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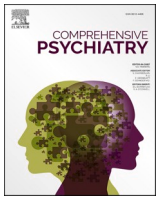

Attentional bias in people with moderate-to-severe cannabis use disorder☆

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ABSTRACT

Background: Attentional bias to cannabis images is posited to drive loss of control over cannabis use and relapse in cannabis use disorder (CUD), but the literature is mixed and limited by inconsistent measurement of CUD and of confounders, including alcohol and nicotine use. This study examined attentional bias in moderate-to-severe CUD ($n = 66$) compared to controls ($n = 42$), and its relationship with cannabis/nicotine use, accounting for alcohol use.

Methods: We measured attentional bias using the visual probe task, as the difference in reaction times (RTs) for cannabis versus neutral images, in order to account for individual variability. Linear mixed effect models examined how RTs were affected by (i) group (CUD, control), image type (cannabis, neutral), group-by-image type, and group-by-image type-by-Stimulus Onset Asynchrony (SOA, 200/500 milliseconds) in the whole sample; and (ii) by image type, SOA, and moderators in the CUD group only (i.e., Cannabis Use Disorder Identification Test-Revised [CUDIT-R], subjective craving, arousal/valence ratings of the task's cannabis/neutral images, and nicotine). All models were adjusted for alcohol use.

Results: There were no significant group differences in attentional bias. In the CUD group, image type-by-CUDIT-R subgroups differed on RTs ($\beta = -0.748$, $p = .014$), whereby the high-CUDIT-R versus lower CUDIT-R subgroups had significantly faster RTs to cannabis versus neutral images ($p = .034$, $d = -0.10$), but this effect did not survive Bonferroni correction for multiple comparisons. No other results were significant.

Conclusion: Attentional bias might not be a robust feature of CUD, though this notion requires validation in a larger sample using more direct measures of attentional bias.

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1. Introduction

Cannabis use disorder (CUD) affects over 20 million people worldwide, and the number of people meeting the criteria for a CUD has increased by 32% over the past three decades [1,2]. People with a CUD often use cannabis compulsively despite the experience of negative consequences [3], such as risk-taking behaviours (e.g., operating heavy machinery while intoxicated), the experience of elevated cannabis cue-induced cravings [4,5], and poorer mental health (e.g., greater symptoms and prevalence of depression, anxiety and psychotic disorders) [6–9].

Prominent theories of addiction suggest that attentional bias plays a critical role in the escalation and maintenance of substance use [10–13]. According to these theories, cannabis and related stimuli become highly salient after repeated use, acquiring attention-grabbing properties compared to non-substance-related stimuli [10–13], which leads to the orientation of attention towards substance-related cues and difficulties disengaging from them [14]. These automatic cognitive processes can drive substance-seeking and consumption behaviours and undermine attempts to cut down or quit substance use [11]. Therefore, understanding the association between attentional bias to cannabis cues and CUD may have implications for informing therapies targeting attentional bias to help individuals reduce, manage or eliminate their cannabis use.

The evidence to date on the presence of attentional bias in people who use cannabis is mixed [15]. Specifically, some studies demonstrate that people who use cannabis, compared to controls, have an attentional bias towards cannabis versus neutral stimuli [16–21], while other studies suggest that this difference may only be present in participants who endorse a CUD [16,22]. In contrast, other studies have failed to detect any evidence of attentional bias [20,21,23]. The mixed findings might be due to methodological inconsistencies in the existing literature. First, no study of attentional bias to date has examined if participants endorsed a CUD using the most recent diagnostic systems, with one exception in treatment seekers [23]. Thus, there are no studies examining non-treatment seeking individuals with a CUD – (the majority of people who use cannabis [24]) using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [3] or measurement tools to confirm the presence and severity of CUD, such as the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV) [25]. Instead, the literature to date has measured cannabis dependence based on currently outdated diagnostic systems, such as the Diagnostic Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [15,26]. As the DSM-5 is the current diagnostic system and does not directly overlap with the DSM-IV (e.g., different symptoms and severity thresholding), it is essential to fill an existing gap in non-treatment-seeking individuals with moderate-to-severe CUD.

Second, the literature has inconsistently measured the level of cannabis consumption (e.g., quantity in grams, number of joints; frequency in days/per week, days/per month) and metrics of cannabis use-related problems (e.g., Severity of Dependence Scale [27], Cannabis Use Disorder Identification Test-Revised scores [CUDIT-R]) [28]. Therefore, it is unclear if attentional bias is exacerbated in individuals with greater severity of cannabis use and associated problems. Third, the role of alcohol and nicotine use, which commonly co-occur with CUD [29], has been poorly examined. Importantly, these variables can affect attentional bias independently and through interactions with cannabis use [30]. Therefore, whether attentional bias is specific to cannabis or comorbid substance use remains unresolved. Fourth, some variables may moderate attentional bias performance in people who use cannabis. For example, participants' subjective ratings of the valence and arousal of the images used in the attentional bias tasks have rarely been measured, and, when assessed, inconsistent metrics have been used (e.g., implicit association test, valence ratings). Thus, it is unclear if participants' subjective perception of the images used in the task influences attentional bias performance in CUD, as previously theorised [11].

Fifth, most studies have not accounted for parameters within the attentional bias task, including the timing of onset of cannabis and neutral images (stimuli onset asynchrony or SOA) [31]. Of note, different durations of SOA tap into distinct cognitive aspects of attentional bias; whereby longer stimuli exposures (e.g., $\geq$ 500 milliseconds) measure sustained attention, while shorter exposures measure automatic attention (e.g., $\leq$ 200 milliseconds). As a consequence, the role of automatic versus sustained processes in attentional bias remains unclear [31]. Lastly, different methods for computing attentional bias scores have been used, with the most common approach involving subtracting the average reaction time (RT) to cannabis stimuli from the average RT to neutral stimuli [16,18,19,23,32]. Of relevance, these methods can remove important intra-individual variability in RTs, which can contribute to attentional bias performance at an individual level and when comparing cannabis and control groups.

Overall, emerging evidence on attentional biases in CUD, combined with the rising prevalence of CUD, and the increased liberalisation, advertisement, access, and availability of cannabis products globally [33], highlight an urgent need to understand if attentional bias is affected in CUD, particularly in more severe presentations. Such findings could inform whether attentional bias is an important target for harm reduction, preventative interventions and treatment, and inform public health policies such as the regulation of cannabis advertisements.

We aimed to compare for the first time how attentional bias towards cannabis-related images versus neutral images differs between non-treatment-seeking participants who endorsed moderate-to-severe CUD and controls. This was achieved by adjusting for image exposure time (i.e., 200 and 500 milliseconds) and alcohol consumption (i.e., number of standard drinks in the past month). Based on neuroscientific theories of addiction [10] and emerging evidence [15,16], we hypothesised that attentional bias towards cannabis versus neutral images would be stronger in the CUD group than in controls.

As a secondary aim, within the CUD group, we explored whether the strength of attentional bias was associated with cannabis quantity used in the past month, subjective cannabis craving, cannabis use-related problems (i.e., CUDIT-R scores), valence/arousal ratings, and number of cigarettes in the past month, adjusting for number of alcohol standard drinks in the past month.

2. Methods

This study was nested within a larger project and received ethics approval from the Australian Catholic University Human Research Ethics Committee (HREC ID: 2019-71H), the methodology of which was pre-registered. A detailed description of the overarching study methodology, eligibility criteria and metrics is included in the larger project's pre-registration (www.isrctn.com/ISRCTN76056942).

2.1. Recruitment

One hundred and eight participants were recruited from the Melbourne metropolitan area via flyers in the general community, university campuses and online platforms (e.g., Facebook, Gumtree, TikTok, and others). The advertisement included general information about the study, eligibility criteria and a QR code and web link to the study's online screening survey screened against the study's eligibility criteria, followed by a detailed phone call to confirm study inclusion. Details of the recruitment procedure and final sample are included in Supplementary Methods 1.1.5.

2.2. Study eligibility criteria

Inclusion criteria for *all participants* were: (i) age 18 to 55 years; (ii) normal-to-corrected vision; and (iii) fluent in English. Inclusion criteria for the participants in the CUD group were: (i) daily/almost daily cannabis use for $\geq$ 12 months prior to testing; (ii) meeting diagnostic

criteria for a moderate-to-severe CUD determined via the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV) [25] and iii) ≥ 1 attempt to reduce or quit cannabis use in the last 24 months.

Exclusion criteria for *all participants* were: (i) diagnosis of psychiatric disorders, other than severe depression/anxiety due to their high co-morbidity with CUD [34], assessed by the Mini International Neuropsychiatric Interview (MINI) [35]; (ii) current prescribed medication affecting the central nervous system (e.g., antipsychotics), except for anti-depressants due to high prevalence of depression in people with a CUD [34]; (iii) history of neurological disorders or significant medical conditions (e.g., multiple sclerosis); (iv) history of traumatic brain injury or unconsciousness for >5 min; (v) any use of substances other than nicotine within 12 h before testing, confirmed by self-report; (vi) any use of substances - except for alcohol and nicotine in all participants, and additionally cannabis in the CUD group - in the last 30 days before testing, confirmed by the timeline-follow back (TLFB) [36]; (vii) any significant use of substances - other than alcohol and nicotine for both groups, plus cannabis in the CUD group (i.e., > 50-lifetime episodes of use and/or weekly use over a 3-month period); (viii) pregnancy or breastfeeding; (x) MRI contraindications (e.g., surgical clips), and (xi) IQ < 80 assessed by the Weschler Abbreviated Standardised Intelligence-II (WASI-II) [37]. We also excluded participants with invalid data in the visual probe task, such as those with a substantial amount of RT data (i.e., 15%, 40% or more) reflecting outliers or incorrect trials (i.e., 98% of incorrect data). *Controls* were required to: (i) not have used cannabis in the last 12 months; (iii) never have used cannabis fortnightly or less; and (iii) not have used cannabis more than 50 occasions over a lifetime.

2.3. Assessment procedure

Face-to-face testing was completed at the Monash Biomedical Imaging Centre in Clayton, Victoria, Australia. Participants provided written informed consent before commencing face-to-face assessment. Testing included a series of questionnaires administered via Qualtrics Version XM (www.qualtrics.com); semi-structured interviews for CUD and lifetime substance use characterisation; as well as the visual probe task. Assessments were conducted by researchers and psychology students, who underwent extensive and standardised training for accurate and consistent administration of all measures. The testing session lasted approximately 4-to-6 h as part of a larger study, with select measures being utilised for addressing the current study aims. After completing the assessment, participants were reimbursed with local store vouchers, specifically $100 for controls and $150 for participants in the CUD group due to the completion of additional testing outside the scope of this study.

2.4. Measures

2.4.1. Sociodemographic data and IQ

A detailed socio-demographic and medical questionnaire was administered to collect data on participants' age, sex, and total number of full-time years of education completed. An estimate of IQ was measured via the vocabulary and matrix reasoning subtests of the WASI-II [37].

2.4.2. Mental health

The *State-Trait Anxiety Index – Y* Form is a 20-item questionnaire administered to measure state anxiety (STAI-Y) [38]. Total scores are interpreted within three levels of severity, which range from "no or low anxiety" (20–37), "moderate anxiety" (38–44) and "high anxiety" (45+). Stress was measured via the *Perceived Stress Scale* - 10 item version (PSS) [39], rated on a 5-point Likert scale with higher scores indicating greater stress. The *Community Assessment of Psychic Experiences* is a 42-item questionnaire administered to measure frequency and distress levels of psychotic experiences, including positive and negative psychotic symptoms and depressive symptoms (CAPE) [40]. Items are rated on a Likert scale for frequency (i.e., "never" to "nearly always") and distress scales (i.e., "not distressed" to "very distressed").

2.4.3. Substance use and related problems

2.4.3.1. Presence and severity of CUD. The *Structured Clinical Interview for DSM-5 Diagnoses - Research Version* (SCID-5-RV) was administered to confirm the presence of a moderate-to-severe CUD (4+ symptoms) and the total number of CUD symptoms endorsed (i.e., severity determined via the SCID-5-RV) [25]. Items include criteria such as failed attempts to cut down/quit, experience of craving and withdrawal symptoms, among others. The level of cannabis use-related problems was measured via the CUDIT-R [28], an 8-item self-report questionnaire. Items include questions on patterns of use, dependence symptoms (e.g., difficulty controlling use), and related impairment (e.g., using cannabis even when hazardous). Scores range from 1 to 32, with a clinical cut-off of ≥13 indicating the likelihood of a CUD.

A *Visual Analogue Scale (VAS)* [41] was administered pre and post the visual probe task to measure subjective craving with the item "How much do you feel like smoking cannabis right now?". The item was rated on a 10-point scale whereby "0" indicated "Not at all" and 10 "Extremely". The *Marijuana Craving Questionnaire* (MCQ) was also included to characterise the sample's levels of craving [42]. The MCQ comprises 45 items rated on a 7-point Likert scale (i.e., *"strongly disagree"* to *"strongly agree"*) to measure four different factors: compulsivity, emotionality, expectancy and purposefulness. Scores range from 40 to 280. The *Cannabis Withdrawal Scale* (CWS) was administered to measure the intensity of withdrawal symptoms over the last 24 h [43]. The 19 items of the CWS are rated on a 10-point scale (i.e., "not at all" to "extremely"). Scores range from 0 to 190, with higher total scores reflecting more severe withdrawal symptoms.

2.4.3.2. Motivation to change cannabis use. The *Contemplation Ladder* is an adaptation of two original versions [44–46], administered to examine participants' motivation to change their cannabis use. It comprises two items, one confirming regular cannabis use. The second item includes statements indicating different stages of change, from "0", indicating pre-contemplation (i.e., enjoying cannabis use and not having interest in changing their use) to "9", meaning action (i.e., having changed their cannabis use, although worrying about slipping back).

2.4.3.3. Additional metrics of substance use. The *Alcohol Use Identification Test* was administered to ascertain the level of problematic alcohol consumption (AUDIT) [47]. The AUDIT is a 10-item scale that provides a clinical cutoff to identify likely alcohol dependence (i.e., scores ≥19). Similarly, the level of problems with nicotine use was measured by the *Fagerström Test for Nicotine Dependence* (FNTD) [48]; a six-item questionnaire with items scored from 0 to 3, and total scores ranging from 0 to 10. Items include difficulty in refraining from smoking in forbidden places and smoking even when ill, among other items. Scores ≥3 indicate potential nicotine dependence.

The *Timeline Follow-Back* (TLFB) [36] is a semi-structured interview which uses a calendar-based format to map participants' key dates in the last month as "anchors" (e.g., payday, birthdays) to remember substance use. The TLFB was administered to measure substance exposure in the last 30 days before testing, including the number of days of use and quantity in the past month (e.g. cannabis grams, the gold standard measure to quantify cannabis use in the field [49], number of standard drinks of alcohol, and number of cigarettes). We also measured the number of hours since last cannabis use and the methods of cannabis consumption (e.g. joints, bongs). Additionally, a *semi-structured interview* [50,51] was administered to extract age of onset, duration of regular use defined as the total number of years since at least monthly use, and the estimated cumulative number of cannabis grams consumed over the last

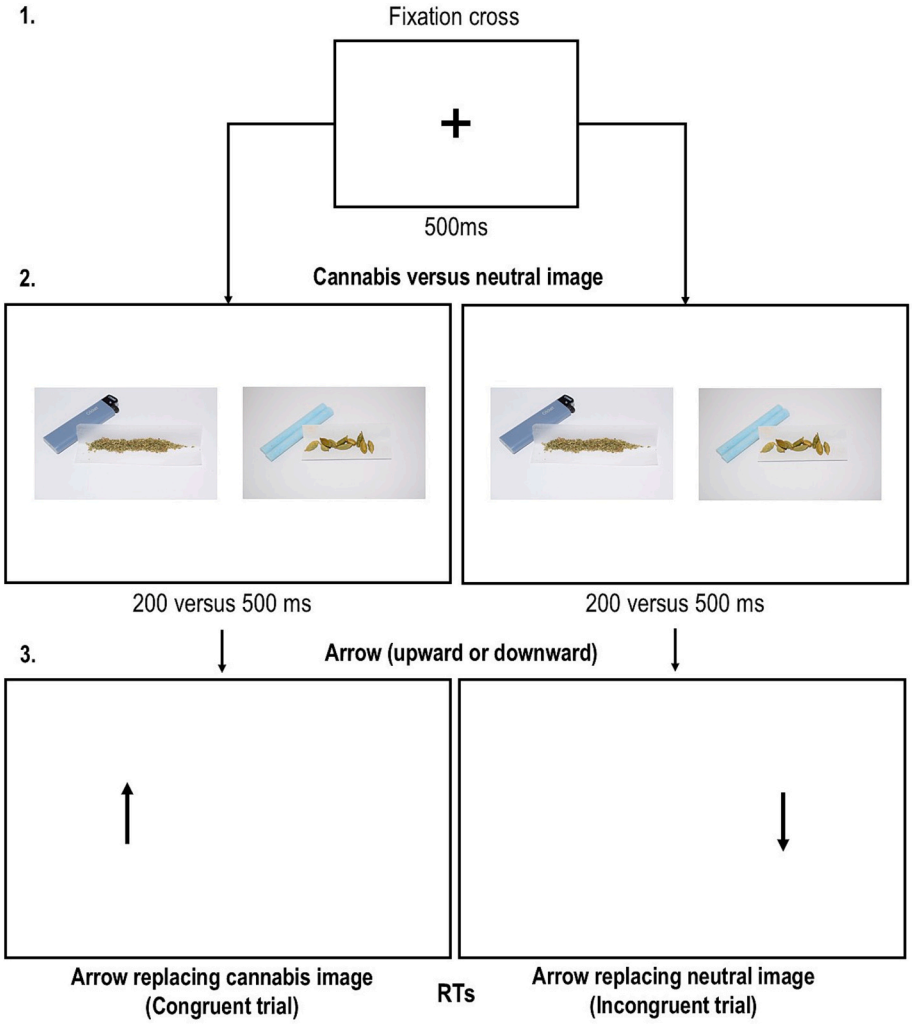

Fig. 1. Example of a cannabis trial (on the left) and neutral trial (on the right), with a pair of matched images (a cannabis image on the left and a neutral image on the right). Adapted from Hindocha and colleagues [52]. Ms. = milliseconds. SOA = stimulus onset asynchrony.

year and over participants' lifetime.

2.4.4. The visual probe task to measure attentional bias

A visual probe task was used to measure attentional bias, with the task structure overviewed in Fig. 1 [52]. The task consisted of 164 trials, including four buffer trials, 83 cannabis trials and 77 neutral trials. The task lasted approximately 15 min. For each trial, a fixation cross appeared at the centre of a white screen for 500 milliseconds. Then, two images, one cannabis-related and one neutral, appeared on opposite sides of the screen. A total of ten pairs of cannabis and neutral images, validated in previous studies of cannabis attentional bias and cannabis cue reactivity [53,54] were presented 16 times across the task. Cannabis images included photos of cannabis (e.g., grass, hashish), people using cannabis, and cannabis paraphernalia (e.g., rolling paper, bongs). Control images were non-cannabis related and included people and objects matched on composition, complexity, brightness and colour (when possible) to the cannabis counterpart to minimise the effect of confounding factors [55]. The image pairs were presented for either 200 or 500 milliseconds (SOA) to measure automatic orienting and controlled attention processes, respectively. Last, a probe (i.e., a black arrow pointing upwards or downwards) replaced either the cannabis-related image (i.e., congruent trial) or the neutral image (i.e., incongruent trial). The probe remained on the screen until participants indicated its orientation using the up or down response key.

Participants were instructed to respond as promptly and accurately as possible. RTs to respond to the probe were the key outcome variable (See Supplementary Methods 1.1.1. and 1.1.2 for additional details on the task). The probe position, image type, target position and SOA were counterbalanced. The task was programmed with Experiment Builder (SR Research, Kanata, ON, Canada) and administered via two testing laptops with identical specs. Log files were saved in a password-protected online folder shared with the research team in Cloudstor and Sharepoint, and were entered into a spreadsheet for data quality checks and pre-processing.

2.4.4.1. Reliability of the visual probe task. Cronbach's alpha coefficients were calculated for RTs to assess the internal consistency of the visual probe task. RTs were averaged within each pair of images across the different task parameters relevant to the main analysis (i.e., cannabis versus neutral, 200 versus 500 SOA). For comparability purposes, Cronbach's alpha coefficients were calculated for attentional bias scores, as well as split-half reliability for both RTs and attentional bias scores.

Further details regarding the reliability analyses and results are outlined in Supplementary Methods 1.1.3. and 1.1.4 and Supplementary Results 2.1.

2.4.4.2. Subjective ratings of images from the attentional bias task: Valence and arousal. Participants completed a 'picture rating task' via Qualtrics XM, to rate the affective valence and arousal they experienced in relation to each of the cannabis-related and neutral images that they were administered in the visual probe task. Image ratings were obtained for one image presented at a time. The valence and arousal of each image were assessed by VAS scales from 1 to 9. Affective valence was measured by the item "*Below you see mannequins ranging from 'very unpleasant' to 'very pleasant'. Click on the mannequin that reflects how pleasant you think the above picture is*". The answers ranged from 1 for "unpleasant" to 9 for "pleasant", with 5 signifying "neutral". Arousal was measured by the item "*Below you see mannequins ranging from 'calm' to 'excited '. Click on the mannequin that reflects your feeling when looking at the above picture*", with answers ranging from 1 for "calm" to 9 for "excited".

2.4.4.3. Measuring attentional bias. RTs to cannabis and neutral images were used as outcome variables of the experiment to capture individual variability, whereby the presence of an attentional bias was indicated by a significant effect of group-by-image type on RTs.

Additionally, to permit comparison with previously published work measuring attentional bias using distinct methods that do not account for individual variability [16,18,19,23,32], individual attentional bias scores were also computed by subtracting – within each participant - their average RTs to all cannabis images from their average RTs to all neutral images, where positive values indicate an attentional bias to cannabis versus neutral images [21]. This calculation resulted in a single attentional bias score per participant, which we compared between the CUD and control groups.

3. Statistical analyses

3.1. Normality checks and outliers

All variables were inspected for normality using the Kolmogorov-Smirnov test. Outliers, identified by the Tukey's method (data points 1.5 interquartile range below Q1 and above Q3), were excluded from the analysis for the primary and secondary aims. In addition, for RTs, only correct trials (i.e., where participants entered the right response key) were included in the analysis. We excluded individual RTs <200 and >2000 and then if they were more than 3 SDs above the mean at a trial level (see Supplementary Methods 1.1.5 for details about outliers removed).

3.2. Descriptives

Groups were compared using Chi-squared tests for categorical variables (i.e., sex), *t*-tests for normally distributed data (i.e., IQ, completed education years, perceived stress), and Mann-Whitney *U* tests for the remaining non-normally distributed variables. Wilcoxon signed-rank tests were used to examine differences between mean valence and arousal ratings and RTs in relation to cannabis and neutral images within the CUD and control groups, respectively.

3.3. Aim 1: Group differences in attentional bias

To address the primary aim, we ran a linear mixed-effect model using subject as a random intercept. Predictors included: group (i.e., CUD, controls); image type (i.e., cannabis or neutral image); SOA (i.e., 200, 500 milliseconds); group-by-image type to measure attentional bias differences between groups (i.e., group comparison of RTs for cannabis versus neutral images); group-by-image type-by-SOA to measure attentional bias differences between groups as a function of SOA. The dependent variable was RTs. The number of standard drinks of alcohol consumed over the past month was used as a covariate. A likelihood ratio test was conducted to examine the significance of the variation across participants.

3.4. Aim 2: Association between level of attentional bias and cannabis use levels

To address the secondary exploratory aim, we performed a series of eight linear mixed-effect models, each one including an additional moderator as a predictor (i.e., cannabis grams past/month, CUDIT-R scores, VAS subjective craving, arousal and valence; and cigarettes past/month). All analyses for aim 2 were adjusted for alcohol standard drinks/past month as a covariate. Other predictors in all models were: image type (i.e., cannabis or neutral image), SOA (i.e., 200, 500 milliseconds), as well as the interaction terms between each moderating variable and image type. The outcome variable was RTs in response to cannabis and neutral images.

The nature of any significant interaction and omnibus tests was explored with post-hoc pairwise Mann-Whitney *U* tests using residualized RTs, which were adjusted for key covariates used in the main model (i.e., SOA, standard drinks/past month). Additionally, the CUD group was split into three groups: low CUDIT-R (i.e., <1 standard deviation [SD] from the mean), moderate CUDIT-R (i.e., between 1 SD below and above the mean), and high CUDIT-R (i.e., >1 SD above the mean). Aim 2 analyses underwent Bonferroni correction for multiple comparison, with significance being set at $p < 0.006$. The Statistical Package for Social Scientists was used to complete all statistical analyses (SPSS version 29; IBM, Chicago, IL, USA). The likelihood ratio test analysis for the primary aim was run via R version 4.4.1. GraphPad Prism version 10.0 was used for data visualisation.

4. Results

4.1. Sample characteristics

The sample characteristics are summarised in Table 1. The sample consisted of 108 participants (34 females and 74 males) with a median age of 28.3 years, including 66 individuals with a CUD and 42 controls. Details of the final sample are included in Supplementary Methods 1.1.5. Groups were matched by sex and age. The CUD group, compared to controls, had significantly lower mean IQ and years of education. Groups did not differ in state anxiety and perceived stress, but the CUD group had significantly higher symptoms of depression, positive and negative psychotic-like symptoms. The CUD group, compared to controls, also had significantly higher levels of alcohol/nicotine use and related problems. Eleven participants of the CUD group (15.94%) and one control (0.02%) obtained FTND scores indicating nicotine dependence (i.e., FTND score ≥ 3).

4.2. Cannabis use and related problems

Table 2 overviews the level of cannabis consumption and cannabis-related variables in the CUD group. All participants in the CUD group met criteria for a moderate-to-severe CUD and reported consuming about a gram of cannabis almost every day in the past month prior to testing. The most endorsed method of use was smoking (including joints, bongs and vaping) (i.e., 61.2% of the sample), with other methods including edibles (11.7%). They self-reported abstaining from using cannabis around 17 h before testing, corroborating their 'non-intoxicated' status; and withdrawal symptoms were relatively low. Cannabis VAS craving ratings completed after the visual probe task were also relatively low. Overall, 82.1% of the CUD sample endorsed at least a contemplative stage of changing their cannabis use (50.1% indicated being in a contemplative stage, 24.2% in the preparation stage and

Table 1
Overview of sample descriptives.

Variable		CUD		Controls		Group differences	
		M (*SD*)	Range	*M* (*SD*)	Range	$x^a/t^b/U^c$	*p*
Total [females]		66 [18]	_	42 [16]	_	.73[a]	0.39
Age, years		27.37 (7.70)	18.25–56.67	29.36 (9.91)	18.17–55.33	1306.50[c]	0.49
Education, years		15.48 (2.79)	11–23.00	15.70 (3.74)	6.50–25	0.34[b]	0.07
IQ, WASI-II		107.33 (9.37)	90.00–129	108.72 (13.58)	84–135	0.61[b]	0.020*
State anxiety, STAI-Y		31 (8.95)	20–60	29.70 (7.71)	20–53	1135[c]	0.10
Perceived stress, PSS		15.67 (7.36)	1–33	13.63 (7.07)	1–29	0.62[b]	0.43
CAPE symptoms frequency	Positive psychotic	38.95 (12.27)	20–76	30.47 (9.35)	0–56	785.5[c]	0.001***
	Depressive	22.94 (8.84)	8–45	18.51 (7.79)	0–47	964[c]	0.012*
	Negative psychotic	40.10 (14.48)	14–82	30.56 (12.53)	0–53	852[c]	0.001***
Alcohol	AUDIT	6.90 (4.78)	0–22	3.07 (2.81)	0–13	671.50[c]	0.001**
	Days of use/ past month, TLFB	5.97 (6.91)	0–30	3.26 (4.98)	0–25	985.5[c]	0.009**
	Drinks/pastmonth, TLFB	31.55 (48.50)	0–206.80	12.09 (19.51)	0–81.20	950[c]	0.005**
Nicotine	FNTD	1.02 (1.68)	0–6	0 (0)	0–0	881.5[c]	0.001***
	Days of use/ pastmonth, TLFB	10.19 (13.27)	0–30	0 (0)	0–0	444[c]	0.001***
	N cigarettes/ pastmonth, TLFB	63.52 (126.09)	0–600	0 (0)	0–0	4446[c]	0.001***

Note. WASI-II = Wechsler Abbreviated Scale of Intelligence, 2nd Edition; STAI-Y = State-Trait Anxiety Index - Y Form; PSS = Perceived Stress Scale; CAPE = Community Assessment of Psychic Experiences; AUDIT = Alcohol Use Disorder Identification Test; TLFB = Timeline Follow-back; FTND = Fagerström Test for Nicotine Dependence.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 2
Overview of cannabis use and related problems, ratings of arousal and valence and RTs of cannabis and neutral images in the CUD and control groups.

Variable		CUD		Controls		Group differences	
		M (*SD*)	Range (min-max)	*M* (*SD*)	Range (min-max)	*U*	*p*
CUD symptoms, SCID-5-RV		7 (1.87)	4–11	_	_	_	_
CUDIT-R		15.84 (5.02)	7–30	_	_	_	_
Days of use/past month, TLFB		25.63 (5.19)	13–30	_	_	_	_
Grams	Past month, TLFB	26.97 (20.70)	0.9–84	_	_	_	_
	Past year	325.96 (269.17)	0.48–1247.50	_	_	_	_
	Lifetime	2352.65 (3488.52)	56.54–16,339.99	_	_	_	_
Craving	MCQ	35.56 (13.81)	13–75	12.88 (2.33)	12–23	30.5	0.001***
	VAS pre-visual probe task	3.57 (2.64)	1–10	1 (0)	1–1	351.5	0.001***
	VAS post visual probe task	3.69 (2.70)	1–10	1 (0)	1–1	351.5	0.001***
Withdrawal, CWS		32.59 (27.62)	0–118	10.12 (11.72)	0–50	570.5	0.001***
Age of onset	First use, years	16.70 (2.82)	12.83–32.08	20.29 (3.80)	14.25–30.50	201	0.001***
	At least monthly, years	18.84 (3.53)	14.33–32.08	_	_	_	_
Duration of at least monthly use, years		7.96 (7.24)	0.88–39.75	_	_	_	_
THC-COOH in urine, ng/mL		243.55 (254.03)	0–1053	0 (0)	0–0	21.50	0.001***
Arousal	Cannabis images	4 (2.22)	1–8.60	1.40 (0.90)	1–4.80	378.50	0.001***
	Neutral images	2 (1.34)	1–5.70	1.46 (1.12)	1–5.30	799	0.001***
Valence	Cannabis images	6.06 (1.16)	3.90–9	3.98 (1.51)	1–8.40	265.50	0.001***
	Neutral images	4.86 (0.61)	2.70–6.30	4.82 (0.66)	1.40–5.40	1298.5	0.981
Reaction times	Cannabis images	498.73 (58.81)	387.91–642.20	519.83 (67.58)	411.61–683.43	−6.711	0.001***
	Neutral images	499.22 (56.17)	385.13–639.91	519.02 (69.09)	420.34–721.16	−7.541	0.001***
AB scores		0.49 (13.47)	−35.23-32.60.62	−0.82 (12.78)	−33.90-37.73	−0.756	0.450

Note. AB = Attentional bias scores computed as per Field and colleagues [21], subtracting, within each participant, the average RTs to all cannabis images, from the average RTs to all neutral images, resulting in a single attentional bias score per participant. CUD = Cannabis use disorder. SCID-5-RV = Structured Clinical Interview for DSM-5 Diagnoses Research Version; CUDIT-R = The Cannabis Use Disorder Identification Test–Revised; TLFB = Timeline Follow back; MCQ = Marijuana Craving Questionnaire; CWS = Cannabis Withdrawal Scale; VAS = Visual Analogue Scale; THC-COOH = 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol; ng/mL = Nanograms per millilitre.
*$p < .05$. **$p < .01$. ***$p < .001$.

7.81% in the action stage).

In controls, the age of onset of cannabis use was around 20 years, and this was significantly later than participants with a CUD. 19 out of 43 controls endorsed using cannabis at least once in their lifetime. Over their lifetime, control participants reported using cannabis on a median of 3 occasions (range: 1–7 occasions) and 4 g (range: 3–6 g), with their last cannabis use occuring between 1.33 and 8.5 years before testing.

4.3. Group differences in ratings of arousal, valence, and RTs in relation to cannabis and neutral images and attentional bias scores

Table 2 summarises group differences in the subjective ratings of valence and arousal of the cannabis-related and neutral images included in the visual probe task. The CUD group, compared to controls, rated cannabis images to elicit significantly greater levels of arousal and positive valence, with CUD participants indicating that cannabis images were moderately pleasant and controls indicating that cannabis images were moderately unpleasant. The CUD group rated neutral images as significantly more arousing than controls. There were no group differences in the subjective valence ratings of neutral images.

Within the CUD group, cannabis images, compared to neutral images, were rated as eliciting significantly higher levels of subjective arousal ($Z = -6.260$, $p \leq 0.001$, $d = 0.78$). In terms of valence, the CUD group rated cannabis images as significantly more pleasant than neutral images, which they rated as slightly neutral ($Z = -6.072$, $p \leq 0.001$, $d = 0.82$). Within controls, subjective ratings of arousal did not differ

between cannabis and neutral images, though control participants rated neutral images as being significantly less unpleasant than cannabis images ($Z = -4.013$, $p < .001$, $d = 0.694$).

The CUD group showed significantly faster average RTs to cannabis and neutral images compared to controls. We did not find significant group differences in attentional bias scores computed using traditional methods for descriptive purposes [21] (See Table 2).

4.4. Reliability of the visual probe task

A reliability analysis of the visual probe task was conducted by estimating the internal consistency of the RTs, measured by Cronbach's alpha, which was excellent at α >0.90 across cannabis versus neutral images, 200 versus 500 SOA separately and together (See Supplementary Methods 1.1.3 and Supplementary Results 2.1.1 for details on reliability). Internal consistency of the traditional attentional bias scores used for descriptive purposes and based on Field and colleagues [21] was also calculated, resulting in a poor Cronbach's alpha at α <0.295 (Supplementary Methods 1.1.4 and Results 2.1.2). Lastly, split-half reliability was calculated following similar procedures as those described previously for internal consistency (See Supplementary Methods 1.1.3 and Supplementary Results 2.1.3 and 2.1.4).

4.5. Main and interaction effects of group, image type and SOA on RTs, adjusting for standard drinks/past month

The CUD group showed significantly faster mean RTs to both cannabis and neutral images compared to controls. We found a significant random effect of subjects on RTs, indicating significant variation in RTs across participants ($X^2(1) = 8039.5$, $p < .001$). There was no significant effect of group, image type (i.e., cannabis versus neutral image) or standard drinks past/month on RTs. We found a significant effect of SOA, with faster RTs at 500 than 200 milliseconds ($p < .001$).

There were no significant effects of group-by-image type and of group-by-image type-by SOA on RTs, indicating no statistical differences in attentional bias between CUD and controls, and this was regardless of SOA.

4.6. Associations between levels of cannabis use and related problems on reaction times as a function of image type (i.e., cannabis image, neutral image)

Regarding associations between RTs and CUDIT-R scores, there was a significant main effect of image type, meaning faster RTs to cannabis than neutral images, and a significant main effect of SOA, with faster RTs at 500 than 200 milliseconds. We also found a significant main effect of image type and SOA on RTs, and a significant image type-by-CUDIT-R scores interaction effect on RTs, showing higher CUDIT-R scores predict slower RTs ($F = 6.039$, $SE = 0.305$, $t(9164.052) = 2.457$, $p = .014$, $d = 0.49$). However, the finding did not survive Bonferroni correction for multiple comparisons ($p > .006$).

There were no significant effects of image-type-by-cannabis grams/past month, craving, or image type-by-craving on RTs ($F = 3.591$, $SE = 3.30$, $t(60.01) = 0.409$, $p = .058$). We did not find significant effects of number of cigarettes/past month, of image arousal/valence ratings, or their interaction with image type and SOA on RTs.

Exploratory post-hoc analyses of the image type-by-CUDIT-R interaction (Fig. 2) showed that participants in the high-CUDIT-R group demonstrated significantly faster RTs to cannabis images compared to neutral images, with a small effect size ($Z = -2.117$, $p = .034$, $d = -0.10$); however, this effect did not survive Bonferroni correction for multiple comparisons. In contrast, the participants in the low and moderate-CUDIT-R subgroups showed similar RTs to cannabis and neutral images. Lastly, individuals in both the low and moderate-CUDIT-R subgroups had significantly faster RTs to neutral versus cannabis images compared to the high-CUDIT-R subgroup ($p < .01$), which again did not survive Bonferroni corrections for multiple comparisons.

5. Discussion

This is the first study to examine attentional bias towards cannabis images in individuals with a moderate-to-severe CUD who are not currently in treatment. In contrast to our hypothesis, we did not find significant group differences in attentional bias based on RTs to cannabis versus neutral images, accounting for alcohol use; or on pair-wise comparisons of traditionally computed attentional bias scores. Additionally, we found a significant image type-by-CUDIT-R effect on RTs, whereby individuals with the highest CUDIT-R scores reacted significantly faster to cannabis versus neutral images compared to the low and moderate-CUDIT-R subgroups; however, this effect did not survive Bonferroni correction for multiple comparisons. We did not find any other significant associations between RTs towards cannabis and neutral images and cannabis quantity/past month, craving, cigarettes/past month, arousal/valence ratings of cannabis and neutral images; or standard drinks/past month.

The lack of an attentional bias in CUD versus controls, evidenced by a lack of group-by-image type interaction on RTs, also contrasts with current evidence on cannabis users [16,19] and with prominent neuroscientific theories of addiction, which postulate higher attentional bias and salience towards substance versus non-substance related

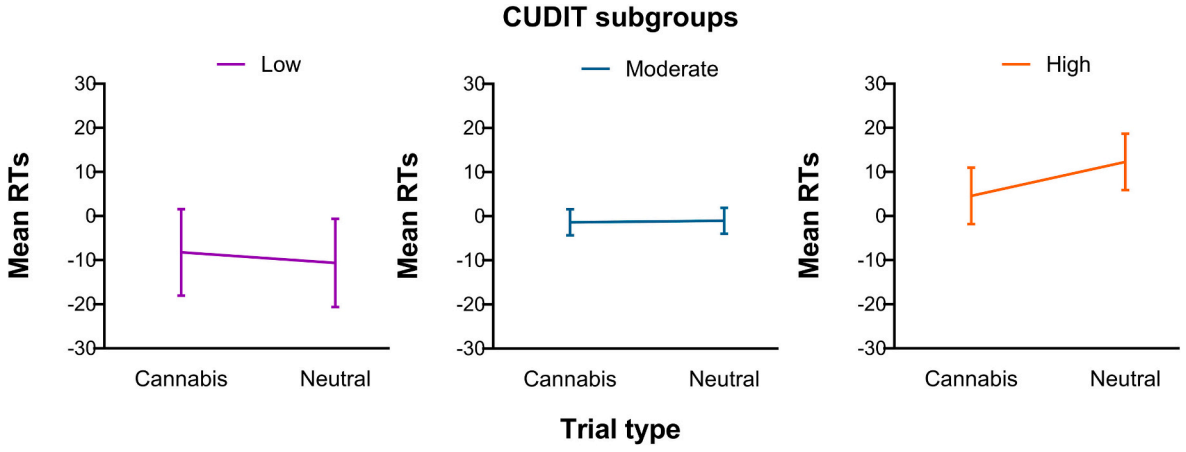

Fig. 2. Visualisation of the emerging effect of image type-by-CUDIT-R on residualised reaction times (RTs, y-axis) with mean and confidence interval (vertical bars), for image type-by-CUDIT-R subgroups shown in distinct plots (low CUDIT-R in purple, moderate CUDIT-R in blue and high CUDIT-R in orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

stimuli in people with substance use disorders [11]. Interestingly, the CUD group rated cannabis images as significantly more pleasant and arousing than neutral images, a pattern of rating that was not observed in the control group, which suggests that cannabis images were indeed more salient for the CUD group than controls. However, the CUD levels of craving pre and post the visual probe task were relatively low (i.e., 3.57 and 3.69 means respectively, range 1–10) and did not differ significantly from each other ($p = .340$). The positive association between craving and attentional bias has been previously theorised [11] and confirmed by emerging evidence [16,21]. Our study failed to find evidence of an association between craving and attentional bias (i.e., based on RTs towards cannabis and neutral images). It is possible that despite their salience, our cannabis images were not sufficiently craving-inducing to elicit attentional bias in a moderate-to-severe CUD sample with prolonged cannabis use.

We obtained a similar lack of group differences when comparing attentional bias scores computed as per previous methodologies [21]. Despite the CUD group showing a modest positive value (i.e., suggestive of cannabis attentional bias) and the control group a small negative value (i.e., indicative of an absence of attentional bias), the groups' mean attentional bias scores did not differ significantly. The non-significant group differences in attentional bias, and the concurrent lack of significant changes in subjective craving pre-to-post the task ($p = .340$) support the notion that the cannabis images used in our study did not elicit the necessary level of craving and, therefore, attentional bias. Alternatively, since other studies have failed to find evidence of attentional bias in people with CUD, it may not be a robust feature of CUD, or it might be confined to participants who are undergoing treatment. However, we observed high individual variability of RTs to cannabis and neutral images, which we statistically adjusted for by including subjects as a random effect. Thus, these differences between our negative findings and significant results from previous work may (in part) be explained by inconsistent approaches regarding individual-level variability.

It is also possible that the absence of attentional bias is due to the specific characteristics of the sample examined (e.g., moderate-to-severe CUD, with past quit attempts, at a contemplative stage yet non-treatment seeking) and therefore, they may not generalise to a broader sample with CUD. Additionally, our sample's age of onset of regular use appears to be later than the ones reported by other studies where attentional bias was evidenced [16,19,56]. As younger age of onset has been associated with negative outcomes (e.g., neuropsychological deficits, psychosis) [57–59], later onset for our sample might have functioned as a protective factor.

Our secondary analyses demonstrated that within the CUD group, there was an association between attentional bias towards cannabis versus neutral images as a function of the CUDIT-R severity. Indeed, the cannabis users having the highest CUDIT-R scores (i.e., score of 20.84+) showed faster RTs to cannabis versus neutral images compared to participants with lower CUDIT-R scores (i.e., scores <20.84). Previous work has shown associations between attentional bias in CUD and the severity of cannabis use-related problems (e.g., CUDIT-R scores of +15) [16,19]. This outlines the potential role of CUDIT-R severity in attentional bias, suggesting heightened salience of cannabis cues in those with greater dependence. However, this notion requires further examination, as this interaction did not survive Bonferroni corrections for multiple comparisons. Additionally, in our sample, attentional bias still did not differ between the highest CUDIT-R sub-group and controls ($p = .088$), which throws into question the role of CUDIT-R scores in attentional bias.

This was the first study to examine associations between arousal and valence and attentional bias, which is key due to their theorised role in incentive-salience [13]. Whilst our findings in relation to mean valence and arousal scores were in line with our hypothesis/expectations, suggesting cannabis images compared to neutral images elicited stronger responses for CUD than controls, we did not find significant effects of arousal and valence on RTs to either cannabis or neutral images.

5.1. Limitations and future directions

The results from this study must be interpreted in the context of several methodological limitations. Firstly, considerations around the poor *reliability* of the visual probe task [60] highlight the importance of incorporating more sensitive measures of attentional bias, such as the dual probe task [61]. Our task showed excellent internal consistency. However, more direct measures, such as eye tracking, could more accurately capture the dynamic nature of attentional bias [19,62].

Secondly, the *ecological validity* of the visual probe task might have been limited by the testing environment, whereby attentional biases present in the real world may be less prominent when at a testing facility (e.g., neuroimaging lab) [63]. Future studies on people who use cannabis should consider testing in naturalistic settings (e.g., locations where participants consume cannabis). Further, the use of personalised images could be considered, as these may be more likely to elicit attentional bias [22].

Lastly, the eligibility criteria used in this study excluded comorbidities, such as major psychiatric disorders other than severe depression and anxiety (e.g., psychosis, trauma-related disorders) as well as substance use disorders (SUD) for substances other than cannabis and nicotine. This might have resulted in a curated sample to detect cannabis-specific effects. However, our results might not be generalisable to the wider population who endorse a CUD, who present with high comorbidity, including other SUD and psychiatric disorders [64]. Future studies are required to confirm the generalisability of the results reported herein in other populations with confirmed comorbidity [65].

In conclusion, this study has filled an important gap in the field, as no research to date has examined attentional bias in community samples including individuals with moderate-to-severe CUD who are thinking about changing their cannabis use despite not being actively in treatment. Our findings challenge the notion of attentional bias as a key feature of CUD, at least among populations akin to those represented in this study and warrant replication in future studies using more sensitive measures.

CRediT authorship contribution statement

Marianna Quinones-Valera: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gary Chan:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Madeleine I. Fraser:** Writing – review & editing, Supervision. **Andrew Jones:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Tom P. Freeman:** Writing – review & editing, Resources, Methodology. **Chandni Hindocha:** Writing – review & editing, Resources, Methodology. **Hannah Thomson:** Writing – review & editing, Investigation, Data curation. **Eugene McTavish:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Hannah Sehl:** Writing – review & editing, Investigation, Conceptualization. **Adam Clemente:** Writing – review & editing, Project administration, Investigation. **Janna Cousijn:** Writing – review & editing, Resources, Methodology. **Izelle Labuschagne:** Writing – review & editing, Funding acquisition. **Peter Rendell:** Writing – review & editing, Funding acquisition. **Gill Terrett:** Writing – review & editing, Investigation, Funding acquisition. **Lisa-Marie Greenwood:** Writing – review & editing, Resources, Methodology, Conceptualization. **Govinda Poudel:** Writing – review & editing, Methodology, Conceptualization. **Chao Suo:** Writing – review & editing, Visualization, Investigation, Formal analysis, Conceptualization. **Victoria Manning:** Writing – review & editing, Supervision, Project administration, Investigation, Formal analysis, Conceptualization. **Valentina Lorenzetti:** Writing – review & editing,

Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

Dr. Adam Clemente reports no financial relationships with commercial interests.

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Dr. Chandni Hindocha joined GW/Jazz Pharmaceuticals after the major contribution to this paper. She has since left GW/Jazz Pharmaceuticals.

Dr. Chao Suo reports no financial relationships with commercial interests.

Dr. Eugene McTavish reports no financial relationships with commercial interests.

Dr. Gary Chan reports no financial relationships with commercial interests.

Dr. Gill Terrett 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.

Dr. Hannah Sehl reports no financial relationships with commercial interests.

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

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

Dr. Janna Cousijn reports no financial relationships with commercial interests.

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

Dr. Madeleine I. Fraser reports no financial relationships with commercial interests.

Ms. Marianna Quinones-Valera reports no financial relationships with commercial interests.

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Appendix A. Supplementary data

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Glossary

AUDIT: Alcohol Use Identification Test
CAPE: Community Assessment of Psychic Experiences
CUD: Cannabis Use Disorder
CUDIT-R: Cannabis Use Disorder Identification Test - Revised
CWS: Cannabis Withdrawal Scale
DSM-IV: Diagnostic and statistical manual of mental disorders (4th ed.)
DSM-5: Diagnostic and statistical manual of mental disorders (5th ed.)
FTND: Fagerström Test for Nicotine Dependence
IQ: Intelligence Quotient
MCQ: Marijuana Craving Questionnaire
MINI: Mini International Neuropsychiatric Interview
MRI: Magnetic Resonance Imaging
ng/mL: Nanograms per millilitre
PSS: Perceived Stress Scale
RTs: Reaction Times
SCID-5-RV: Structured Clinical Interview for DSM-5 Research Version
SOA: Stimulus Onset Asynchrony
STAI-Y: State-Trait Anxiety Index – Y Form
THC-COOH: 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol
TLFB: Timeline Follow-Back
VAS: Visual Analogue Scale
WASI-II: Weschler Abbreviated Standardised Intelligence-II