protocols. These paradigms are commonly employed to model the persistence of drug-associated memories and relapse. Alternatively, reconsolidation procedures can be used, in which previously consolidated memories become temporarily labile after reactivation, allowing them to be modified or weakened [12].

CBD can disrupt the reconsolidation of cocaine-induced CPP memories, thereby reducing the risk of relapse [9]. Ledesma et al. [10] found that CBD not only prevents priming-induced reinstatement of cocaine CPP, but also reduces locomotor stimulation and mitigates memory deficits associated with cocaine withdrawal in mice. Nevertheless, some studies have found that CBD does not reduce cocaine self-administration or cue-induced cocaine seeking, suggesting inconsistent behavioral outcomes [13]. It is reported that CBD suppresses cocaine-induced CPP in rodents with a U-shaped dose-response profile, affecting neuronal activation in the prelimbic cortex. According to the authors, intermediate doses of CBD (20 to 30 mg/kg) are more effective modulating behavioral responses in cocaine-induced CPP than high doses (120 mg/kg) or low doses (10 mg/kg) [14]. Doses of 10 mg/kg or less are ineffective in treating the acquisition of cocaine self-administration, extinction, or reconsolidation of cocaine-induced CPP, but can produce significant effects on acquisition [8,13]. Additionally, the authors found that doses of 20-30 mg/kg produce significant effects on indicators of reinstatement and reconsolidation of cocaine-induced CPP [10,15], but have limited effects on abstinence-related behaviors and craving resulting from cocaine consumption [16].

Although numerous preclinical studies have demonstrated beneficial effects of CBD on cocaine addiction, research in humans has shown that CBD may have mixed effects [17–19]. In a double-blind study conducted by Meneses-Gaya et al. [17], it was found that CBD is ineffective in treating withdrawal symptoms associated with crack cocaine addiction. Similarly, Mongeau-Pérusse et al. [18] reported that CBD has no significant effects on CUD in a placebo-controlled trial. Recent studies have shown that doses of 800 mg of CBD are insufficient to improve cognitive performance in individuals diagnosed with CUD, which may indicate that it is not effective in controlling CUD symptoms in humans [19]. In contrast, whole-plant cannabis and its constituent cannabinoids have been increasingly recognized as a potential therapeutic option for CUD in humans. In this regard, Murray et al. [20] investigated the pharmacokinetic interactions between cannabis and cocaine, reporting that cannabis use reduced plasma concentrations of cocaine and improved subjective measures related to smoked cocaine addiction. Observational studies suggest that the intentional use of cannabis, as part of a crack cocaine recovery program, may help control subjective symptoms of

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this addiction, such as sleep loss, legal problems, reduced paranoia, and decreased craving [21]. Labigalini et al. [22] also reported beneficial effects of cannabis use as a treatment for crack cocaine addiction. These researchers found that cannabis helped 68% of participants manage their addiction, facilitating abstinence from crack cocaine, reducing craving, and alleviating subjective symptoms of dependence. The preclinical use of isolated CBD to address behavioral outcomes of cocaine addiction has not yet been confirmed in clinical studies. In contrast, full-spectrum cannabis may be associated with beneficial outcomes.

This may indicate full-spectrum cannabis offers greater effectiveness in treating behavioral outcomes of CUD, whereas isolated cannabinoids are less effective. The interactions among the various constituents of cannabis, known as the entourage effect involves several pharmacokinetic and pharmacodynamic mechanisms, including the competitive inhibition of cannabinoid metabolism by cytochrome P450 enzymes and carboxylesterases [23], modulation of cannabinoid and vanilloid receptor activity [24], and interactions between cannabinoid receptor type 2 (CB2) and cannabis-derived terpenes [25]. These synergistic effects have demonstrated therapeutic potential in disorders such as cancer [26] and epilepsy [27]; however, they remain insufficiently explored within the context of SUD, including CUD. Evidence from a preclinical study suggests that the combined administration of CBD and (Δ9-tetrahydrocannabinol) THC facilitates the extinction of cocaine-induced CPP, although it appears to have no effect on the context-dependent sensitization of cocaine [28]. Beyond these findings, the available literature addressing the effects of cannabinoid combinations on cocaine addiction remains limited and warrants further investigation. In a previous preclinical study conducted by our research group, a non-psychoactive cannabis extract (NPCE) rich in cannabidiol was evaluated using a murine smoked cocaine model. The extract showed promising effects in reducing behavioral indicators associated with smoked cocaine consumption [29]. These findings suggest that complex cannabinoid mixtures may represent a potential therapeutic strategy for cocaine addiction. For this reason, the present study aimed to evaluate the use of the NPCE in inhibiting reinstatement (priming dose- and stress-induced) and reconsolidation of cocaine-induced CPP. Additionally, the addictive potential of NPCE was evaluated using an NPCE-induced CPP design, in order to ensure that a possible treatment with this derivative would not produce reinforcing or aversive effects in the proposed CPP behavioral outcomes.

2. Materials and Methods

2.1. Animals

The study was approved by the Ethics Committee of the Faculty of Sciences at the Universidad Nacional de Colombia (Approval No. Acta 06-2023). All experimental procedures were conducted in accordance with Good Laboratory Practice (GLP) guidelines and the ARRIVE quality reporting standards [30]. A total of 63 male CD1 mice, aged 8 to 10 weeks, weighing 35–40 g, were housed in groups, in standard stainless-steel cages (30 cm x 20 cm x 15 cm) under controlled environmental conditions. Temperature was maintained at 22 ± 2°C with a relative humidity of 60-65%. The mice were kept on a 12-hour light/dark cycle, water and food *ad libitum* (LabDiet standard rodent chow). For this study, the animals were randomly assigned to six experimental groups, as described in Table 1. All behavioral experiments were conducted during the light phase of the cycle.

Table 1. Groups of study. Overview of experimental groups, procedures, reinforcing substance and treatments.

CPP study	Experimental group (n)	Reinforcing substance	Treatment
Experiment 1. Cond NPCE	CNPCE (n = 10)	NPCE 20 mg/kg	-
	CVEH (n = 10)	VEH (0.01 mL/g)	-

 doi:10.20944/preprints202604.1650.v1

Experiment 2. Reinstatement (priming dose and stress)	ECOC (NPCE+COC) (n = 10)	Cocaine 15 mg/kg	NPCE 20 mg/kg
	CECOC (VEH+COC) (n = 10)		VEH (0.01 mL/g)
Experiment 3. Reconsolidation	RCOC (NPCE+COC) (n = 10)		NPCE 20 mg/kg
	CRCOC (VEH+COC) (n = 10)		VEH (0.01 mL/g)

Vehicle solution (VEH), cocaine (COC), non-psychoactive cannabis extract (NPCE).

2.1. Chemical and NPCE

Reference standards of cocaine (1 mg/mL solution in methanol), cannabinoid mix (1 mg/mL solution in methanol of mixed CBD, THC and CBN) and AEME (1 mg/mL in methanol) were obtained from Merck (Darmstadt, Germany). These standards were used for the quantification of cannabinoids, the determination of cocaine potency, and the monitoring of the potency of injectable preparations. The NPCE was obtained by supercritical fluid extraction, donated by Medcolcana Organics (Colombia). This extract presented the following cannabinoid composition (%, w/w): CBD 41.05%, tetrahydrocannabinol (THC) 0.70%, cannabinol (CBN) 0.61%, cannabigerol (CBG) 0.24%, cannabichromene (CBC) 0.04%, and its most abundant terpenes were α-pinene (0.037%), α-terpinolene (0.019%), caryophyllene (0.248%), α-humulene (0.023%), α-bisabolol (0.077%), aromandendrene (0.047%), zingiberene (0.027%), cis-3-hexenyl benzoate (0.017%), and 2-naphthalenemethanol (0.014%) (Supplementary Material 1). The cocaine (97.5%) used as a reinforcing drug, was donated by the Anti-Narcotics Directorate of the National Police (DIRAN). Working solutions of NPCE and cocaine were freshly prepared prior to each experiment.

2.1. Doses

Dose of cocaine (15 mg/kg) was selected according to Farrell et al.[31], and was prepared daily in 0.9% NaCl saline solution (SAL). The dose of NPCE, equivalent to 20 mg/kg of CBD, was determined in accordance with the findings reported by Nedelescu et al. [14] and Galaj et al. [32]. NPCE was dissolved in a vehicle solution (VEH) consisting of SAL and 2% Tween 80 (polysorbate 80). All substances were administered intraperitoneally (i.p.) in a volume of 0.01 mL/g to the experimental animals. As demonstrated in prior studies such as Rodriguez-Arias et al. [33], Tween 80 exhibits no intrinsic effects on the cocaine-induced CPP paradigm, confirming its suitability as a pharmacologically inert vehicle control in CPP.

2.1. Experiments

In this research, a CPP box (CPPb) with dimensions of 90 cm x 25 cm x 20 cm was designed, featuring two separate chambers with distinct visual (gray chamber and blue chamber), tactile, and olfactory cues, connected by a neutral zone to enhance the response to cocaine conditioning, according to previous reports [34]. All animals (n = 60) underwent both a Pre-C and a Cond following a biased protocol, meaning that cocaine conditioning was performed in the chamber least preferred by each animal during the Pre-C phase.

- **Pre-conditioning (Pre-C phase)**

On day 1, animals were allowed to explore the CPPb freely for 15 minutes, with unrestricted access to both chambers. Animals that spent ≥ 65% of the time in either chamber during the Pre-C test were excluded from the study.

- **Conditioning phase (Cond phase)**

From days 4 to 7, animals received VEH i.p. in the morning and were placed in the CPPb for 20 minutes in the chamber they had shown the highest preference for during Pre-C. Six hours later, animals were administered cocaine (i.p.) at a dose of 15 mg/kg (see Table 1) and placed in the conditioning chamber (i.e., the one with lowest initial preference, conditioned chamber) for 20

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minutes. On day 8, a conditioned preference test was conducted, allowing all animals to freely explore the CPPb for 15 minutes. Conditioning was considered successful when animals spent more than one minute longer in the conditioned chamber compared to the unconditioned (VEH) chamber; therefore, a statistically significant difference (α = 0.05) between Pre-C and Cond exploration times was expected. Animals that did not meet the conditioning criteria during the Cond phase were excluded from further analysis. In Experiment 1, cocaine was replaced with NPCE, which was administered during the Cond phase as the reinforcing stimulus in order to evaluate whether the extract itself could induce conditioned place preference or aversion.

2.1.1. Experiment 1: Evaluation of NPCE in acquisition of CPP

Experiment 1 was adapted from the protocol described by Viudez-Martínez (2019) and aimed to evaluate the abuse potential of NPCE using the CPP paradigm. Animals (n = 20) underwent the Pre-C phase as described in Section 2.4. However, the conditioning phase followed the protocol previously described for CBD in this paradigm [3]. On day 4, animals were randomly divided into two groups and began the Cond phase with the administration of VEH (0.01 mL/g). They were placed in their initially preferred chamber (biased protocol) and confined for 15 minutes. On day 5, animals received either NPCE (20 mg/kg) or VEH (0.01 mL/g), according to the groups presented in Table 1, and were confined to initially non-preferred chamber for 15 minutes. Alternate-day conditioning with NPCE or VEH continued until day 14. On day 15, animals were allowed to freely explore the CPP box for 15 minutes, and the time spent in each chamber was recorded.

2.1.1. Experiment 2: Evaluation of NPCE in the Reinstatement of CPP Induced by Cocaine

In Experiment 2, the reinstatement evaluation procedure was adapted from de Carvalho and Takahashi et al. [9]. Following the completion of the Pre-C and Cond phases, animals (n = 20) that demonstrated a significant preference for the conditioned chamber (i.e., >1 minute) were maintained in their respective home cages until day 14. On day 15, after memory reactivation, animals were administered either NPCE (20 mg/kg) or VEH, as outlined in Table 1. Memory reactivation was induced by confining animals to the previously cocaine-paired chamber for 10 minutes. From days 16 to 33, animals continued to remain in their home cages. On day 34, recovery test was conducted by allowing the animals to freely explore the CPPb for 15 minutes, without any treatment or drug administration under continuous video recording.

The extinction phase began on day 35 and lasted one week. During this week, animals were placed daily the VEH chamber for 20 min early in the morning and after an interval of 6 hours, they were placed in the conditioned chamber for an additional 20 minutes. On day 43, animals underwent a preference test during which they explored the CPPb for 15 minutes. Video recordings were analyzed with software AnyMaze® to detect significant differences (α = 0.05) between exploration times in the cocaine and VEH chamber, compared to the Pre-C (extinction criterion).

On day 44, animals that reached the extinction criteria received a priming dose of cocaine (7.5 mg/kg) and were allowed to explore the CPPb for 15 minutes (reinstatement test), with continuous recording. On day 51, animals were exposed to a 5-minutes auditory stressor (100 dB, between 500–8000 Hz; stress-induced) and subsequently allowed to explore the CPPb for 15 minutes, again under continuous video recording.

2.1.1. Experiment 3: Evaluation of NPCE in the Reconsolidation of CPP Induced by Cocaine

In Experiment 3, the reinstatement evaluation procedure was adapted from the protocol described by de Carvalho et al. [9]. Following completion of the Pre-C and Cond phases, animals (n = 20) that demonstrated a significant preference for the conditioned chamber (i.e., >1 minute) were maintained in their respective home cages until day 14. On day 15, animals were placed in the conditioned chamber for 10 minutes to induce memory reactivation, and immediately afterward, animals received either NPCE (20 mg/kg) or VEH, as indicated in Table 1. On days 21 and 28, memory

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tests were conducted. Animals were allowed to freely explore the CPPb for 15 minutes, with behavior recorded for subsequent analysis.

2.1. Software and Statistical Analysis

Exploratory activity in all experiments was recorded using digital cameras (Brave 7 LE) and analyzed using AnyMaze® software (version 7.15, Stoelting Co.) to detect significant differences ($\alpha = 0.05$). Data processing and statistical analyses were performed using GraphPad Prism (version 9.5.1, GraphPad Inc., USA). Comparisons between the Pre-C and Cond phases were conducted using a two-tailed paired t-test. Experiment 1, extinction, reinstatement (priming- and stress-induced), and reconsolidation of cocaine-induced CPP were assessed using two-tailed unpaired t-tests.

2.1. Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized the ChatGPT service to refine spelling, grammar, sentence structure, and technical terminology, ensuring greater clarity and readability. Following this process, the authors thoroughly reviewed and edited the content as needed and assume full responsibility for the final published article.

3. Results

A total of 63 animals were tested and three of them were excluded from the study: one due to a strong initial preference (> 10 minutes) for one chamber during the Pre-C phase and two due to failure to develop a conditioned preference during the Cond phase. Among the remaining animals (n = 60), 33 showed a preference for the gray chamber during Pre-C, while the remaining 30 preferred the blue chamber. No baseline preference bias toward either chamber was observed across animals. Pre-C versus Cond data of Experiments 1, 2 and 3 are presented in Figure 1. The results of Experiments are expressed as the difference between the mean time spent in the conditioned chamber (conditioned chamber for Experiments 2 and 3) and the VEH chamber.

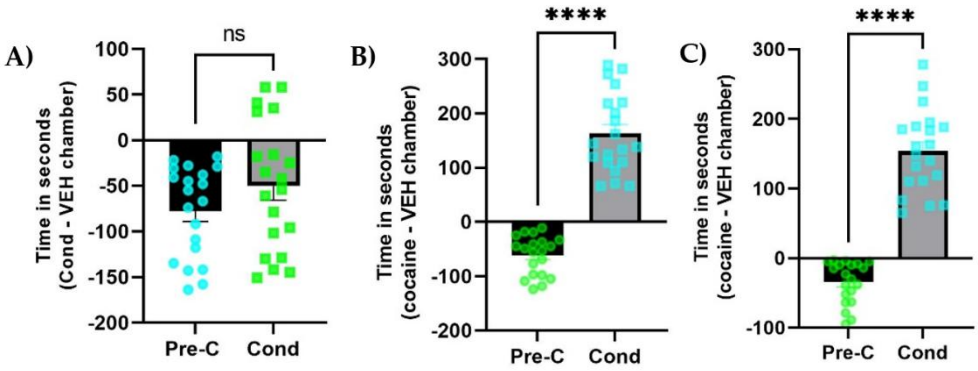

Figure 1. Results for Pre-C and Cond for A) Experiment 1, **B)** Experiment 2 and **C)** Experiment 3. Data are presented as mean ± standard error of the mean (SEM). The symbol (****) indicates a $p < 0.0001$.

4. Experiment 1: Results of evaluation of NPCE in the acquisition of CPP.

In this experiment, 20 mice were evaluated. Ten animals showed an initial preference for the gray chamber, whereas the remaining ten preferred the blue chamber. Results were expressed as the difference in exploration time between the conditioned chamber and the VEH chamber (Figure 2). Data were analyzed using two-tailed paired t-tests to compare the Pre-C and Cond phases, and two-tailed unpaired t-tests to compare the NPCE- and VEH-conditioned groups. No significant differences were observed between the Pre-C and Cond phases ($p = 0.218$) or between the NPCE and VEH groups ($p = 0.536$).

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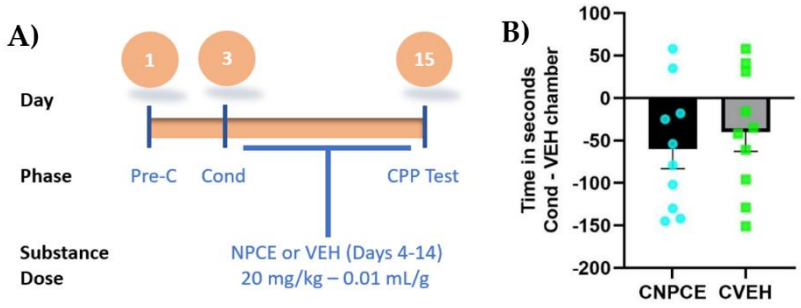

Figure 2. Results Effect of NPCE of CPP acquisition. A) Timeline for procedures performed in Experiment 1. **B)** Presented as mean ± SEM (standard error of the mean) for the comparison between the CNPCE and CVEH groups.

5. Experiment 2: Evaluation of NPCE in the Reinstatement of CPP Induced by Cocaine

Results of Experiment 2 are presented in Figure 3. Cond, extinction, and reinstatement (priming dose and stress) for cocaine-induced CPP were analyzed comparing CECOC (VEH, n = 10) and ECOC (NPCE 20 mg/kg, n = 10) groups, using two-tailed unpaired t-tests. Significant differences were observed in reinstatement times following both the priming dose and stress exposure between CECOC and ECOC groups (priming: $p = 0.0396$ $t = 2.21$; stress: $p = 0.0144$, $t = 2.71$). No significant differences were detected between CECOC and ECOC groups during the recovery or extinction phases. These results indicate that NPCE significantly reduced both priming- and stress-induced reinstatement of cocaine-induced CPP.

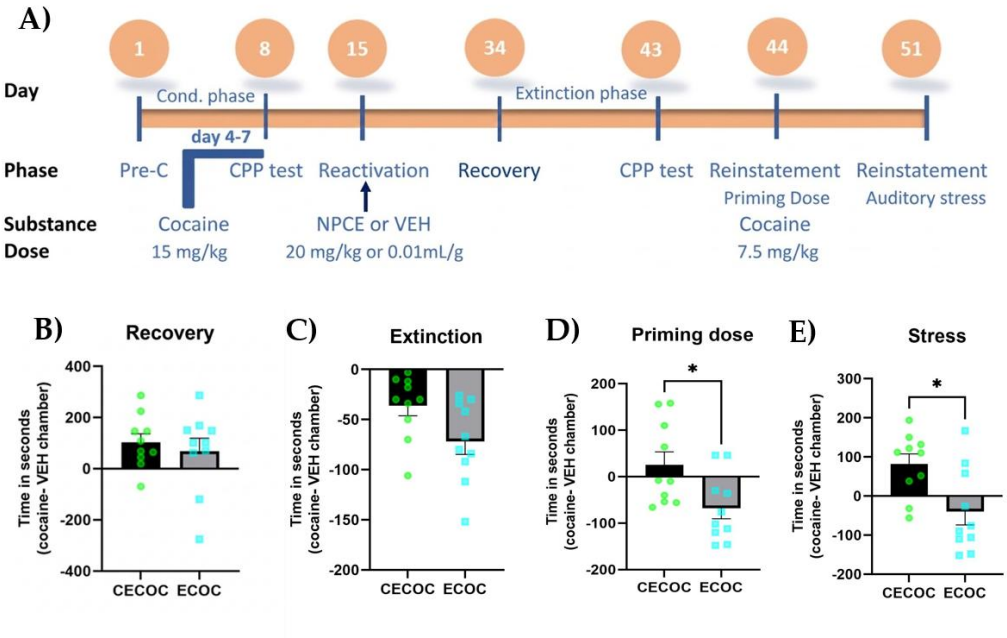

Figure 3. Results for Experiment 2. A) Timeline for procedures performed in Experiment 2. **B)** Data are presented as mean ± SEM (n = 20), for the time spent in the conditioned chamber minus the time in the VEH chamber between CECOC (VEH) and ECOC (NPCE 20 mg/kg), during recovery, **C)** extinction, and **D)** reinstatement priming dose and by **E)** stress. The symbol (*) indicates a $p < 0.05$.

6. Experiment 3: Evaluation of NPCE in the reconsolidation of CPP induced by cocaine

Results of experiment 3 are shown in Figure 4. Reconsolidation memory tests conducted at one-week (Memory test 1) and two weeks (Memory test 2) after memory reactivation were analyzed using

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two-tailed unpaired t-tests comparing the CRCOC (VEH, n = 10) and RCOC (NPCE, 20 mg/kg, n = 10) groups. The RCOC group showed significantly reduced CPP responses compared with the CRCOC group at both one week (t = 3.2, p = 0.004) and two weeks (t = 2.8, p = 0.011) after memory reactivation. These results indicate that NPCE significantly disrupted the reconsolidation of cocaine-associated contextual memory.

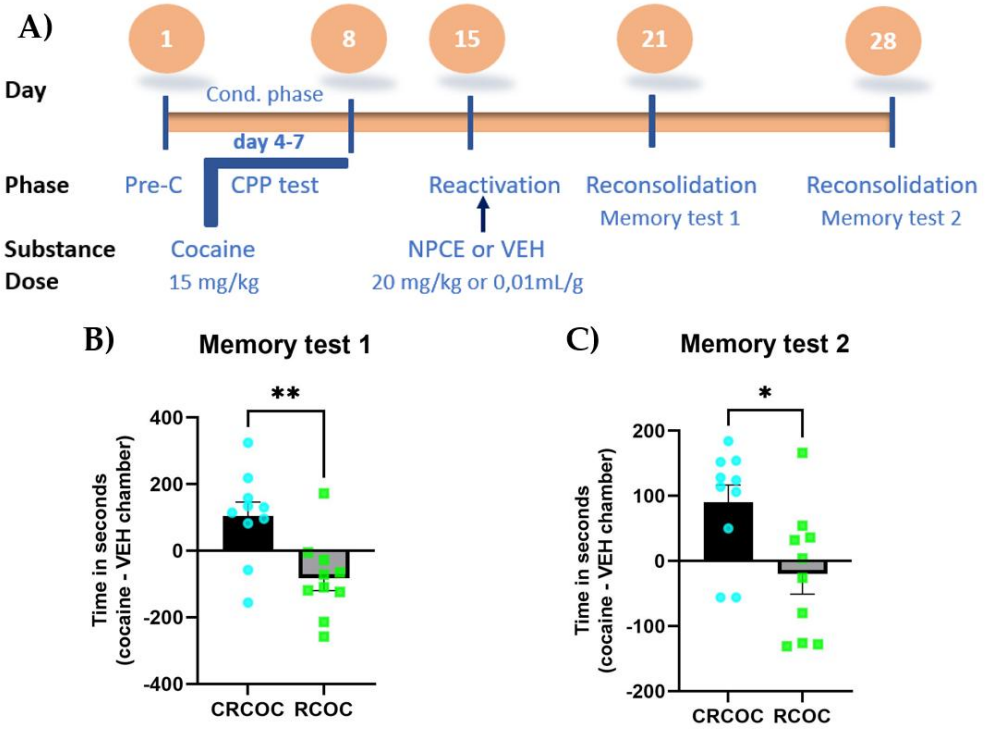

Figure 4. Results of Experiment 3. A) Timeline for procedures performed in Experiment 3. **B)** Data are presented as means ± SEM (n = 20) for the time spent in the conditioned compartment minus the time in the VEH chamber between CRCOC (VEH) and RCOC (NPCE 20 mg/kg) groups, memory test 1 and C) memory test 2. Symbol (**) indicates $p < 0.005$ and (*) indicates $p < 0.05$.

4. Discussion

This study evaluates the potential of an NPCE to modulate cocaine-associated memory processes, including reinstatement and reconsolidation, using a cocaine-induced CPP model. The results indicate that the animals did not exhibit any preliminary preference for a particular chamber, as these chambers offer similar cues. This absence of initial preference is crucial to the validity of the CPP model, as it ensures that any subsequently observed preference is due to the effect of the administered substances and not to a pre-existing bias. In Experiment 1, the effect of NPCE (20 mg/kg) on CPP acquisition was evaluated in comparison with VEH administration alone. It was found that NPCE did not produce aversion or preference in the conditioning chamber (Figure 2B). To the best of our knowledge, this is the first study to evaluate the acquisition of CPP using a NPCE extract. Viudez-Martínez et al. [3], demonstrated that CBD alone has no effect on CPP acquisition or other behavioral markers of addiction, in agreement with our findings. However, further studies are needed to confirm these results under different experimental conditions. Previous studies have shown that administering high doses of THC or CBD, or using extracts with a higher THC ratio, can induce notable neurochemical alterations in mice, resulting in behavioral modifications [35]. In the case of THC, low doses (below 0.5 mg/kg) appear to promote the extinction of cocaine-induced CPP [28], whereas higher doses may negatively affect working memory and produce aversive responses toward the conditioned chambers in the CPP paradigm [36,37]. For this effect of THC, a non-psychoactive extract was selected from the outset of our study, containing 0.7% of this substance and a CBD:THC ratio of 58:1 (corresponding to 20 mg/kg of CBD and 0.34 mg/kg of THC).

 doi:10.20944/preprints202604.1650.v1

NPCE effectively inhibited both the reconsolidation and reinstatement of cocaine-associated contextual memories. However, no significant effects were observed during extinction or during the recovery conducted in Experiment 2 (Figure 3A–B). Previous studies have reported that CBD does not influence the extinction of conditioned behaviors [38], a finding consistent with our observations for NPCE. Moreover, extinction latency, as evaluated in protocols such as that described by Calpe-López et al. [7], was not included in our experimental design. Incorporating this assessment would have allowed a more detailed analysis of the long-term effects of NPCE on extinction, which represents a limitation of the present study. Current hypotheses posit that CBD's therapeutic potential in substance use disorders may arise from its capacity to disrupt drug-related memory processes, particularly through interference with memory reinstatement and reconsolidation mechanisms, as evidenced in CPP experimental paradigms [9,39]. When administered as a single dose during the reactivation period, the extract exhibited a notable long-term effect on cocaine-associated memories. This influence on reinstatement and reconsolidation may be interpreted as part of the broader memory reconsolidation process [40]. Previous studies have shown that this effect is primarily mediated by cannabinoid receptor type 1 (CB1) [41–44] and dopaminergic receptors [32,45], in the medial prefrontal cortex, specifically in the anterior cingulate cortex and prelimbic cortex, key areas in the formation of aberrant-associated memories [39]. These effects may occur through interactions with molecular signaling pathways such as cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) [46], which are crucial for memory reconsolidation [40,47]. Additionally, studies have shown that rimonabant, a CB1 receptor antagonist, can disrupt memory reconsolidation in models of nicotine-induced CPP [41] and methamphetamine-induced CPP [42,48]. This antagonist has also been reported to disrupt cocaine-associated memories [49,50]. We acknowledge as a limitation of our study the absence of a CBD control group to directly compare the effects of NPCE on CPP indicators. Nevertheless, several studies available in the scientific literature provide a valuable basis for comparison with our findings in this regard.

Beyond the reconsolidation of aberrant memories associated with cocaine use, the reduction of stress has been proposed as a central pharmacological mechanism underlying the potential therapeutic effects of CBD in the treatment of CUD. Stress can induce relapse in cocaine addiction by reinstating drug-seeking behavior in rats, even after prolonged periods of extinction and abstinence [51–53]. This effect is mediated through the activation of neurotransmitter systems such as corticotropin-releasing factor (CRF) and norepinephrine (NE) in regions including the bed nucleus of the stria terminalis (BNST), hippocampus, and prefrontal cortex [51–53]. Among the mechanisms contributing to stress-induced reinstatement, serotonin signaling in the prefrontal cortex particularly through the 5-HT$_{1A}$ receptor plays a prominent role [54]. CBD acts as partial agonist of the 5-HT$_{1A}$ receptor, and recent findings by Shu et al. [55] support that the anxiolytic and antipsychotic effects of CBD are mediated by this signaling pathway [55,56]. This interaction between CBD and the 5-HT$_{1A}$ receptor, subsequently activating the mammalian target of rapamycin (mTOR) signaling pathway, has been reported to improve markers of cocaine addiction in CPP [32,46,57]. This mechanism may help explain the effectiveness of NPCE in attenuating stress-induced reinstatement observed in our study. Moreover, stressful experiences are known to dysregulate serotonin levels, which can subsequently elevate dopamine levels in the nucleus accumbens (NAc), a mechanism related to stress-induced reinstatement [53,58]. In the study conducted by Galaj et al. [32] it was demonstrated that systemic administration of CBD (10-40 mg/kg) inhibited cocaine self-administration and attenuated cocaine-enhanced brain reward. The effects were reported to be mediated by CB2, 5-HT$_{1A}$, and TRPV1 receptors, because the inhibition of these receptors attenuated the evaluated action of CBD. Moreover, the authors reported that systemic administration of CBD normalizes dopamine transporter expression in the ventral tegmental area (VTA), followed by cocaine exposure. This may be a key mechanism in its protective effect against drug-induced reinstatement [7,8,32], as also observed in our results with NPCE.

The NPCE used in this study is rich in cannabinoids and terpenes (Supplementary Material 1), which may individually contribute to its pharmacological effects treating the reinstatement and

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reconsolidation of cocaine-induced CPP. However, it is important to consider that, although the effects can be analyzed on a compound-by-compound basis, the overall impact of NPCE may be mediated by the so-called the entourage effect among its constituents. This synergistic interaction within cannabis is still under investigation [59], but it may involve mechanisms such as competitive inhibition of metabolic enzymes, particularly cytochrome P450 and carboxylesterases [23,60]. Additionally, terpenes such as bisabolol and terpinolene have a selective preference for CB2 receptor sites, modulating the response of cannabinoids that interact with this receptor [25]. Cannabinoids such as CBN and CBC may interact with CB1, CB2, TRPV1, and peroxisome proliferator-activated receptors (PPARs) when present at low concentrations, producing anti-inflammatory, analgesic, hypolocomotive, and anxiolytic effects [61,62]. A recent study by Hayduk et al. [63], demonstrated that a high dose of CBG (100 mg/kg) can reduce opioid withdrawal symptoms, whereas a lower dose (10 mg/kg) does not produce the same effects. Interestingly, the study found that the impact on withdrawal is significantly enhanced (by up to fourfold) when a low dose of CBG (2.48 mg/kg) is combined with a low dose of CBD (3.02 mg/kg) [63]. This finding suggests that combinations of low dose cannabinoids may yield beneficial effects in the context of SUD, highlighting the importance of analyzing their synergistic effects. Nevertheless, there is a lack of evidence regarding the effects of low concentrations of other cannabinoids and terpenes, such as those found in NPCE, on behavioral outcomes of SUD.

In conclusion, the present study demonstrates that NPCE inhibits both priming dose- and stress-induced reinstatement, as well as the reconsolidation of cocaine-induced CPP in mice, without producing reinforcing or aversive effects during CPP acquisition. These findings suggest that non-psychoactive full-spectrum cannabis extracts may represent a promising pharmacological strategy for disrupting drug-associated memories and reducing relapse-like behaviors in cocaine use disorder. While these preclinical results are encouraging, further research is required to confirm these effects under additional experimental conditions and to clarify the synergistic contributions of the cannabinoids and terpenes present in NPCE.

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Institutional Review Board Statement: The study was approved by the Ethics Committee of the Faculty of Sciences at the Universidad Nacional de Colombia (Approval No. Acta 06-2023). All experimental procedures were conducted in accordance with Good Laboratory Practice (GLP) guidelines and the ARRIVE quality reporting standards.

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