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Adjunctive delta-9-tetrahydrocannabinol during prolonged exposure therapy for PTSD: A randomized, double-blind feasibility pilot trial with mechanistic assessment of extinction recall

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Abstract

Posttraumatic stress disorder (PTSD) is a chronic and debilitating condition. Delta-9-tetrahydrocannabinol (THC) has been shown to influence fear extinction learning and recall, providing a mechanistic rationale for its use as an adjunct to exposure-based therapy. We conducted a randomized, double-blind, placebo-controlled pilot feasibility trial evaluating low-dose oral THC administered during Prolonged Exposure (PE) therapy for PTSD. Twenty-three adults with PTSD completed massed PE delivered via telehealth and were randomized to receive either 7.5 mg oral dronabinol (THC) or placebo prior to PE sessions 3–6. Primary outcomes included clinician-rated PTSD severity assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and self-reported symptoms assessed with the PTSD Checklist for DSM-5 (PCL-5). Mechanistic assessments examined extinction recall using behavioral, psychophysiological, and neuroimaging measures. Across both drug conditions, clinician-rated and self-reported PTSD symptoms decreased substantially, and improvements were maintained through 3-month follow-up, at which point 91% of participants no longer met diagnostic criteria for PTSD. Significant improvements were also observed for anxiety, depression, sleep quality, and dissociative symptoms. The study was not powered to detect between-group differences; however, descriptive contrasts yielded numerically lower PTSD severity and reduced persistence of dissociative symptoms among THC-treated participants. THC was well tolerated, with no serious adverse events. During extinction recall, THC was associated with greater hippocampal differentiation between extinguished and unextinguished threat cues, whereas behavioral and psychophysiological measures did not differ between groups. These findings demonstrate the feasibility and tolerability of pairing low-dose THC with PE therapy and support evaluation in adequately powered randomized trials.

Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric condition characterized by intrusive trauma memories, avoidance of trauma-related cues, negative alterations in cognition and mood, hyperarousal, and, in some individuals, dissociative symptoms (DSM-5)[1]. PTSD affects approximately 6–10% of individuals across the lifespan and is associated with substantial functional impairment and psychiatric comorbidity[2]. Despite advances in treatment, PTSD remains a leading cause of disability worldwide.

Pharmacological treatment options for PTSD remain limited. Only two medications—sertraline and paroxetine—are approved by the U.S. Food and Drug Administration for PTSD, and their clinical efficacy is modest, with high rates of nonresponse and adverse effects contributing to poor adherence[3]. As such, trauma-focused psychotherapies are widely recommended as first-line interventions. Among these, Prolonged Exposure (PE) therapy is one of the most extensively-studied and empirically-supported treatments for PTSD[4]. PE is grounded in emotional processing theory and involves repeated imaginal and in vivo exposure to trauma-related memories and cues to promote fear extinction and inhibitory learning. Across randomized controlled trials and clinical settings, PE produces large and enduring reductions in PTSD symptom severity[5,6]. However, considerable variability in treatment engagement and

clinical response remains, motivating interest in adjunctive strategies targeting extinction learning processes during exposure-based therapy[7–9].

One neurobiological system that has received increasing attention in this context is the endocannabinoid (eCB) system. This system plays a central role in fear extinction, stress reactivity, affect regulation, and sleep, all of which are processes directly relevant to PTSD symptomatology and PE treatment mechanisms[10–14]. Preclinical studies demonstrate that cannabinoid signaling facilitates fear extinction and extinction memory retention[15–18], whereas disruption of eCB signaling impairs these processes[12,19–24]. In humans, converging evidence suggests altered endocannabinoid function in PTSD, including reduced circulating endocannabinoid levels and altered CB1 receptor availability. Experimental studies further indicate that cannabinoids influence emotional processing, threat reactivity, and sleep quality, which are domains frequently disrupted in individuals with PTSD[14,25,26]. These findings suggest cannabinoid signaling may be a relevant target for adjunctive interventions delivered alongside exposure-based psychotherapy.

Delta-9-tetrahydrocannabinol (THC), the primary psychoactive constituent of cannabis, acts as a partial agonist at CB1 receptors and has been shown under controlled conditions to influence fear learning, emotional reactivity, and sleep architecture[13,14,26–28]. When administered at low doses in supervised laboratory and clinical settings, oral THC demonstrates a favorable safety and tolerability profile[29]. In the present study, THC was administered during early imaginal exposure sessions to influence extinction learning and subsequent memory retrieval processes. To date, no randomized clinical trials have evaluated THC as an adjunct to PE therapy for PTSD. Potential effects on emotional engagement, reinforcement liability, and dissociative symptoms underscore the need for controlled clinical investigation.

The present randomized, double-blind, placebo-controlled pilot trial was designed to evaluate the feasibility, safety, and preliminary clinical effects of low-dose oral THC administered during early PE sessions in adults with PTSD. Primary outcomes were clinician-rated and self-reported PTSD symptom severity. Secondary outcomes were anxiety, depression, sleep quality, dissociative symptoms, trauma-related psychosocial processes, and drug-related safety and tolerability. Given the pilot design, analyses emphasized characterization of clinical trajectories and mechanistic indices of extinction learning and memory. The overarching goal was to inform the design of future adequately-powered trials examining cannabinoid-based augmentation of exposure-based psychotherapy.

Method

Study Design and Oversight

This study was a randomized, double-blind, placebo-controlled pilot clinical trial designed to evaluate the feasibility, safety, and preliminary clinical effects of low-dose THC administered as an adjunct to PE therapy for PTSD. Participants completed PE delivered in massed (rather than spaced) format and via

telehealth, with study medication administered prior to early imaginal exposure sessions. Participants were randomized in a 1:1 ratio to receive either placebo or 7.5 mg oral dronabinol (THC) administered prior to PE sessions 3 through 6. As a pilot study, the primary objectives were feasibility assessment and effect-size estimation rather than definitive efficacy testing.

Dronabinol is an U.S. Food and Drug Administration (FDA)-approved medication. Based on the approved formulation, dose, and study procedures, the trial was determined by the FDA to be exempt from Investigational New Drug (IND) requirements, and an exemption determination was issued for regulatory tracking purposes. The study was approved by the Institutional Review Boards at Wayne State University and Emory University and was registered on ClinicalTrials.gov (NCT04080427). Participant safety and study conduct were overseen by an independent Data and Safety Monitoring Board.

In-person study visits were conducted at Wayne State University in Detroit, Michigan, and PE therapy sessions were delivered via telehealth by licensed clinical psychologists at Emory University in Atlanta, Georgia. Participant enrollment began in April 2021, and all follow-up assessments were completed by March 2025.

Participants

Participants were adults aged 18–60 years with a current diagnosis of PTSD as determined by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[30]. Inclusion criteria required exposure to at least one DSM-5 Criterion A traumatic event and clinically significant PTSD symptom severity at screening (CAPS-5 total score ≥ 25).

Key exclusion criteria included psychotic or bipolar disorder, severe substance use disorder, moderate or severe traumatic brain injury, active safety concerns, pregnancy, MRI contraindications, and inability to complete study procedures. Complete eligibility criteria are provided in the Supplementary Methods. Baseline demographic and clinical characteristics are presented in Table 1.

Table 1
Baseline demographic and clinical characteristics of participants

Characteristic	Overall (N = 23)	PBO (N = 12)	THC (N = 11)	*p*-values
Biological Sex				
Female	17 (73.9%)	8 (66.7%)	9 (82.0%)	.64
Age, years	31.3 (12.1)	28.7 (9.4)	34.1 (14.5)	.33
Racial identity				.68
White	17 (73.9%)	10 (83.3%)	7 (63.6%)	
Black/African American	2 (8.7%)	1 (8.3%)	1 (9.1%)	
Native American	1 (4.3%)	0 (0%)	1 (9.1%)	
Multiracial/Other	3 (13%)	1 (8.3%)	2 (18.2%)	
Education level				.53
Some college	10 (43.5%)	4 (33.3%)	6 (54.6%)	
2-year college	3 (13.0%)	3 (25.0%)	0 (0%)	
4-year college	3 (13.0%)	2 (16.7%)	1 (9.1%)	
Some graduate training	2 (8.7%)	1 (8.3%)	1 (9.1%)	
Graduate degree	5 (21.7%)	2 (16.7%)	3 (27.3%)	
Index trauma type				.66
Sexual Assault	10 (43.5%)	6 (50.0%)	4 (36.4%)	
Life-threatening event	7 (30.4%)	4 (33.3%)	3 (27.3%)	
Serious injury	6 (26.1%)	2 (16.7%)	4 (36.4%)	
Baseline clinical measures				
CAPS-5 total score	39.1 (7.4)	40.3 (7.3)	37.8 (7.1)	.44
PCL-5 total score	44.9 (9.21)	44.8 (10.2)	45.0 (8.5)	.97
HAM-A total score	21.6 (9.8)	22.8 (10.9)	20.2 (8.7)	.52
HAM-D total score	16.4 (6.0)	18.0 (6.5)	14.6 (5.0)	.18

Note. Data are presented as mean (standard deviation) for continuous variables and count (percentage) for categorical variables. CAPS-5 = Clinician Administered PTSD Scale for DSM-5; PCL-5 = PTSD Checklist for DSM-5; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; PSQI = Pittsburgh Sleep Quality Index; THC = delta-9-tetrahydrocannabinol; PBO = placebo

Characteristic	Overall (N = 23)	PBO (N = 12)	THC (N = 11)	*p*-values
Biological Sex				
PSQI global score	11.3 (4.1)	11.8 (4.1)	10.8 (4.3)	.58

Note. Data are presented as mean (standard deviation) for continuous variables and count (percentage) for categorical variables. CAPS-5 = Clinician Administered PTSD Scale for DSM-5; PCL-5 = PTSD Checklist for DSM-5; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; PSQI = Pittsburgh Sleep Quality Index; THC = delta-9-tetrahydrocannabinol; PBO = placebo

Table 2
Clinical outcomes at baseline, post-treatment, and 3-month follow-up

Outcome	Drug Condition	n	Baseline Mean (SD)	Post-treatment Mean (SD)	3-month Follow-up Mean (SD)	Δ BL→FU Mean (SD)	ΔΔ (THC–PBO)	Between Group Cohen's *d*
CAPS-5 Total (clinician-rated)	PBO	12	40.25 (7.74)	15.50 (11.68)	15.25 (14.20)	-25.00 (16.04)		
	THC	11	37.82 (7.14)	12.82 (11.12)	9.27 (10.08)	-28.55 (14.20)	-3.55	-0.23
PCL-5 Total (self-report)	PBO	12	44.83 (10.21)	17.83 (10.22)	15.58 (13.41)	-29.25 (17.44)		
	THC	11	45.00 (8.47)	19.64 (13.22)	10.36 (9.70)	-34.64 (13.38)	-5.39	-0.34

Notes: Values are mean (SD). BL = baseline; FU = follow-up. Change scores are expressed as FU − BL, such that negative values indicate symptom improvement. ΔΔ represents the between-group difference in change scores (THC − PBO). Cohen's d is based on the between-group difference in change scores; negative values indicate greater improvement in the THC condition relative to placebo. CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; PCL-5 = PTSD Checklist for DSM-5; THC = delta-9-tetrahydrocannabinol; PBO = placebo.

Recruitment and Screening

Participants were recruited through online advertisements and community-based recruitment strategies. Following written informed consent, participants completed diagnostic and eligibility assessments, including the CAPS-5 and the Mini International Neuropsychiatric Interview (MINI 7.0.2)[31]. Eligibility was

confirmed prior to randomization. Additional screening procedures are described in the Supplementary Methods.

Randomization and Blinding

Participants were randomized 1:1 to receive placebo or 7.5 mg oral dronabinol using a covariate-adaptive allocation procedure designed to balance key demographic and clinical characteristics. Participants, therapists, assessors, and study staff remained blinded throughout the trial. Additional details regarding randomization and blinding procedures are provided in the Supplementary Methods.

Intervention

PE therapy was delivered according to the standard therapist manual and patient workbook and consisted of 10 sessions administered in a massed format of up to three sessions per week. Massed PE has been shown to be comparable to traditionally delivered (weekly) PE, with some evidence of improved treatment retention[32]. Sessions 1 and 2 focused on psychoeducation, treatment rationale, breathing retraining, preparation for exposure, and development of an in vivo exposure hierarchy. Sessions 3 through 10 included imaginal exposure to the index trauma memory and systematic in vivo exposure exercises[4]. Additional details regarding treatment delivery and fidelity procedures are provided in the Supplementary Methods and the published trial protocol[33].

Participants randomized to the active condition received 7.5 mg oral dronabinol prior to PE sessions 3 through 6, corresponding to the first four imaginal exposure sessions. Participants randomized to placebo received identically encapsulated inert capsules on the same schedule. Study medication was administered approximately 120 minutes prior to each session to coincide with peak plasma THC concentrations during exposure[34]. Medication administration was restricted to the early imaginal exposure sessions to maximize engagement of extinction-learning processes while minimizing cumulative drug exposure and potential tolerability concerns associated with repeated dosing.

Outcome Measures

Primary Outcomes

Primary clinical outcomes were blinded clinician-rated PTSD symptom severity assessed with the CAPS-5[30] and self-reported PTSD symptom severity assessed with the PTSD Checklist for DSM-5 (PCL-5)[35]. Assessments were conducted at baseline, during treatment, immediately post-treatment, and at follow-up visits (Fig. 1; Table S1). The primary clinical endpoint was post-treatment PTSD symptom severity following completion of PE Session 10.

Secondary Outcomes

Secondary clinical outcomes included clinician-rated anxiety assessed with the Hamilton Anxiety Rating Scale (HAM-A)[36], clinician-rated depressive symptoms assessed with the Hamilton Depression Rating Scale (HAM-D)[37], and self-reported sleep quality assessed with the Pittsburgh Sleep Quality Index (PSQI)[38]. Additional prespecified secondary and exploratory outcomes included cognitive avoidance, trauma-related cognitions, resilience, posttraumatic growth, and dissociative symptoms. Detailed descriptions of all outcome measures are provided in the Supplementary Methods.

Feasibility Outcomes

Feasibility outcomes included recruitment, retention, treatment initiation, treatment completion, and completion of post-treatment and follow-up assessments. These outcomes were summarized descriptively.

Subjective Drug Effects, Blinding, and Safety

Acute subjective drug effects were assessed during medication-paired sessions using the Drug Effects Questionnaire (DEQ)[39], which assessed perceived drug effects, intoxication, positive and negative subjective effects, and desire for additional drug. Participant safety was monitored throughout the study using the Columbia-Suicide Severity Rating Scale (C-SSRS)[40], adverse event monitoring, medication review, urine toxicology testing, breath alcohol testing, and pregnancy testing when applicable. Blinding integrity was assessed for participants and research staff at study completion (Supplemental Methods).

Statistical Analysis

Clinical outcomes were analyzed using linear mixed-effects models implemented in R (lme4 package)[41]. Models included fixed effects of drug condition, time, and their interaction, with participant-specific random intercepts to account for repeated observations. Consistent with the covariate-adaptive randomization procedure and the pilot nature of the study, demographic covariates were not included in primary analyses.

Two complementary longitudinal modeling approaches were used. First, linear mixed-effects models treating assessment time as a continuous variable were used to estimate overall symptom trajectories across the study period. Second, piecewise mixed-effects models were specified to estimate separate rates of change from baseline to post-treatment and from post-treatment to the three-month follow-up assessment. Additional modeling details are provided in the Supplementary Methods.

Given the pilot nature of the trial, analyses emphasized effect-size estimation and characterization of longitudinal trajectories rather than definitive hypothesis testing. Drug condition-by-time interactions were included to describe differential change over time but were considered exploratory because the study was not powered to detect anything other than large interaction effects. Analyses followed a modified intention-to-treat approach, including all randomized participants who contributed at least one

post-randomization assessment. Feasibility outcomes, subjective drug effects, blinding assessments, and safety outcomes were summarized descriptively.

Mechanistic Assessments

Participants completed an immersive virtual reality fear conditioning and extinction paradigm during fMRI at pre-treatment and post-treatment assessments (Fig. 1). Extinction recall served as the primary mechanistic outcome and was operationalized as differential responding to extinguished versus unextinguished CSs (CS + E − CS + U) during early recall. Behavioral (US expectancy), psychophysiological (skin conductance response), and neuroimaging measures were examined as indices of extinction memory retrieval. Neuroimaging analyses focused on a priori HPC, vmPFC, and amygdala regions implicated in extinction memory. Additional acquisition, preprocessing, task, and analytic details are provided in the Supplementary Methods and previous publications[26,42,43].

Results

Participant Characteristics and Retention

Participant flow is shown in Fig. 1. Twenty-seven participants were randomized and 23 participants contributed at least one post-randomization assessment and were included in the modified intention-to-treat analyses (placebo: n = 12; THC: n = 11). Follow-up data were available for all participants included in the modified intention-to-treat sample at the three-month assessment. Baseline demographic and clinical characteristics are presented in Table 1. No significant between-group differences were observed for demographic characteristics, trauma type, or baseline clinical symptom severity measures (all *ps* > .17). Additional trauma characteristics are presented in Table S3.

Subjective Drug Effects and Blinding

Participants receiving THC reported greater subjective drug effects than participants receiving placebo, whereas ratings of desire for additional drug did not differ between drug conditions (Table S4). Blinding integrity was generally preserved for both participants and research staff (Table S5; Supplemental Results).

Safety and Tolerability

No serious adverse events occurred. A total of 43 adverse events were reported, and no adverse event resulted in study discontinuation. Treatment-emergent adverse events were generally mild and transient, and included nausea, headache, and motion-related discomfort. Adverse-event frequencies are summarized in Table S6. No suicide attempts, preparatory behaviors, or study discontinuations related to suicidality occurred during the trial.

Primary PTSD Outcomes

Clinician-Rated PTSD Symptoms (CAPS-5)

Clinician-rated PTSD symptom severity (CAPS-5) decreased substantially over the course of treatment in both drug conditions (Fig. 2a). Linear mixed-effects models revealed a significant effect of time, indicating robust reductions in PTSD symptoms from baseline through the three-month follow-up (β = −0.51, SE = 0.12, $p < .001$, $\eta p^2 = .35$). There was no significant main effect of drug condition (β = 0.62, SE = 2.20, $p = .78$, $\eta p^2 = .01$) and no significant drug condition-by-time interaction. Piecewise analyses indicated significant reductions in CAPS-5 scores from baseline to post-treatment (β = −0.63, SE = 1.57, $p < .001$, $\eta p^2 = .29$), followed by maintenance of treatment gains through the three-month follow-up (β = −0.01, SE = 0.44, $p = .98$, $\eta p^2 = .009$). Mean CAPS-5 scores decreased from 40.3 to 15.3 in the placebo condition and from 37.8 to 9.3 in the THC condition over the course of the study. Estimated marginal means and drug condition contrasts are presented in Table S7.

Self-Reported PTSD Symptoms (PCL-5)

Self-reported PTSD symptoms, assessed using the PCL-5, also declined significantly over time (Fig. 2b). Linear mixed-effects models revealed a significant effect of time, reflecting reductions in PTSD symptom severity from baseline through three-month follow-up (β = −0.29, SE = 0.10, $p = .004$, $\eta p^2 = .42$). There was no significant main effect of drug condition (β = 0.48, SE = 2.17, $p = .83$, $\eta p^2 = .006$) and no significant drug condition-by-time interaction. Piecewise analyses demonstrated significant symptom reduction from baseline to post-treatment (β = −0.34, SE = 0.15, $p = .02$, $\eta p^2 = .30$), followed by relative stability from post-treatment to three-month follow-up (β = −0.11, SE = 0.42, $p = .80$, $\eta p^2 = .02$). Mean PCL-5 scores decreased from 44.8 to 15.6 in the placebo condition and from 45.0 to 10.4 in the THC condition over the course of the study. Estimated marginal means and drug condition contrasts are presented in Table S8.

PTSD Diagnostic Status and Remission

Consistent with the observed reductions in PTSD symptom severity, most participants achieved remission by the three-month follow-up assessment. Remission was defined as loss of PTSD diagnosis and a CAPS-5 total score < 20 (see Supplementary Methods). Overall, 21 of 23 participants (91.3%) met remission criteria at follow-up. Remission rates were similar across drug conditions, with 11 of 12 participants (91.7%) in the placebo condition and 10 of 11 participants (90.9%) in the THC condition achieving remission.

Exploratory Dissociative Symptom Outcomes

Among participants endorsing dissociative symptoms at baseline (n = 15), dissociative symptoms declined over the course of treatment in both drug conditions. At post-treatment, persistent dissociative symptoms were observed in 4 of 8 placebo-treated participants (50.0%) but only 1 of 7 THC-treated participants (14.3%). At the three-month follow-up, dissociative symptoms persisted in 4 of 8 placebo-treated participants (50.0%) but in none of the THC-treated participants (0%).

A Fisher's exact test comparing persistence of dissociation at follow-up did not reach statistical significance (p = .077). THC-treated participants nevertheless demonstrated lower rates of persistent dissociative symptoms at both post-treatment and follow-up (Table S9). Given the small sample size, these findings should be considered exploratory and hypothesis-generating.

Secondary Clinical Outcomes

Secondary clinical outcomes also improved over time across both drug conditions, including anxiety, depression, and sleep quality. Significant reductions were observed in clinician-rated anxiety (HAM-A; β = −0.62, SE = 0.14, p < .001, ηp^2 = .42), clinician-rated depressive symptoms (HAM-D; β = −0.37, SE = 0.12, p = .005, ηp^2 = .22), and self-reported sleep disturbance (PSQI; β = −0.21, SE = 0.06, p < .001, ηp^2 = .29). Between-group differences were small and inconsistent across outcomes. Descriptive statistics, change scores, and effect size estimates are provided in Table S10, and symptom trajectories are shown in Figure S2.

Exploratory Psychosocial Outcomes

Exploratory psychosocial outcomes, including trauma-related cognitions, cognitive avoidance, resilience, and posttraumatic growth, demonstrated modest changes over time with small and inconsistent between-group differences. Descriptive statistics and effect-size estimates are presented in Table S10.

Mechanistic Outcomes

To examine potential mechanisms underlying drug-related effects, we next evaluated extinction recall behavior, psychophysiological responding, and neural activation during the fear conditioning paradigm.

Unconditioned Stimulus (US) Expectancy Ratings

US expectancy ratings were analyzed as a behavioral measure of explicit threat expectancy during post-treatment early extinction recall. Neither the main effect of drug condition (OR = 0.19, p = .62), the main effect of stimulus type (OR = 1.59, p = .37), nor the drug condition-by-stimulus interaction (OR = 0.78, p = .75) reached statistical significance. Response distributions were highly similar across drug conditions and stimulus types, with approximately 75–80% of responses indicating no expectation of the aversive outcome and fewer than 11% indicating positive expectancy (Table S11). These findings suggest successful extinction recall across drug conditions and provide no evidence that THC altered explicit threat expectancy.

Skin Conductance Responses

Usable post-treatment SCR data were available for 12 participants. Differential SCR during early extinction recall did not differ between drug condition (β = 0.03, SE = 0.12, p = .79), providing no evidence that THC altered physiological indices of extinction memory retrieval. Additional SCR results are provided in the Supplemental Results.

Neural Correlates of Extinction Memory

Whole-brain voxelwise analyses of the post-treatment early extinction recall contrast (CS + E − CS + U) did not identify drug-related effects that survived whole-brain FWE correction. Anatomically-defined ROI and literature-based SVC analyses were subsequently conducted within the HPC, vmPFC, and amygdala based on a priori hypotheses regarding their involvement in extinction memory retrieval. Anatomical ROI analyses within bilateral HPC, vmPFC, and amygdala masks did not reveal significant drug-related effects following FWE correction within the anatomical search volumes.

Literature-based SVC analyses revealed significantly greater HPC activation in the THC condition relative to the placebo condition during post-treatment early extinction recall (CS + E − CS + U). Two significant clusters were identified within the left HPC (Cluster 1: MNI = − 28, − 4, −18; Z = 2.90, k = 34, $pFWE$ = .04; Cluster 2: MNI = − 22, − 20, −8; Z = 2.90, k = 22, $pFWE$ = .04; Fig. 3a; Table S12). No significant drug-related effects were observed within vmPFC or amygdala coordinates following correction for multiple comparisons.

To characterize the direction and magnitude of these effects, first eigenvariates were extracted from 5-mm spheres centered on the peak voxel of each significant HPC cluster (Fig. 3b). Across both HPC clusters, participants receiving THC exhibited greater activation than participants receiving placebo. Descriptive statistics and effect size estimates are presented in Table S12.

Discussion

This randomized, double-blind, placebo-controlled pilot trial evaluated the feasibility, safety, and preliminary effects of adjunctive low-dose THC administered during massed PE therapy for PTSD. Across both drug conditions, PE was associated with large and clinically meaningful reductions in PTSD symptom severity that were maintained through the 3-month follow-up. Feasibility was supported by successful recruitment, low attrition, high treatment completion, and favorable tolerability. Although the study was not powered to detect between-group differences, adjunctive THC was associated with exploratory patterns suggestive of lower PTSD symptom severity, reduced persistence of dissociative symptoms, and greater HPC differentiation during extinction recall clinical and mechanistic patterns that warrant evaluation in adequately powered trials.

Prolonged Exposure Produced Robust and Durable Clinical Improvement

Participants in both drug conditions demonstrated substantial reductions in clinician-rated and self-reported PTSD symptom severity[5,37]. Symptom improvement occurred primarily during the acute treatment phase and was maintained at follow-up, with minimal evidence of symptom rebound. By 3 months, more than 90 percent of all participants no longer met diagnostic criteria for PTSD, underscoring the strength and stability of PE when delivered in a massed, telehealth-based format. The exceptionally strong response to PE observed in both conditions may also have limited the ability to detect incremental benefits associated with adjunctive THC, particularly within the constraints of a pilot

sample. Improvements were also observed across secondary domains, including anxiety, depression, sleep quality, and dissociative symptoms, highlighting the breadth of clinical benefit associated with PE. Given these large effects for PE, to detect potential augmentation, future trial designs may benefit from either reducing the PE dose or focusing on time to remission as the primary outcome.

Safety, Subjective Effects, and Blinding

Low-dose THC administered prior to early exposure sessions was well tolerated. No serious adverse events occurred, and adverse events possibly related to study participation were mild and transient. Ratings of desire for additional drug were not elevated in the THC condition. Blinding integrity was largely preserved. Participant and staff guesses regarding drug assignment approximated chance levels. These findings support the practicality of maintaining blinding in future trials using low-dose oral THC.

Exploratory Patterns Associated with Adjunctive THC

Although the study was not powered to detect statistically significant between-group differences, several converging exploratory patterns suggest potential domain-specific benefits associated with adjunctive THC. Numerically lower clinician-rated PTSD severity was observed among THC-treated participants at post-treatment and follow-up assessments, with a similar numerical pattern observed for self-reported symptoms at follow-up. Secondary clinical and psychosocial outcomes improved across drug conditions, with small and inconsistent between-group differences. There was no evidence that adjunctive THC interfered with cognitive or avoidance-related processes during exposure therapy.

Neural and Behavioral Mechanisms of Extinction Recall

The present findings provide preliminary evidence that adjunctive THC may influence neural processes associated with extinction memory retrieval, despite limited effects on clinical and peripheral behavioral outcomes. During extinction recall, participants receiving THC exhibited greater differential activation within hippocampal regions in response to extinguished versus unextinguished cues during early recall. This pattern is consistent with involvement of hippocampal circuitry implicated in context-dependent retrieval of extinction memory and discrimination between safety and threat cues. Contrary to our hypotheses and some prior cannabinoid-extinction studies[13,45], we did not observe significant drug-related effects within vmPFC or amygdala regions. This may reflect limited statistical power, differences in task design, or the possibility that HPC mechanisms are more sensitive to THC-related effects during extinction memory retrieval in this context.

In contrast to neural findings, SCRs and US expectancy ratings did not differ significantly between drug conditions, suggesting that neural modulation associated with THC may not translate directly to overt differences in fear expression. The divergence between neural and behavioral findings is consistent with prior work indicating that extinction-related neural change may not be fully reflected in peripheral measures of fear expression. The observed HPC effects may therefore reflect more precise or differentiated encoding of extinction memory representations, rather than global reductions in fear responding. Together, these findings suggest that adjunctive THC may selectively modulate neural

systems underlying extinction memory retrieval without producing robust changes in symptom expression or behavioral indices of fear.

Dissociative Symptoms as an Important Future Direction

One of the most notable exploratory findings involved dissociative symptoms. Dissociation declined substantially across the full sample during PE treatment, consistent with prior evidence that exposure-based therapies can reduce dissociative responses. Among participants endorsing dissociative symptoms at baseline, persistent dissociative symptoms at follow-up were observed only among those assigned to placebo and not among those receiving THC. Although these subgroup analyses were exploratory and based on a small sample, the consistency of this pattern suggests that dissociation warrants further investigation in future cannabinoid-augmented psychotherapy trials. Dissociation has been associated with poorer engagement and outcomes in exposure-based treatments[40]. Although the current study was not designed to determine whether dissociation functions as a predictor, moderator, or treatment-sensitive process, the present findings highlight dissociation as a potentially important target for future investigation.

Limitations

Several limitations should be considered when interpreting these findings. First, the final sample (N = 23) was substantially smaller than originally planned, reducing statistical power and limiting sensitivity to detect anything other than large between-group effects. Accordingly, the absence of statistically significant drug condition effects should not be interpreted as evidence of no effect. The exploratory between-group differences observed in this pilot sample may nevertheless provide useful benchmarks for effect-size estimation and sample-size planning in future trials.

Second, only a single THC dose and administration schedule were examined. Cannabinoid effects may vary as a function of dose, timing, and individual differences[13,26,47,48]. Third, interpretation of subjective drug effect measures is further limited by exclusion of individuals with current substance use disorders and the absence of longer-term follow-up of substance use behavior. Finally, participants were recruited from the community rather than clinical treatment settings, which may limit generalizability to populations engaged in routine clinical care, where factors such as comorbidity profiles, access to treatment, and patterns of care may differ.

Clinical and Research Implications

Despite these limitations, the present findings support the feasibility and safety of pairing low-dose THC with PE therapy. Larger, adequately powered trials incorporating mechanistic endpoints, longer follow-up periods, and stratification by dissociative symptom status will be needed to clarify the role of cannabinoid-based augmentation strategies in exposure-based psychotherapy.

Conclusion

This study represents the first randomized clinical trial to evaluate adjunctive THC administered during PE therapy for PTSD. PE produced large and durable clinical improvements, and adjunctive THC was feasible, well tolerated, and associated with exploratory signals suggestive of domain-specific effects. These findings highlight the endocannabinoid system as a promising target for augmentation strategies aimed at enhancing evidence-based psychotherapies for PTSD.

Declarations

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Author Contributions: ***CAR*** – Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review & editing; ***CJH*** – Data curation, formal analysis, investigation, visualization, writing – original draft, writing – review & editing; ***SAMR*** – Conceptualization, investigation, supervision, methodology, project administration, formal analysis, writing – original draft, writing – review & editing; ***ML*** – Conceptualization, methodology, writing – review & editing; ***PK*** – Investigation, methodology, supervision, writing – review & editing; ***AI*** – data curation, investigation, project administration, writing – review & editing; ***SD*** – data curation, investigation, project administration, writing – review & editing; ***KT*** - investigation, project administration, writing – review & editing; ***MF*** – Investigation, methodology, writing – review & editing; ***KMN*** - Investigation, writing – review & editing; ***AW*** - Investigation, writing – review & editing; ***MMojallal*** - Investigation, writing – review & editing; ***MMorgan*** - Investigation, writing – review & editing; ***JC*** - Investigation, writing – review & editing; ***SH*** - Investigation, writing – review & editing.

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Data Availability: De-identified data supporting the findings of this study are available through the NIMH Data Archive DOI: 10.15154/cwxw-3191

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Figures

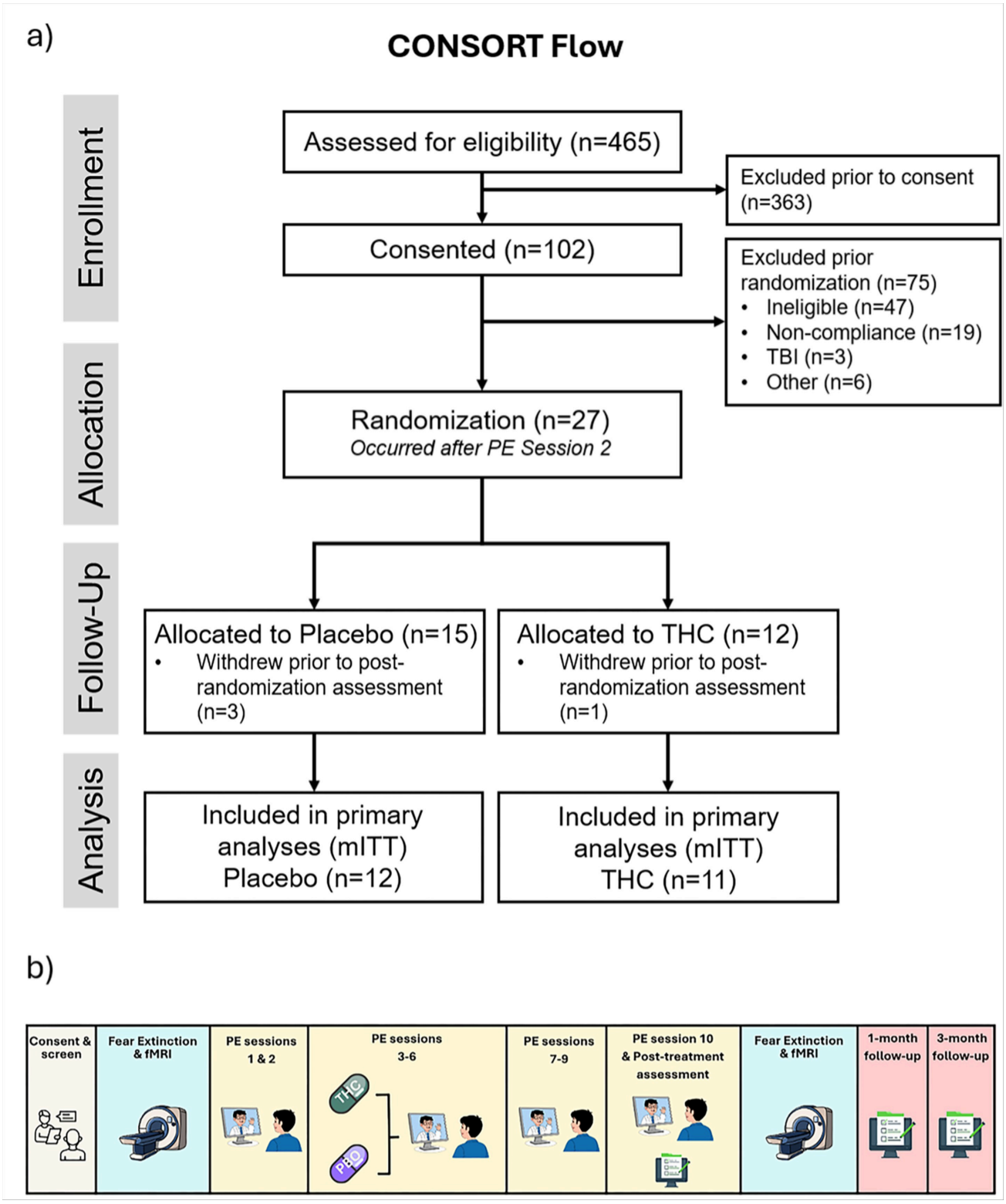


Figure 1

CONSORT flowchart and intervention timeline. (a) CONSORT flowchart of participants through screening, consent, allocation, follow-up, and inclusion in primary analyses. Of 465 individuals assessed for eligibility, 102 provided informed consent and 27 participants were randomized after completion of Prolonged Exposure (PE) Session 2. Participants were allocated to placebo (PBO; n = 15) or delta-9-tetrahydrocannabinol (THC; n = 12). Four participants withdrew prior to providing post-randomization outcome data (PBO: n = 3; THC: n = 1). The final analytic sample included 23 participants (PBO: n = 12; THC: n = 11) and reflects modified intention-to-treat (mITT) inclusion criteria. (b) Schematic of study procedures showing screening and consent, pre- and post-treatment mechanistic assessments, Prolonged Exposure (PE) therapy sessions, timing of study medication administration (THC or PBO administered prior to PE sessions 3–6), post-treatment assessment (PE session 10), and 1- and 3-month follow-up visits.

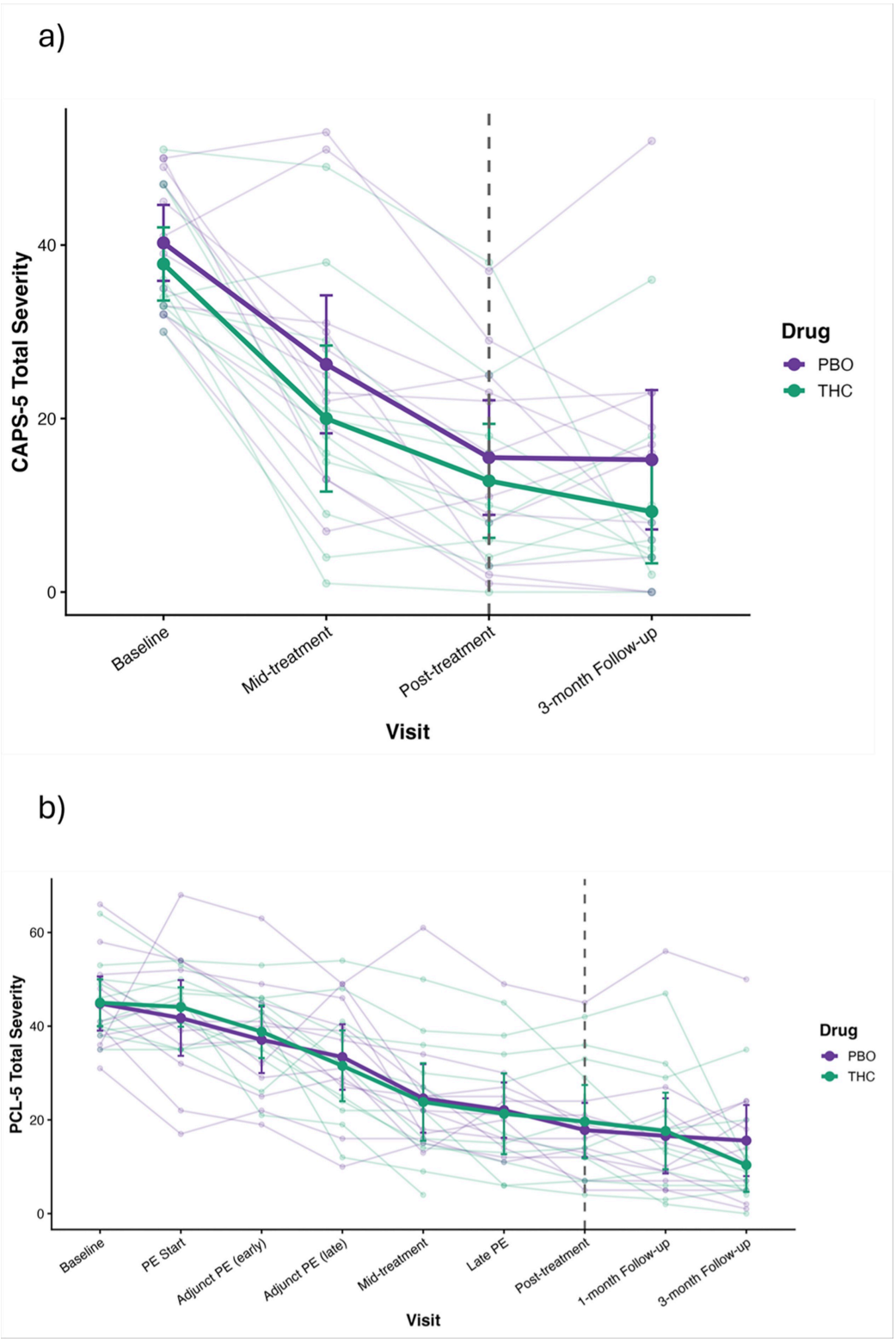


Figure 2

PTSD symptom severity across treatment and follow-up. (a) Clinician-rated PTSD symptom severity measured by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). (b) Self-reported PTSD symptom severity measured by the PTSD Checklist for DSM-5 (PCL-5). Trajectories are shown across the course of Prolonged Exposure (PE) therapy with adjunctive delta-9-tetrahydrocannabinol (THC; green) or placebo (PBO; purple). Thin lines represent individual participant trajectories. Thick lines and points

represent estimated marginal means from linear mixed-effects models, and error bars represent 95% confidence intervals. Assessments were conducted from baseline through treatment and follow-up. Dashed vertical lines indicate completion of PE Session 10 (post-treatment assessment). Lower scores indicate lower PTSD symptom severity. Both drug conditions demonstrated substantial symptom improvement over time, with generally comparable trajectories during acute treatment.

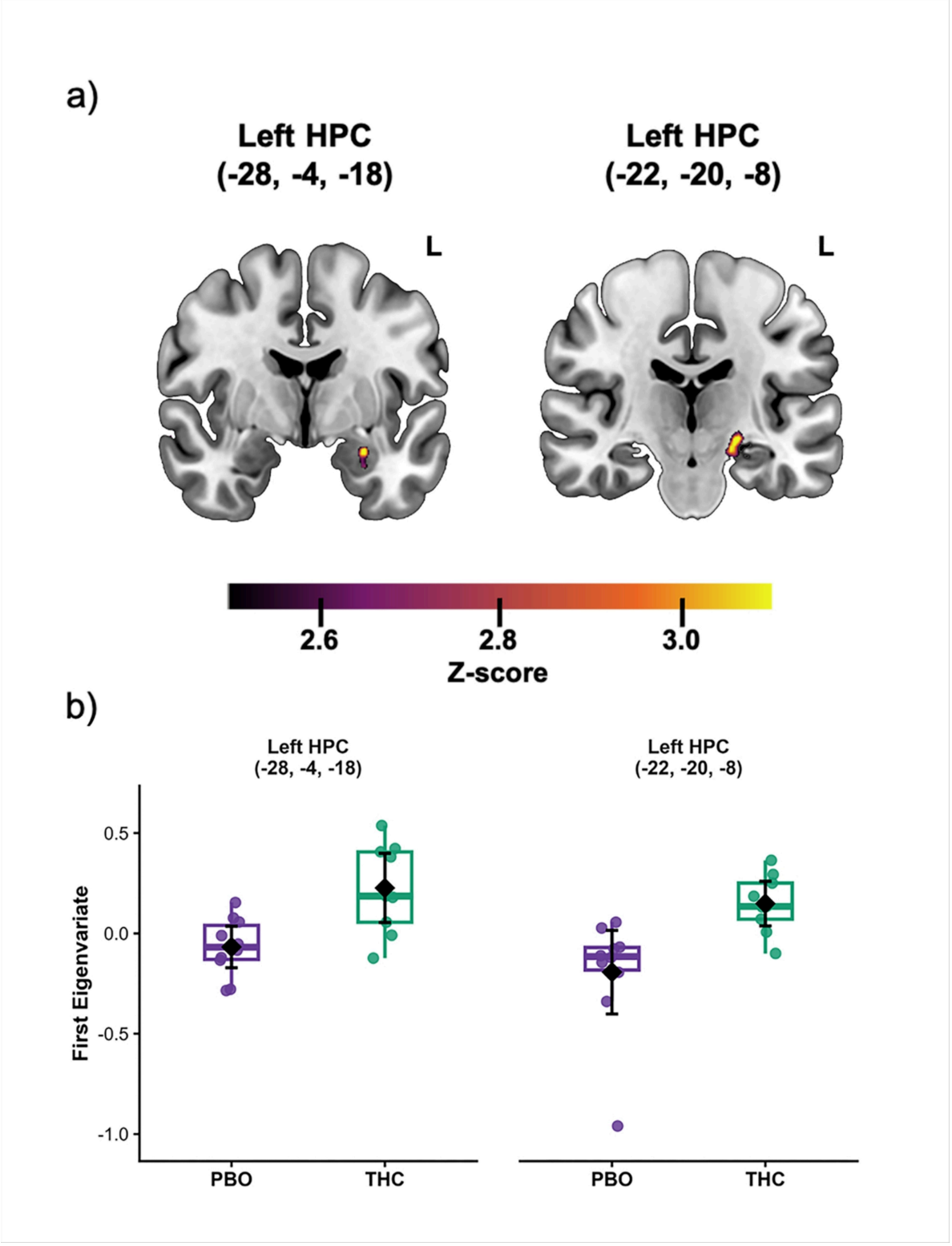


Figure 3

Hippocampal activation during post-treatment early extinction recall. (a) Significant left hippocampal (HPC) clusters identified in literature-based small-volume correction analyses of the post-treatment early extinction recall contrast (CS+E – CS+U). Statistical maps are displayed on a standardized anatomical template. Color bar represents Z-statistic values. (b) Extracted first eigenvariates from 5-mm-radius spheres centered on the peak voxel of each significant HPC cluster. Individual points represent participant-level values. Diamonds indicate drug condition means and error bars represent 95% confidence intervals. Participants receiving delta-9-tetrahydrocannabinol (THC; green) exhibited greater activation than participants receiving placebo (PBO; purple) in both HPC clusters.

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