A Mindfulness-Based Intervention to Reduce Altered Brain Reward Function in Cannabis Use Disorder: A Double-Blind, Active and Passive, Randomised Controlled fMRI Trial

Emillie Beyer
Australian Catholic University
Martine Skumlien
King's College London
Govinda Poudel
Australian Catholic University
Arush Honnedevasthana Arun
Australian Catholic University
Eugene McTavish
Australian Catholic University
Hannah Thomson
Australian Catholic University
Hannah Sehl
Australian Catholic University
Rebecca Segrave
Monash University
Adam Clemente
Australian Catholic University
Izelle Labuschagne
Australian Catholic University
Peter Rendell
Australian Catholic University
Gill Terrett
University of Queensland
Lisa-Marie Greenwood
Australian National University College of Health and Medicine, The Australian National University
Victoria Manning
Turning Point, Monash University
Tom P. Freeman
Addiction and Mental Health Group (AIM), University of Bath
Sunjeev K. Kamboj
University College London
Chao Suo
Monash University
Valentina Lorenzetti
valentina.lorenzetti@gmail.com

Australian Catholic University

Research Article

Keywords:

Posted Date: December 16th, 2025

DOI: https://doi.org/10.21203/rs.3.rs-8283090/v1

Additional Declarations: Competing interest reported. - Ms Emillie Beyer reports no financial relationships with commercial interests. - Dr Martine Skumlien reports no financial relationships with commercial interests. - Dr Govinda Poudel is the founder, director and CTO of BrainCast Pty Ltd which has developed novel brain imaging markers for monitoring brain injury. - Arush Honnedevasthana Arun reports no financial relationships with commercial interests. - Dr Eugene McTavish reports no financial relationships with commercial interests. - Dr Hannah Thomson contracts for Syneos Health Learning Solutions, with the Insights and Evidence Generation Team in Patient Insights and Assessment Research (Implementation Science). - Dr Hannah Sehl reports no financial relationships with commercial interests. - Dr Rebecca Segrave has no financial relationships with commercial interests - Dr Adam Clemente reports no financial relationships with commercial interests. - Dr Izelle Labuschagne is the founder and director of Complete Thesis Support, which provides developmental programs for research students. - Professor Peter Rendell reports no financial relationships with commercial interests. - Associate Professor Gill Terrett reports no financial relationships with commercial interests. - Dr Lisa-Marie Greenwood reports no financial relationships with commercial interests. - Dr Victoria Manning was the Founder, CEO, Director and a shareholder of Cognitive Training Solutions Pty Ltd between March 2021 and Aug 2023, which commercialised the SWiPE app which delivers Cognitive Bias Modification to reduce alcohol use. - Professor Sunjeev Kamboj reports no financial relationships with commercial interests. - Professor Tom Freeman reports no financial relationships with commercial interests. - Dr Chao Suo reports no financial relationships with commercial interests. - Professor Valentina Lorenzetti reports no financial relationships with commercial interests.

Abstract

Cannabis Use Disorder (CUD) affects ~50 million individuals worldwide and is associated with alterations in brain reward pathways. Mindfulness-based interventions (MBIs) show promise in reducing substance use and aberrant brain function in substance use disorders (SUD), but the effects on CUD or brain reward function have not been investigated. To examine whether a 2-week MBI vs. active control (i.e., closely matched relaxation) and passive control (i.e., no intervention) affected brain reward function in CUD using the Monetary Incentive Delay fMRI task, 49 individuals with moderate-to-severe CUD were randomised to: a 2-week MBI (n = 18), active control condition (n = 15), or passive control condition (n = 16), and assessed before and after the intervention. The effect of intervention-by-time was analysed using an exploratory whole-brain approach and a priori regions-of-interest approach (ROIs; ventral striatum, dorsal caudate, putamen, insula, cingulate, and orbitofrontal cortices). Whole-brain results revealed significant intervention-by-time effects. Post-MBI, there was: decreased cerebellum activity while anticipating monetary cues, increased parietal activity while receiving monetary wins, and decreased fusiform/superior frontal gyri (SFG) activity while receiving monetary wins. Post-relaxation, activity increased in several regions (i.e., hippocampus, insula, parietal cortex, fusiform, and SFG) during the receipt of monetary wins. Post-no intervention, activity increased in the cerebellum while anticipating monetary cues, and decreased in other areas (i.e., parietal cortex, hippocampus, and insula) while receiving monetary wins. There were no significant intervention-by-time effects using the ROI approach. Overall, MBI, matched relaxation, and no intervention may share changes in partially overlapping brain regions in distinct directions.

1. Introduction

Cannabis use disorder (CUD) affects ~ 50 million people globally (Leung et al., 2020; United Nations Office on Drugs and Crime, 2024). CUD has been associated with frequent attempts to cut down or quit use (Hughes et al., 2016), affective flattening, apathy, anhedonia (Skumlien et al., 2021), and a high risk of relapse (Connor et al., 2021). Prominent neuroscientific theories posit that addiction is underscored by altered prefrontal-striatal-insular brain function during reward processing (e.g., dorsal and ventral striatum, insula, anterior cingulate cortex [ACC], and orbitofrontal cortex [OFC]), which manifests as increased response to drug reward and decreased response to non-drug reward (Everitt & Robbins, 2016; Koob & Volkow, 2016; Robinson & Berridge, 2025). Although these theories are primarily based on substances other than cannabis, altered brain reward function has been documented in people who consume cannabis and meet criteria for CUD (Beyer et al., 2024; Skumlien et al., 2021), including more severe forms of CUD (Beyer et al., under review). Specifically, in CUD, changes in brain activity during the *receipt of monetary wins* have been reported in selected brain pathways (Beyer et al., under review) implicated in habit formation (e.g., dorsal striatum) and interoception (e.g., insula; Everitt & Robbins, 2016; Koob & Volkow, 2016). As such, it is imperative to explore new interventions that target potentially aberrant brain reward function in CUD.

Mindfulness-based interventions (MBIs) involve directing individuals to pay attention to the present moment and their experience without judgment or attachment (Kabat-Zinn, 2003). MBIs have been suggested to target brain pathways implicated in addiction-relevant cognitive processes, including: interoception (e.g., insula), habit formation (e.g., dorsal striatum), memory (e.g., hippocampus), metacognitive attention (e.g., ACC, and parietal cortex), and reappraisal (e.g., OFC; Garland & Howard, 2018). Further, MBIs have been proposed to help restore reward processing (e.g., in prefrontal-striatal pathways) by shifting attention away from drug-related rewards back to natural rewards that were salient before addiction developed (Garland et al., 2014). Only three studies have examined MBIs in cannabis users (de Dios et al., 2012; Schneegans et al., 2022; Stanger et al., 2025). de Dios et al. (2012) found that after two face-to-face sessions of MBI (combined with motivational interviewing), the number of days cannabis was used was significantly lower at the 3-month follow-up. The other two studies found no significant differences between MBIs and treatment as usual in people who used cannabis regularly (Schneegans et al., 2022; Stanger et al., 2025). Meanwhile, emerging functional neuroimaging (fMRI) evidence examining the neurobiological changes underlying MBIs for SUDs has shown changes in brain activity in prefrontal-striatal pathways (e.g., striatum, ACC; Lorenzetti et al., 2023); and MBI-related brain changes were associated with lower drug quantity, lower drug craving, and greater mindfulness levels (Lorenzetti et al., 2023). Yet, how MBIs affect brain reward function in CUD remains unexamined.

Despite the potential for improved brain outcomes in SUDs, to date, none of the fMRI studies that examined the impact of MBIs on brain integrity included participants who were confirmed to meet criteria for a CUD. Furthermore, the evidence lacks repeated-measures studies using active and passive control interventions, which have prevented an assessment of MBI-specific changes. As a result, fMRI research with rigorous designs is needed to understand how MBIs influence brain reward function in CUD.

To address this gap, the primary aim of this study was to investigate whether a brief MBI targeting cannabis craving, compared to a closely-matched active control condition (i.e., relaxation) and passive control (i.e., no intervention), could change brain reward function in people with a moderate-to-severe CUD, who have tried to cut down or quit using cannabis in the past 24 months. In line with evidence on MBI-related brain changes in SUDs (Lorenzetti et al., 2023), it was hypothesised that a MBI, compared to an active and a passive placebo, would change brain reward function in regions implicated in addiction, and in MBI-targeted processes, including reward processing (e.g., striatum), interoception (e.g., insula), memory (e.g., hippocampus), metacognitive attention (e.g., ACC, parietal cortex), and reappraisal (e.g., OFC; Garland & Howard, 2018). The secondary aim was to explore how intervention-related brain changes correlated with measures of intervention compliance, MBI, relaxation, and cannabis use-related metrics, including cannabis use over the past two weeks.

2. Experimental Procedures

This study was nested within a larger pre-registered project (http://www.isrctn.com/ISRCTN76056942), and received ethical approval by the Australian Catholic University Human Research Ethics Committee (HREC ID: 2019-71H).

2.1 Participants

Participants were recruited from the general community in the Melbourne metropolitan area via online advertisements (e.g., Facebook) and local flyers between 2019 and 2022. We recruited adults aged 18–55 years, who (i) met DSM-5 criteria for moderate-to-severe CUD, defined as four or more symptoms, confirmed by the Structured Clinical Interview for DSM-5 (SCID-5-RV; First et al., 2015), (ii) had attempted to quit cannabis use at least once in the last 24 months month, and (iii) used cannabis daily or almost daily in the last 12 months. A detailed description of the study's inclusion and exclusion criteria is outlined in Supplementary Section 1.1.

2.2 Testing Protocol

The testing protocol included three phases: i) baseline face-to-face assessment, which included pre-intervention testing, and concluded with the administration of the first brief intervention session, ii) 2-week off-site intervention, and iii) follow-up face-to-face assessment, ~ 2 weeks later, starting with the delivery of the last brief intervention session and continuing with the post-intervention assessment. Face-to-face testing was conducted at the Monash Biomedical Imaging facility in Clayton, Melbourne, Australia.

2.3 Randomisation and Blinding

To investigate the effects of MBI vs. active placebo vs. passive placebo on brain reward function, a double-blind, randomised control trial (RCT) was conducted. Participants and outcome assessors were blind to participants' allocation to either of the three intervention conditions, which were assigned by a study co-ordinator who was not involved in blinded data collection. The study co-ordinator implemented block randomisation stratified by age (i.e., 18–24, 25–35, 36–55) and sex (i.e., males and females), assigning participants to groups in a 1:1:1 ratio. Senior researchers and trained student researchers were blind to participant allocation for the non-intervention section of the assessment, and an unblinded researcher conducted the intervention component of the study. Participants and researcher blinding was achieved through personnel and documentation that referred to all conditions as 'daily task' or 'brief strategies' and the 'BrainCann study', without mentioning 'mindfulness' or 'relaxation'.

2.4 Face-to-face Testing Procedure

A detailed description of the testing measures and intervention protocol is outlined in Supplementary Sections 1.2–1.3.

2.4.1 Baseline Assessment

The face-to-face baseline assessment lasted ~ 5 hours and included several assessments in addition to the ones described below, which are outlined in the study's registration.

2.4.1.1 Baseline: Pre-Intervention

Participants were required to provide a urine sample to confirm the level of cannabis metabolites, specifically 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid: creatinine (THC-COOH: creatinine). The pre-intervention session consisted of: i) study explanation, questions and participants written informed consent; ii) MRI safety protocols and MRI scan including the MID fMRI task to measure brain reward function; iii) semi-structured interviews relating to substance use, CUD; iv) IQ testing; v) self-reported questionnaires measuring substance use, mental health, and mindfulness.

2.4.1.2 Baseline: First Delivery of Intervention, at the End of Testing

The unblinded researcher, who was aware of participants' group allocation, instructed the participants on how to complete the intervention for the first time. All participants received a link to where they could access their assigned audio-recorded intervention. A backup USB stick containing the intervention recording was also provided in case they did not have access to Wi-Fi. The intervention is described in the section below.

2.4.1.2.1 Content of the Interventions

The practices involved listening to a 7-minute audio recording of either mindfulness or relaxation instructions, which were adapted from previous scripts used with hazardous drinkers (Kamboj et al., 2017) and were tailored for cannabis. The intervention scripts are provided in the Supplementary Section 1.4, Table 1.

2.4.2 Follow-up Face-to-Face Assessment

The follow-up face-to-face assessment, conducted after the 2-week intervention, was largely identical to that of the baseline assessment, with a few noted exceptions.

The intervention (i.e., MBI or relaxation) was completed at the start of follow-up testing, directly after participants provided informed consent. Second, some measures were not re-administered at follow-up as they were redundant (i.e., socio-demographic data, lifetime of cannabis use history) or not sensitive to change (e.g., IQ, Structured Clinical Interview for DSM-5 Research Version [SCID-5-RV]). The follow-up testing concluded with debriefing and reimbursing all participants with a A$150 Coles-Myer voucher.

2.5 Two-Week Intervention between Baseline and Follow-Up

Three intervention conditions (i.e., MBI, relaxation, and no intervention) were conducted off-site, daily for ~ 2 weeks between baseline and follow-up face-to-face testing. The MBI and relaxation conditions were delivered via the 7-minute audio file. Participants in the no intervention condition did not complete an intervention, but like those in the MBI and relaxation conditions, they completed daily items measuring cannabis consumption.

2.6 Statistical Analysis

All behavioural data analyses and correlations were run using SPSS (version 30).

2.6.1 Sociodemographic Descriptives

Normality checks were conducted for each socio-demographic variable (Supplementary Section 1.5). A series of ANOVAs were used to examine the effects of the intervention conditions (i.e., MBI, relaxation, no intervention), time (i.e., baseline and follow-up), and intervention-by-time on socio-demographic data for context.

2.7 Neuroimaging Procedure

All participants were scanned using a 3T Skyra MRI scanner at the Monash Biomedical Imaging facility, using acquisition parameters outlined in Supplementary Section 1.16.

2.7.1 Monetary Incentive Delay (MID) fMRI Task

A modified version of the original MID fMRI task (Knutson et al., 2001) was used to measure brain reward function during the anticipation and receipt of monetary rewards, illustrated in Fig. 1 (Hoogendam et al., 2013). The instructions for the MID task are in Supplementary Section 1.7.

2.7.2 fMRI Task Design

The fMRI task ran for 9 minutes and 36 seconds. Participants underwent 20 practice trials to confirm their understanding of the task and to adjust the task to each participant's mean reaction times (RTs). The fMRI task was programmed to allow participants to press the button fast enough to win approximately 50% of the trials, which were presented in randomised order (i.e., 15 reward trials out of 30, same for the neutral trials).

During the 30 neutral trials, participants were able to *win* if they hit the button fast enough, but they did not receive any money. Participants completed 30 reward trials, represented by a smiley face cue, and 30 neutral trials, represented by a neutral face. Each cue was presented for 750 ms. Then, a *star symbol* appeared for a mean duration of 3,286 ms (range: 779-6,729 ms), indicating the task's anticipatory phase, followed by an *inter-trial interva*l with a mean duration of 3,535 ms (range: 1,029 – 6,979 ms). Then, participants saw an *exclamation mark*, which indicated that they needed to press a button as quickly as possible to be able to win if they were fast enough. Finally, participants received *feedback* on their performance on the screen, including whether they won money and their cumulative total. Participants could win a total of A$15. This was virtual money; participants understood they would not receive this sum in actual A$ (see Fig. 1).

2.8 fMRI Data Analyses

The data was pre-processed and quality-checked using fMRI prep https://fmriprep.org/en/stable/ (Esteban et al., 2019). Supplementary Section 1.8 outlines fMRI data pre-processing and extraction of ROI data values.

2.8.1 First Level Analysis

We examined three contrasts: i) *anticipation of monetary cues vs. anticipation of neutral cues*, ii) *receipt of monetary wins vs. receipt of neutral wins*, and iii) *receipt of monetary wins vs. receipt of monetary missed wins*. A detailed description of the first-level analysis is outlined in Supplementary Section 1.8.2.

2.8.2 Second-level Analysis: Whole Brain Voxel-Wise

The main statistical tests were conducted using a flexible factorial design in SPM version 12, with the following factors: intervention condition (i.e., MBI, active placebo, passive placebo), time (i.e., baseline, follow-up), and intervention-by-time effect (2 x 3 = 6 levels). Age and sex were included as covariates. Significant intervention-by-time interactions were examined using an *F*-contrast, with cluster-level family-wise error (FWE) corrections at $p = 0.05$, with an initial cluster-defining threshold of $p = 0.001$ and a minimum cluster size of 40 voxels. Values from the significant area were extracted from the whole-brain analyses, and a line plot was created to illustrate the direction of the effect. Post-hoc analyses were used to examine the within-group changes.

2.8.3 ROI Analysis

ROI analyses were performed in a priori regions (i.e., ventral striatum, insula, putamen, dorsal caudate, ACC, and OFC) identified as crucial for brain reward function, during anticipation of rewards and receipt of rewards, by previous work administering the MID fMRI task to normative samples (Chen et al., 2022; Hoogendam et al., 2013; Oldham et al., 2018).

ROIs were defined using the Anatomic Automatic Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and generated using the WFU PickAtlas Toolbox implemented in SPM (version 12). Specifically, the ventral striatum and dorsal caudate were defined as parts of the caudate nucleus located above and below the Z = 0 mm plane. The OFC included the orbital sections of both the middle and superior frontal gyri. The ACC comprised the anterior and medial parts of the cingulate cortex. All other ROIs matched the anatomical regions defined in the AAL atlas. All ROIs were visualised on representative MNI slices at y = 8 (coronal) and z = -8 (axial) (Supplementary Section 1.8.3, Fig. 1). Mean beta values within each ROI were extracted by overlapping the ROI masks with the three contrast-of-interest maps generated at the first-level analysis.

We ran separate repeated-measures analysis of covariance (ANCOVAs) for each ROI, with time as a within-subjects factor (i.e., baseline, follow-up), intervention condition as a between-subjects factor (i.e., MBI, active placebo, passive placebo), and age and sex as covariates.

2.8.4 Brain-Behaviour Correlations

Spearman's rank correlations were run to investigate if any significant brain changes that occurred pre-to-post each intervention condition correlated with measures of: (i) intervention compliance, measured by the number of days the audio track was listened to, divided by the total duration of intervention days, and converted into a percentage; (ii) mindfulness measures (i.e., ΔTMS [administered pre-intervention at follow-up *minus* pre-intervention at baseline]), (iii) relaxation measures (i.e., ΔVAS relaxation; [administered pre- intervention at follow-up *minus* pre-intervention at baseline]), and (iv) perceived stress (i.e., ΔPSS; at follow-up *minus* baseline).

3. Results

3.1 Sample Characteristics

Table 1 outlines the baseline sample socio-demographic, substance use, and mental health characteristics in N = 49 participants with a moderate-to-severe CUD (15 females, 34 males), with a mean age of 27 years (range: 18 – 56 years). Participants were allocated to either MBI (*n* = 18), relaxation (*n* = 15), or no-intervention (*n* = 16).

Table 1. *Overview of Mean (SD) or Median [range] Socio-Demographic, Substance Use and Mental Health Characteristics at Baseline*

Variable		MBI	Relaxation	No Intervention
N, total [F]		18 [5]	15 [5]	16 [5]
Age, yrs		27.63 (7.51)	28.87 (9.03)	25.44 (5.33)
Handedness [Left]		18 [1]	15 [1]	16 [2]
Education, yrs		14.32 (2.52)	15.26 (2.15)	16.72 (3.16)
IQ (WASI-II)		108.46 (9.73)	105.13 (8.90)	104.60 (9.68)
Alcohol	AUDIT	7.39 (4.86)	5.60 (3.83)	8.87 (4.44)
	use days/month	7.22 (7.15)	3.47 (3.25)	8.75 (8.12)
	Standard drinks/month	37.43 (56.36)	20.93 (35.48)	42.79 (57.37)
Nicotine	FTND	1.28 (2.14)	1.33 (1.63)	1.00 (1.46)
	Days/month	17.17 (15.50)	14.50 (13.29)	12.00 (13.90)
	N cigarettes/vapes/month	130.90 (230.96)	78.00 (84.16)	53.58 (92.12)
Cannabis	CUD symptoms N	7.22 (1.66)	7.07 (2.09)	6.94 (2.02)
	CUD (CUDIT)	15.89 (4.83)	17.20 (5.09)	16.13 (5.82)
	Days/past month	27.61 (3.99)	26.00 (4.93)	23.62 (6.09)
	Grams/past month	29.64 (23.59)	29.37 (23.87)	21.00 (16.73)
	Age of first use, years (CUI)	17.45 (4.25)	15.72 (1.74)	16.79 (2.04)
	Age of regular use, years (CUI)	19.30 (4.91)	17.43 (2.20)	19.33 (2.95)
	Hour last use	16.23 (1.62)	25.06 (15.16)	23.64 (15.45)
	Withdrawal (CWS)	37.89 (29.86)	37.93 (28.22)	30.00 (28.49)
	Motivation Ladder	5.50 (1.76)	4.53 (2.13)	5.80 (1.61)
	THC-COOH:creatinine ng/mg	222.89 (243.40)	259.17 (195.19)	178.50 (228.28)
Apathy (AES)		30.83 (6.45)	30.67 (8.00)	33.27 (7.65)
Intervention	Duration, days	9.22 (3.37)	9.73 (3.84)	11.00 (2.48)
	Compliance %	53.93 (18.05)	62.63 (27.34)	75.98 (15.62)

Note. *N* = sample size; *SD* = standard deviation; F= Female; WASI-II = Wechsler Abbreviated Scale of Intelligence, 2nd Edition; AUDIT = Alcohol Use Identification Test; /month = in the past month; Age of Onset and Age of Regular Use was measured by Cannabis Use Intervention [CUI], Cannabis/nicotine/alcohol days/hours/grams per month measured by Timeline Follow-Back [TLFB]; CUD symptoms measured by Structured Clinical Interview for DSM-5 Research Version [SCID-5-RV]; CWS = Cannabis Withdrawal Scale; Motivation to Change measured by the Marijuana Ladder [ML]; *FTND* = Fagerström Test for Nicotine Dependence; THC-COOH = 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid; ng/mg = nanograms per milligram.

3.1.1 Cannabis Use, Mental Health, and Mindfulness Characteristics

Table 2 presents descriptives that were measured at baseline and follow-up, by intervention condition, time, and intervention-by-time. There were no significant effects on sample characteristics, except for an intervention effect whereby the MBI condition showed significantly greater cannabis use days over the past 2 weeks than the no-intervention condition (i.e., mean difference of 2.47 days).

Table 2. *Overview of Mean (SD) and Median [Range] for Sample Characteristics Measured at Baseline and Follow-Up for the MBI, Relaxation, and No Intervention Conditions*

Variables			MBI		Relaxation	No Intervention	Intervention		Time		Intervention*Time	
							F(df=2)	*p*	*F(df=1)*	*p*	*F(d=2f)*	*p*
Cannabis		Days/past ~2weeks	BL	14.83 (4.71)	14.15 (3.16)	12.07 (3.05)	3.86	.025*	1.04	.310	.02	.977
			FU	13.78 (4.75)	13.53 (4.82)	11.13 (3.36)						
		Grams/past ~2weeks	BL	15.74 (15.65)	21.03 (18.76)	11.87 (5.96)	2.96	.057	1.08	.302	.12	.885
			FU	14.5 (15.46)	17.28 (20.61)	7.03 (5.40)						
		Hour last use	BL	16.23 (1.62)	25.06 (15.16)	23.64 (15.45)	.09	.916	.19	.661	1.48	.233
			FU	26.57 (34.08)	20.63 (14.47)	22.66 (10.67)						
		Withdrawal (CWS)	BL	37.89 (29.86)	37.93 (28.22)	30.00 (28.49)	.96	.387	.39	.534	.04	.958
			FU	40.50 (28.28)	44.27 (34.27)	32.40 (28.10)						
Mental Health		Depression (BDI-II)	BL	12.17 (6.05)	9.93 (6.99)	9.60 (7.39)	.15	.858	.82	.366	.92	.403
			FU	8.22 (5.56)	10.47 (7.41)	9.07 (9.00)						
		State anxiety (STAI-Y)	BL	34.56 (10.19)	31.53 (5.93)	29.60 (8.69)	2.31	.105	.18	.674	.05	.948
			FU	34.61 (9.09)	33.00 (7.36)	30.33 (9.80)						
		Perceived stress (PSS)	BL	18.00 (8.49)	14.47 (6.00)	14.40 (7.98)	2.47	.091	.89	.347	.10	.905
			FU	19.33 (8.25)	16.87 (6.48)	15.07 (7.57)						
Mindfulness	**TMS**	pre-decentring	BL	13.22 (4.57)	14.20 (4.97)	13.63 (5.57)	.10	.914	.20	.644	.10	.922
			FU	13.17 (5.32)	13.20 (4.43)	13.31 (4.00)						
	FFMQ	observing	BL	27.22 (6.37)	28.00 (5.69)	25.20 (6.65)	2.02	.139	.03	.862	.14	.868
			FU	28.33 (5.47)	27.67 (4.81)	25.07 (6.99)						
		describing	BL	30.61 (5.54)	29.27 (6.57)	26.73 (8.08)	1.45	.239	.01	.930	.23	.792
			FU	29.17 (7.13)	29.60 (6.61)	27.47 (7.74)						
		awareness	BL	26.17 (4.89)	27.33 (6.50)	25.93 (7.51)	.24	.787	.42	.518	.04	.965
			FU	25.33 (4.91)	26.07 (6.97)	25.53 (6.89)						
		non-judging	BL	27.33 (8.52)	27.07 (7.29)	26.80 (8.28)	.02	.978	1.22	.272	.00	.996
			FU	29.06 (7.79)	28.73 (7.70)	28.80 (7.85)						
		non-reactivity	BL	21.50 (4.74)	22.53 (4.12)	23.40 (5.29)	1.70	.189	.09	.766	.02	.983
			FU	21.56 (4.95)	22.87 (4.24)	23.87 (4.39)						

Relaxation (VAS)	Pre-audio session	BL	6.44 (2.41)	7.20 (2.18)	7.56 (2.28)	1.42	.248	.29	.594	1.09	.341
		FU	7.44 (1.79)	6.60 (2.53)	7.88 (1.93)						
MID Reaction Times	Smile	BL	239.32 (17.67)	241.23 (26.13)	241.14 (20.65)	1.08	.344	.19	.142	1.47	.235
		FU	256.01 (26.02)	251.14 (32.61)	237.15 (21.35)						
	Neutral	BL	247.41 (25.60)	244.43 (30.51)	253.20 (47.67)	.35	.704	.01	.929	1.62	.204
		FU	254.65 (28.67)	253.11 (28.95)	235.49 (25.45)						

Note. *SD* = standard deviation; *F* = F-statistic; *df* = degrees of freedom; month = in the past month; CUD severity was measured by the CUIDT [Cannabis Use Disorders Identification Test]; Cannabis/nicotine/alcohol days/hours/grams per month measured by Timeline Follow-Back [TLFB]; CUD symptoms measured by Structured Clinical Interview for DSM-5 Research Version [SCID-5-RV]; CWS = Cannabis Withdrawal Scale; *FTND* = Fagerström Test for Nicotine Dependence; BDI-II = Beck Depression Index – II; STAI-Y = Spielberger State-Trait Anxiety Index – Y; PSS = Perceived Stress Scale; FFMQ = Five-Factor Mindfulness Questionnaire; TMS = Toronto Mindfulness Scale; VAS = Visual Analog Scale.

3.2 fMRI Results: ROI Analysis

There were no significant effects of intervention condition, time, or intervention-by-time on the a-priori ROIs, including the ventral striatum, insula, putamen, dorsal caudate, ACC, and OFC (Supplementary Section 2.1, Tables 2-4).

3.3 fMRI Results: Whole-Brain Analysis

Table 3 overviews the intervention-by-time effects on brain activity using exploratory whole-brain analysis. In brief, MBI, active placebo, and no intervention showed changes in brain activity in partially overlapping brain pathways and directions. Supplementary Section 2.2 overviews whole-brain post hoc analyses and specifies the location and strength of peak cluster activation.

Table 3. *Overview of the Results from Whole-Brain Analysis Examining the Effects of the Interventions Pre-to-Post MBI vs. Relaxation vs. No Intervention on Brain Reward Function*

	Contrast	Regions	D (post *minus* pre)			Comparison of absolute D (post *minus* pre) between interventions		
			MBI	Relaxation	No intervention	D MBI vs. D Relaxation	D MBI vs. D No intervention	DRelaxation vs. DNo intervention
Anticipating Monetary Cues > Anticipating Neutral Cues		cerebellum (left)	¯	=		=	MBI < no intervention	=
Receipt of Monetary Wins >	***Receipt of Neutral Wins***	parietal (right)			¯	=	MBI < no intervention	=
		hippocampus (right), insula (left; superior left), parietal (right; left; middle left)	=		¯	=	=	Relaxation < no intervention
	Receipt of Missed Wins	parietal (right), fusiform gyrus (right), SFG (right)	¯		¯	MBI < relaxation	=	=

Note. ¯ = decrease; = increase; D = change (post *minus* pre); MBI = mindfulness-based intervention; SFG = superior frontal gyrus.

3.3.1 Anticipation of Monetary Cues vs. Anticipation of Neutral Cues

3.3.1.1 Cerebellum (left)

As shown in Figure 2, there was a significant effect of *intervention-by-time* on the activity of the left cerebellum during the *anticipation of monetary cues vs. neutral cues.* Specifically, cerebellar activity decreased post-MBI ($p < 0.05$; $d = 1.01$; large effect size), did not change post-relaxation, and increased post-no intervention ($p < 0.05$; $d = 1.07$; large effect size). The extent of cerebellar activity change was lower in the MBI condition compared to the no intervention condition (Table 3).

3.3.2 Receipt of Monetary Wins vs. Receipt of Neutral Wins

3.3.2.1 Parietal cortex (right)

As shown in Figure 5, during the *receipt of monetary wins vs. neutral wins,* there was a significant effect of *intervention-by-time* on the right parietal cortex. Specifically, parietal activity increased, with medium effect sizes, post-MBI and post-relaxation ($p < 0.05$; $d = 0.76$ and $p < 0.05$; $d = 0.72$, respectively). Meanwhile, parietal activity decreased post-no intervention, with a large effect size ($p < 0.001$; $d = 1.49$). The extent of parietal activity change was lower in the MBI condition than in the no intervention condition (Table 3).

3.3.2.2 Hippocampus, Insula, and other Parietal Regions

As shown in Figure 6, in the MBI group, there was no significant intervention-by-time effect on brain activity when *receiving monetary wins vs. neutral wins*. Instead, post-relaxation and post-no intervention, there were significant intervention by-time effects on the hippocampus, insula, and parietal cortex, all with large effect sizes ($p < 0.001$; $d = 0.96$-2.1) with one exception (i.e., insula, $p < 0.001$; $d = 0.71$). In these regions, activity increases post-relaxation and decreases post-no intervention. The extent of hippocampus/insula/parietal activity change was lower in the relaxation condition compared to the no intervention condition (Table 3).

3.3.3 Receipt of Monetary Wins vs. Receipt of Monetary Missed Wins

3.3.3.1 Parietal Cortex, SFG, and Fusiform Gyrus

As noted in Figure 7, there was a significant *intervention-by-time effect* on several regions when *receiving monetary wins vs. missed wins*. Post-MBI, brain activity decreased in the right *parietal cortex* and the right *SFG* with strong effect sizes ($p < 0.001$; $d = 1.2$ and $p < 0.05$; $d = 1.1$) and in the right *fusiform gyrus,* with a medium effect size ($p < 0.05$; $d = 0.77$). Post-relaxation, brain activity increased in the right *parietal cortex, SFG, and fusiform gyrus* ($p < 0.001$; $d = 1.3$, $p < 0.01$; $d = 1.5$, and $p < 0.01$; $d = 1.4$, respectively). The extent of parietal/SFG/fusiform activity change was lower in the MBI condition compared to the relaxation condition (Table 3).

3.4 Exploratory Correlations

There were no significant correlations between the brain changes pre-to-post each of the intervention conditions and any of the measures of intervention compliance, changes in mindfulness/relaxation measures (i.e., DTMS, DVAS relaxation), perceived stress (DPSS), and cannabis days/past ~2 weeks.

4. Discussion

This is the first RCT to examine whether a brief MBI that targets craving can change brain reward function in CUD, employing a robust double-blind approach and controlling for active placebo and no intervention conditions. We found that post-MBI and post-no intervention, during the *anticipation of monetary wins*, there were changes in the activity of the cerebellum, an integral part of the reward neurocircuitry (Moulton et al., 2014; Ranjbar et al., 2021). During the *receipt of monetary wins*, overlapping brain regions implicated in metacognitive awareness and higher-order cognitive control (i.e., parietal cortex, SFG, fusiform gyrus) showed differential brain activity changes as a function of the intervention, with decreases post-MBI and post-no intervention, and increases post-relaxation in all three intervention conditions (Garland & Howard, 2018; Jiang et al., 2011; Li et al., 2013). Further, during the *receipt of monetary wins*, the activity of the hippocampus, insula, and other parietal cortices involved in MBIs for addiction changed post-relaxation and post-no intervention (Garland & Howard, 2018). Overall, MBI, matched active control, and no intervention may share changes in partially overlapping brain regions (Luberto et al., 2020); therefore, highlighting the importance of using robust control conditions to disentangle MBI-specific effects.

4.1 Mindfulness-Based Intervention

In line with the hypothesis, MBI was associated with changes in the parietal cortex, a region implicated in metacognitive attention (Garland & Howard, 2018). Additionally, post-MBI, activity decreased in brain regions not consistently reported in prominent theories of MBI for SUDs (Garland & Howard, 2018), but yet implicated in the neurobiology of cannabis use (Blest-Hopley et al., 2019; Blithikioti et al., 2019) and in cognitive processes altered in addiction: higher-order cognitive control (i.e., parietal cortex, SFG, fusiform gyrus; Jiang et al., 2011; Li et al., 2013), and reward processing (i.e., cerebellum; Moulton et al., 2014; Ranjbar et al., 2021). Therefore, a brief MBI targeting craving (and other interventions discussed below) may affect core components of the reward neurocircuitry, as previously suggested (Boccia et al., 2015; Lorenzetti et al., 2023; Witkiewitz et al., 2013). Perhaps the inconsistent location of changes reported herein and neurobiological theories of MBIs for SUDs, is due to differences in the

parameters of the brief MBI we used in this experiment, and those of previously examined MBIs, which lasted longer (e.g., ~ 2 months) and included samples using substances other than cannabis (e.g., nicotine, cocaine, prescription opioids; Garland & Howard, 2018). Future studies are required to examine if the effects reported here are specific to the brief MBI implemented or if they generalise to other MBIs.

4.2 Relaxation

The relaxation condition was included as an active control, as it is not generally considered an important component of *bona fide* therapies that is responsible, in isolation, for changes in substance use. Post-relaxation, brain activity increased during *the receipt of monetary wins* in brain pathways also implicated in cognitive processes aberrant in addiction: disinhibition (i.e., parietal cortex, SFG; Chye et al., 2022; Knutson et al., 2015), stress (i.e., hippocampus; Kutlu & Gould, 2016; Wingenfeld & Wolf, 2014), interoception (i.e., insula; Naqvi & Bechara, 2010), and facial/salience processing (i.e., fusiform gyrus; Palejwala et al., 2020). Interestingly, the brain regions where activity changed post-relaxation have previously been shown to be affected by MBIs in addiction (e.g., hippocampus, insula, parietal cortex; Garland et al., 2014; Garland & Howard, 2018; Witkiewitz et al., 2013). Therefore, the relaxation intervention aimed at reducing cravings might also be effective in improving reward brain dysfunction in CUD.

4.3 No intervention

The no intervention condition was associated with increased cerebellar activity during the *anticipation of monetary cues*; and decreased activity in other regions during the *receipt of monetary wins* including: the hippocampus, insula, parietal cortex, SFG, and fusiform gyrus. Importantly, all these regions are broadly implicated in high-order cognitive, emotional, and sensorimotor functions (Beuriat et al., 2022; Jiang et al., 2011; Li et al., 2013; Namkung et al., 2017; Rubin et al., 2014). Of note, the same regions were also affected by MBI, active placebo relaxation, or both. Therefore, our results highlight the importance of using passive placebo control conditions to identify MBI-specific effects. Future work should consider an additional control group with 'treatment as usual' to disentangle the effect of MBI from that of ‘active’ components of interventions.

4.4 Strengths and Limitations

This study demonstrates MBI-related brain changes in a novel sample of individuals with moderate-to-severe CUD who had tried to cut down or quit using cannabis in the past 24 months, using a double-blind active-and-passive-placebo control design to control for expectancy effects (Misra, 2012). However, several methodological limitations must be considered when interpreting the findings. First, given the small sample size (N = 49), the study findings are preliminary and need to be replicated in larger samples (Turner et al., 2018).

Second, intervention compliance in the MBI condition (~ 54%) was lower than in the relaxation (~ 63%) and the no-intervention condition (~ 76%). Low adherence to MBIs has been shown to reduce treatment effectiveness (Marks et al., 2023). Yet, as the intervention was to be administered daily, our sample adhered to the intervention at least every second day, meaning that participants’ engagement was still notable. As such, low intervention compliance may have limited the ability to detect additional brain functional changes typically associated with addiction. Future MBI studies should consider offering additional incentives/reimbursements that are tied to higher engagement with the intervention.

Finally, participants’ motivation to change their cannabis consumption was largely in the preparation stage (e.g., almost ready) or contemplation stage (e.g., not being ready). Previous research suggests that high motivation is a strong predictor of effective behavioural change in individuals with substance use (Laudet & Stanick, 2010) compared to other treatment adherence (Collins et al., 2012). As such, lower motivation to change might have affected the level of engagement in the MBI.

Conclusion

Overall, post-MBI was selectively associated with changes in only one of the hypothesised regions (i.e., parietal cortex). Meanwhile, for post-relaxation and post-no intervention conditions, changes were observed in the insula and hippocampus, and additional parietal regions involved in MBIs in addiction (Garland & Howard, 2018). The findings suggest that MBI, matched relaxation, and no intervention may share changes in partially overlapping brain regions (Luberto et al., 2020) in distinct directions.

Declarations

Acknowledgments: We thank all participants for their contribution of data and time to the project.We acknowledge Ms Natalie DeBono, Dr Matthijs Vin, Dr Leonie Duehlmeyer and Dr Penny Hartman for contributing to the management of the setting up of the project. We acknowledge Dr Alexandra Gaillard, Ms Marianna Quinones, Ms Stephanie Antopolous, Ms Claire Chua, Dr Leonie Duehlmeyer, Mr Lachlan Grant, Ms Kirsty Kearney, Dr Magdalena Kowalczyk, Ms Emily Robinson, Ms Elizabeth Sharp, and Ms Danielle Tichelaar for their contribution to data collection. We acknowledge Professor Shanlin Fu and the team at the Drugs and Toxicology Group, Centre for Forensic Science, University of Technology Sydney, for conducting urine toxicology analyses.

Disclosures:

Ms Emillie Beyer reports no financial relationships with commercial interests.

Dr Martine Skumlien reports no financial relationships with commercial interests.

Dr Govinda Poudel is the founder, director and CTO of BrainCast Pty Ltd which has developed novel brain imaging markers for monitoring brain injury.

Arush Honnedevasthana Arun reports no financial relationships with commercial interests.

Dr Eugene McTavish reports no financial relationships with commercial interests.

Dr Hannah Thomson contracts for Syneos Health Learning Solutions, with the Insights and Evidence Generation Team in Patient Insights and Assessment Research (Implementation Science).

Dr Hannah Sehl reports no financial relationships with commercial interests.

Dr Rebecca Segrave has no financial relationships with commercial interests

Dr Adam Clemente reports no financial relationships with commercial interests.

Dr Izelle Labuschagne is the founder and director of Complete Thesis Support, which provides developmental programs for research students.

Professor Peter Rendell reports no financial relationships with commercial interests.

Associate Professor Gill Terrett reports no financial relationships with commercial interests.

Dr Lisa-Marie Greenwood reports no financial relationships with commercial interests.

Dr Victoria Manning was the Founder, CEO, Director and a shareholder of Cognitive Training Solutions Pty Ltd between March 2021 and Aug 2023, which commercialised the SWiPE app which delivers Cognitive Bias Modification to reduce alcohol use.

Professor Sunjeev Kamboj reports no financial relationships with commercial interests.

Professor Tom Freeman reports no financial relationships with commercial interests.

Dr Chao Suo reports no financial relationships with commercial interests.

Professor Valentina Lorenzetti reports no financial relationships with commercial interests.

Data availability:

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declaration of funding:

Valentina Lorenzetti was supported by an Al and Val Rosenstrauss Research Fellowship (2022-2026), and by a National Health & Medical Research Council (NHMRC) Investigator Grant (2023-2027, ID 2016833) and an Australian Catholic University competitive scheme.

The work within the Neuroscience of Addition and Mental Health Program, Healthy Brain and Mind Research Centre was supported via an ACU competitive scheme.

Emillie Beyer, Hannah Thomson, and Hannah Sehl were funded by Australian Government Research Training Program (RTP) Stipend scholarships.

Victoria Manning has received funding from the National Health and Medical Research Council (NHMRC), VicHealth, Department of Health Victoria, the Victorian Responsible Gambling Foundation, the National Centre for Clinical Research on Emerging Drugs (NCCRED), HCF, and philanthropic organisations.

Tom Freeman was supported by a UKRI Future Leaders Fellowship (MR/Y017560/1).

Authors contribution

· All authors edited the manuscript.

· EB, under the supervision of VL, GP, and CS, developed the manuscript's theoretical framework, performed fMRI quality checks, analysed neuroimaging data, led statistical behavioural analysis, created the initial draft, and integrated subsequent revisions.

· MS provided high-level and ongoing input on the interpretation of results and edited the first full draft of the manuscript and subsequent drafts.

· GP provided high-level and ongoing input on the study's design and provided high-level input into the fMRI analysis.

· AHA contributed to fMRI quality checks and analyses, with general direction on the technical aspects.

· EM provided input on statistical analyses of the behavioural data.

· HT and HS supported the study setup and collected a substantial portion of the data for the sample.

· RS supported the setup of the monetary incentive delay (MID) fMRI task used in this study.

· AC managed all the operations of the study.

· IL, PR, and GT supported the setup of the study protocol.

· LG provided high-level and ongoing input on all aspects of the study.

· VM provided high-level and ongoing input on the study's design

· TPF and SKK created the original intervention trial used in this study and provided ongoing, high-level input on the study's design.

· CS provided high-level and ongoing input on all aspects of the study with a focus on the neuroimaging technical aspects.

· VL designed and led the study as CI, supervised all students and staff involved, created the first draft of the manuscript and led all revisions.

Clinical Trial Registration: ISRCTN Registry Identifier: ISRCTN76056942 (Mapping short-term brain changes in cannabis users). Submission date: 28/04/2020. Registration date: 12/05/2020.

The registration of data and interventions is described here: ISRCTN76056942 https://www.isrctn.com/ISRCTN76056942 (DOI: https://doi.org/10.1186/ISRCTN76056942).

Human Ethics and Consent to Participate Declarations: This study received ethical approval from the Australian Catholic University Human Research Ethics Committee (HREC ID: 2019-71H). All participants provided written informed consent before participating in this study.

References

1. Beuriat, P.-A., Cristofori, I., Gordon, B., & Grafman, J. (2022). The shifting role of the cerebellum in executive, emotional and social processing across the lifespan. *Behavioral and Brain Functions*, *18*(1), 6. https://doi.org/10.1186/s12993-022-00193-5
2. Beyer, E., Poudel, G., Antonopoulos, S., Thomson, H., & Lorenzetti, V. (2024). Brain reward function in people who use cannabis: a systematic review [Review]. *Frontiers in Behavioral Neuroscience*, *17*, 1323609. https://doi.org/10.3389/fnbeh.2023.1323609
3. Beyer, E., Poudel, G., Arun, A. H., McTavish, E., Thomson, H., Sehl, H., Segrave, R., Clemente, A., Labuschagne, I., Rendell, R., Terrett, G., Manning, V., Suo, C., & Lorenzetti, V. (under review). Brain reward function in people with moderate-to-severe cannabis use disorder who tried to cut down or quit: An fMRI study.
4. Blest-Hopley, G., Giampietro, V., & Bhattacharyya, S. (2019). Regular cannabis use is associated with altered activation of central executive and default mode networks even after prolonged abstinence in adolescent users: Results from a complementary meta-analysis. *Neuroscience & Biobehavioral Reviews*, *96*, 45-55. https://doi.org/10.1016/j.neubiorev.2018.10.026
5. Blithikioti, C., Miquel, L., Batalla, A., Rubio, B., Maffei, G., Herreros, I., Gual, A., Verschure, P., & Balcells-Olivero, M. (2019). Cerebellar alterations in cannabis users: A systematic review. *Addiction Biolology*, *24*(6), 1121-1137. https://doi.org/10.1111/adb.12714
6. Boccia, M., Piccardi, L., & Guariglia, P. (2015). The Meditative Mind: A Comprehensive Meta-Analysis of MRI Studies. *BioMed Research International*, *2015*(1), 419808. https://doi.org/10.1155/2015/419808
7. Chen, Y., Chaudhary, S., & Li, C.-S. R. (2022). Shared and distinct neural activity during anticipation and outcome of win and loss: A meta-analysis of the monetary incentive delay task. *Neuroimage*, *264*, 119764. https://doi.org/https://doi.org/10.1016/j.neuroimage.2022.119764
8. Chye, Y., Suo, C., Romero-Garcia, R., Bethlehem, R. A. I., Hook, R., Tiego, J., Goodyer, I., Jones, P. B., Dolan, R., Bullmore, E. T., Grant, J. E., Yücel, M., & Chamberlain, S. R. (2022). Examining the relationship between altered brain functional connectome and disinhibition across 33 impulsive and compulsive behaviours. *The British Journal of Psychiatry*, *220*(2), 76-78. https://doi.org/10.1192/bjp.2021.49
9. Collins, S. E., Malone, D. K., & Larimer, M. E. (2012). Motivation to change and treatment attendance as predictors of alcohol-use outcomes among project-based Housing First residents. *Addictive Behaviors 37*(8), 931-939. https://doi.org/10.1016/j.addbeh.2012.03.029
10. Connor, J. P., Stjepanovic, D., Le Foll, B., Hoch, E., Budney, A. J., & Hall, W. D. (2021). Cannabis use and cannabis use disorder. *Nature Reviews Disease Primers*, *7*(1), 16. https://doi.org/10.1038/s41572-021-00247-4

11. de Dios, M. A., Herman, D. S., Britton, W. B., Hagerty, C. E., Anderson, B. J., & Stein, M. D. (2012). Motivational and mindfulness intervention for young adult female marijuana users. *Journal of Substance Abuse Treatment*, *42*(1), 56-64. https://doi.org/https://doi.org/10.1016/j.jsat.2011.08.001
12. Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., Snyder, M., Oya, H., Ghosh, S. S., Wright, J., Durnez, J., Poldrack, R. A., & Gorgolewski, K. J. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature Methods*, *16*(1), 111-116. https://doi.org/10.1038/s41592-018-0235-4
13. Everitt, B. J., & Robbins, T. W. (2016). Drug addiction: updating actions to habits to compulsions ten years on. *Annual Review of Psychology*, *67*(1), 23-50. https://doi.org/10.1146/annurev-psych-122414-033457
14. Garland, E. L., Froeliger, B., & Howard, M. O. (2014). Mindfulness training targets neurocognitive mechanisms of addiction at the attention-appraisal-emotion interface. *Frontiers in Psychiatry*, *4*, 173. https://doi.org/10.3389/fpsyt.2013.00173
15. Garland, E. L., & Howard, M. O. (2018). Mindfulness-based treatment of addiction: current state of the field and envisioning the next wave of research. *Addiction Science & Clinical Practice*, *13*(1), 14. https://doi.org/10.1186/s13722-018-0115-3
16. Hoogendam, J. M., Kahn, R. S., Hillegers, M. H., van Buuren, M., & Vink, M. (2013). Different developmental trajectories for anticipation and receipt of reward during adolescence. *Developmental Cognitive Neuroscience*, *6*, 113-124. https://doi.org/10.1016/j.dcn.2013.08.004
17. Hughes, J. R., Naud, S., Budney, A. J., Fingar, J. R., & Callas, P. W. (2016). Attempts to stop or reduce daily cannabis use: An intensive natural history study. *Psychology of Addictive Behaviors*, *30*(3), 389-397. https://doi.org/10.1037/adb0000155
18. Jiang, F., Dricot, L., Weber, J., Righi, G., Tarr, M. J., Goebel, R., & Rossion, B. (2011). Face categorization in visual scenes may start in a higher order area of the right fusiform gyrus: evidence from dynamic visual stimulation in neuroimaging. *Journal of Neurophysiology*, *106*(5), 2720-2736.
19. Kabat-Zinn, J. (2003). Mindfulness-based interventions in context: past, present, and future.
20. Kamboj, S. K., Irez, D., Serfaty, S., Thomas, E., Das, R. K., & Freeman, T. P. (2017). Ultra-Brief Mindfulness Training Reduces Alcohol Consumption in At-Risk Drinkers: A Randomized Double-Blind Active-Controlled Experiment. *International Journal of Neuropsychopharmacology*, *20*(11), 936-947. https://doi.org/10.1093/ijnp/pyx064
21. Knutson, B., Adams, C. M., Fong, G. W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *Journal of Neuroscience*, *21*(16), RC159. https://doi.org/10.1523/JNEUROSCI.21-16-j0002.2001
22. Knutson, K. M., Dal Monte, O., Schintu, S., Wassermann, E. M., Raymont, V., Grafman, J., & Krueger, F. (2015). Areas of brain damage underlying increased reports of behavioral disinhibition. *Journal of Neuropsychiatry and Clinical Neurosciences*, *27*(3), 193-198. https://doi.org/10.1176/appi.neuropsych.14060126
23. Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*, *3*(8), 760-773. https://doi.org/10.1016/S2215-0366(16)00104-8
24. Kutlu, M. G., & Gould, T. J. (2016). Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: contributions to development and maintenance of addiction. *Learning & Memory*, *23*(10), 515-533. https://doi.org/10.1101/lm.042192.116
25. Laudet, A. B., & Stanick, V. (2010). Predictors of motivation for abstinence at the end of outpatient substance abuse treatment. *Journal of Substance Abuse Treatment*, *38*(4), 317-327. https://doi.org/10.1016/j.jsat.2010.01.007
26. Leung, J., Chan, G. C. K., Hides, L., & Hall, W. D. (2020). What is the prevalence and risk of cannabis use disorders among people who use cannabis? a systematic review and meta-analysis. *Addictive Behaviors*, *109*, 106479. https://doi.org/10.1016/j.addbeh.2020.106479
27. Li, W., Qin, W., Liu, H., Fan, L., Wang, J., Jiang, T., & Yu, C. (2013). Subregions of the human superior frontal gyrus and their connections. *Neuroimage*, *78*, 46-58. https://doi.org/10.1016/j.neuroimage.2013.04.011
28. Lorenzetti, V., Gaillard, A., Beyer, E., Kowalczyk, M., Kamboj, S. K., Manning, V., & Gleeson, J. (2023). Do mindfulness-based interventions change brain function in people with substance dependence? A systematic review of the fMRI evidence. *BMC Psychiatry*, *23*(1), 407. https://doi.org/10.1186/s12888-023-04789-7
29. Luberto, C. M., Hall, D. L., Park, E. R., Haramati, A., & Cotton, S. (2020). A perspective on the similarities and differences between mindfulness and relaxation. *Global Advances in Health and Medicine*, *9*, 2164956120905597. https://doi.org/10.1177/2164956120905597
30. Marks, E., Moghaddam, N., De Boos, D., & Malins, S. (2023). A systematic review of the barriers and facilitators to adherence to mindfulness-based cognitive therapy for those with chronic conditions. *British Journal of Health Psychology*, *28*(2), 338-365.
31. Misra, S. (2012). Randomized double blind placebo control studies, the "Gold Standard" in intervention based studies. *Indian Journal of Sexually Transmitted Diseases and AIDS*, *33*(2). https://journals.lww.com/ijst/fulltext/2012/33020/randomized_double_blind_placebo_control_studies,.11.aspx
32. Moulton, E. A., Elman, I., Becerra, L. R., Goldstein, R. Z., & Borsook, D. (2014). The cerebellum and addiction: insights gained from neuroimaging research. *Addiction Biolology*, *19*(3), 317-331. https://doi.org/10.1111/adb.12101
33. Namkung, H., Kim, S. H., & Sawa, A. (2017). The insula: an underestimated brain area in clinical neuroscience, psychiatry, and neurology. *Trends in Neurosciences*, *40*(4), 200-207. https://doi.org/10.1016/j.tins.2017.02.002

34. Naqvi, N. H., & Bechara, A. (2010). The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. *Brain Structure and Function*, *214*(5-6), 435-450. https://doi.org/10.1007/s00429-010-0268-7
35. Oldham, S., Murawski, C., Fornito, A., Youssef, G., Yucel, M., & Lorenzetti, V. (2018). The anticipation and outcome phases of reward and loss processing: A neuroimaging meta-analysis of the monetary incentive delay task. *Human Brain Mapping*, *39*(8), 3398-3418. https://doi.org/10.1002/hbm.24184
36. Palejwala, A. H., O'Connor, K. P., Milton, C. K., Anderson, C., Pelargos, P., Briggs, R. G., Conner, A. K., O'Donoghue, D. L., Glenn, C. A., & Sughrue, M. E. (2020). Anatomy and white matter connections of the fusiform gyrus. *Scientific Reports*, *10*(1), 13489. https://doi.org/10.1038/s41598-020-70410-6
37. Ranjbar, H., Soti, M., Banazadeh, M., Saleki, K., Kohlmeier, K. A., & Shabani, M. (2021). Addiction and the cerebellum with a focus on actions of opioid receptors. *Neuroscience & Biobehavioral Reviews*, *131*, 229-247. https://doi.org/https://doi.org/10.1016/j.neubiorev.2021.09.021
38. Robinson, T. E., & Berridge, K. C. (2025). The incentive-sensitization theory of addiction 30 years on. *Annual Review of Psychololgy*, *76*(1), 29-58. https://doi.org/10.1146/annurev-psych-011624-024031
39. Rubin, R. D., Watson, P. D., Duff, M. C., & Cohen, N. J. (2014). The role of the hippocampus in flexible cognition and social behavior. *Frontiers in Human Neuroscience*, *8*, 742. https://doi.org/10.3389/fnhum.2014.00742
40. Schneegans, A., Bourgognon, F., Albuisson, E., Schwan, R., Arfa, M., Polli, L., Moulard, M., Laprévote, V., & Schwitzer, T. (2022). Mindfulness-based relapse prevention for cannabis regular users: Preliminary outcomes of a randomized clinical trial. *L'encephale*, *48*(3), 241-246. https://doi.org/https://doi.org/10.1016/j.encep.2021.02.015
41. Skumlien, M., Langley, C., Lawn, W., Voon, V., Curran, H. V., Roiser, J. P., & Sahakian, B. J. (2021). The acute and non-acute effects of cannabis on reward processing: A systematic review. *Neuroscience & Biobehavioral Reviews*, *130*, 512-528. https://doi.org/10.1016/j.neubiorev.2021.09.008
42. Stanger, C., Anderson, M. A. B., Xie, H., Nnaka, T., Budney, A. J., Qian, T., Yap, J. R. T., & Nahum-Shani, I. (2025). Momentary mindfulness versus distraction coping messages to reduce cannabis craving among young adults: A microrandomized trial. *Psychology of Addictive Behaviors*, *39*(2), 200-211. https://doi.org/10.1037/adb0001029
43. Turner, B. O., Paul, E. J., Miller, M. B., & Barbey, A. K. (2018). Small sample sizes reduce the replicability of task-based fMRI studies. *Communications Biology*, *1*(1), 62. https://doi.org/10.1038/s42003-018-0073-z
44. Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*, *15*(1), 273-289. https://doi.org/https://doi.org/10.1006/nimg.2001.0978
45. United Nations Office on Drugs and Crime. (2024). *World drug report 2024*. https://www.unodc.org/documents/data-and-analysis/WDR_2024/WDR_2024_SPI.pdf
46. Wingenfeld, K., & Wolf, O. T. (2014). Stress, memory, and the hippocampus. *Frontiers in Neurology and Neuroscience 34*, 109-120.
47. Witkiewitz, K., Lustyk, M. K. B., & Bowen, S. (2013). Retraining the addicted brain: a review of hypothesized neurobiological mechanisms of mindfulness-based relapse prevention. *Psychology of Addictive Behaviors*, *27*(2), 351-365. https://doi.org/10.1037/a0029258

Figures

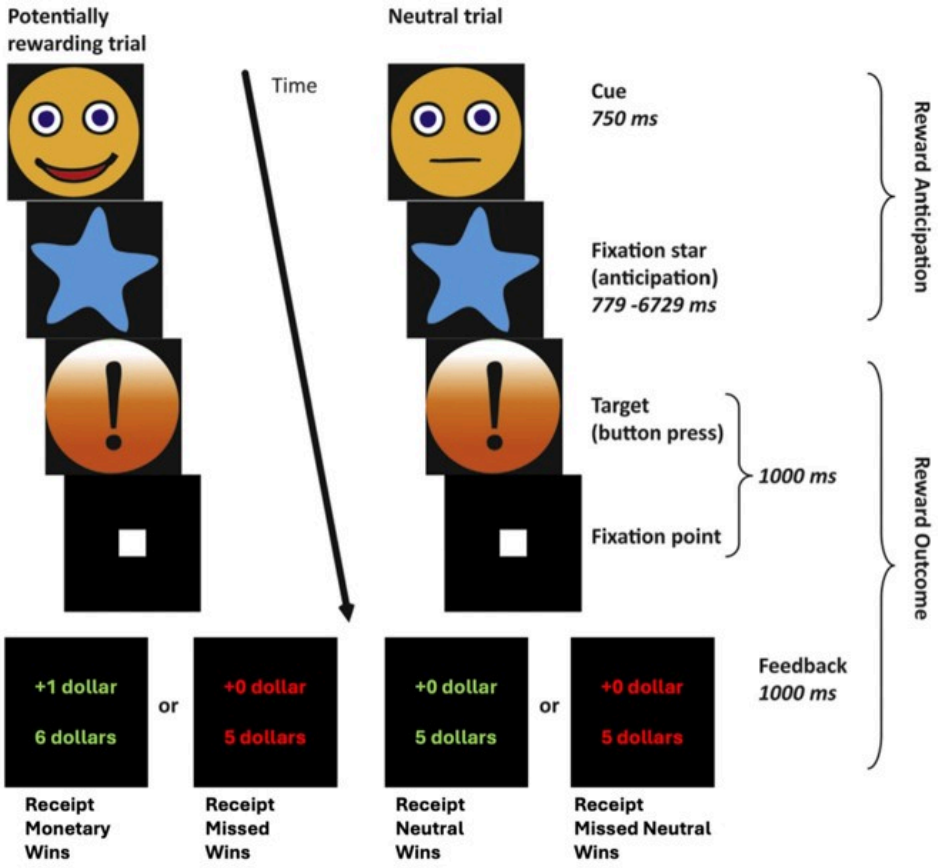

Figure 1

Schematic Representation of the Monetary Incentive Delay Task

Note. Figure 1 is a schematic representation of the MID task, adapted from (Hoogendam et al., 2013); *ms* = milliseconds.

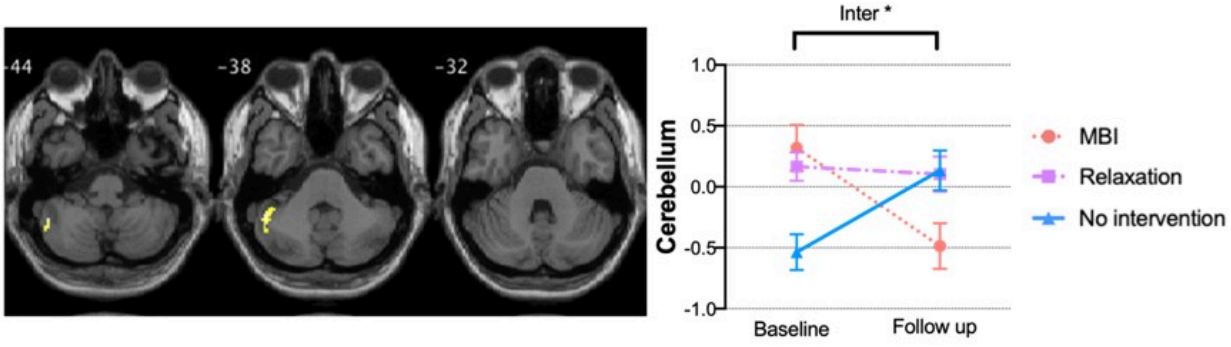

Figure 2

Significant Intervention-by-Time Effects on the Left Cerebellum During the Anticipation of Monetary Cues vs. Anticipation of Neutral Cues, visualised on brain maps (left) and plotted (right)

Note. MBI = mindfulness-based intervention; * = interaction effect is statistically significant; cluster threshold k >84 voxels, initial $p < 0.001$.

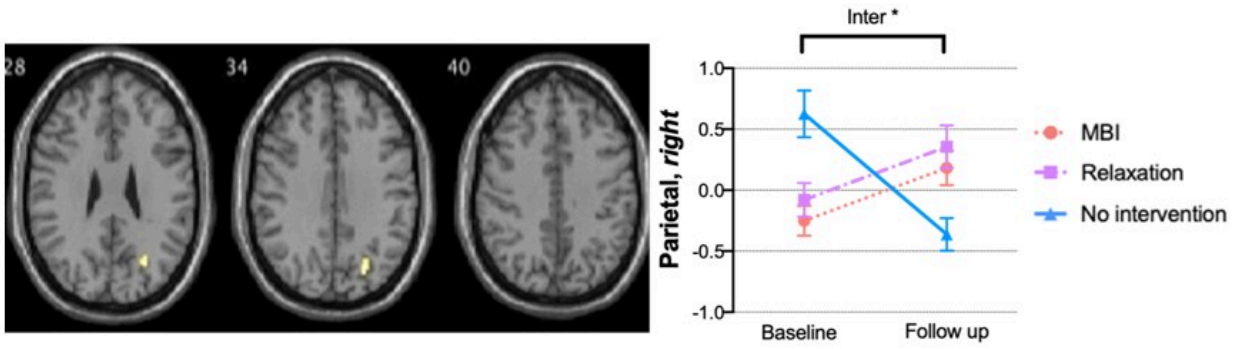

Figure 3

Figure 5. *Significant Intervention-by-Time Effects on the Parietal Cortex During the Receipt of Monetary Wins vs. Receipt of Neutral Wins, visualised on brain maps (left) and then plotted (right)*

Note. MBI = mindfulness-based intervention; * = interaction effect is statistically significant; cluster threshold k >84 voxels, initial $p < 0.001$.

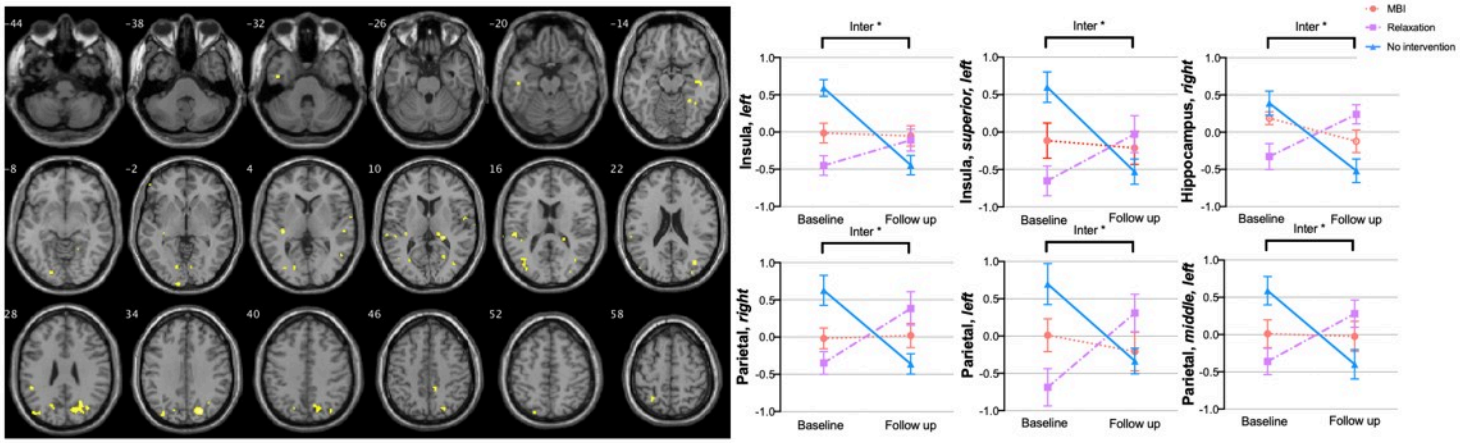

Figure 4

Figure 6. *Significant Intervention-by-Time Effects on the Hippocampus, Insula and Parietal Cortex During the Receipt of Monetary Wins vs. Receipt of Neutral, visualised on brain maps (left) and then plotted (right)*

Note. MBI = mindfulness-based intervention; * = interaction effect is statistically significant; cluster threshold k >84 voxels, initial $p < 0.001$.

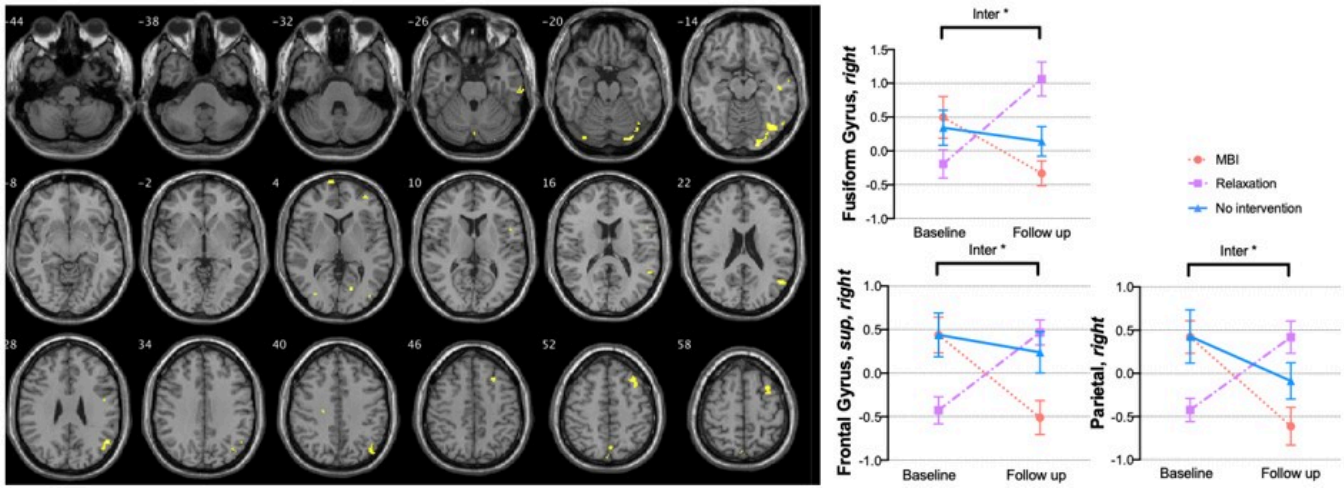

Figure 5

Figure 7. *Significant Intervention-by-Time Effects on the Parietal, Superior Frontal, and Fusiform Gyrus during Receipt of Monetary Wins vs. Receipt of Missed Wins, visualised on brain maps (left) and plotted (right)*

Note. MBI = mindfulness-based intervention; * = interaction effect is statistically significant; cluster threshold k >84 voxels, initial $p < 0.001$.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryData.docx