

Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal

Chandni Hindocha¹ , Tom P. Freeman^{1,2} , Meryem Grabski^{1,3}, Jack B. Stroud¹, Holly Crudgington¹, Alan C. Davies¹, Ravi K. Das¹, William Lawn¹, Celia J. A. Morgan^{1,4} & H. Valerie Curran¹

Clinical Psychopharmacology Unit, University College London, London, UK,¹ National Addiction Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK,² School of Experimental Psychology, University of Bristol, Bristol, UK³ and Psychopharmacology and Addiction Research Centre, University of Exeter, Exeter, UK⁴

ABSTRACT

Background and Aims Cannabidiol (CBD), a non-intoxicating cannabinoid found in cannabis, may be a promising novel smoking cessation treatment due to its anxiolytic properties, minimal side effects and research showing that it may modify drug cue salience. We used an experimental medicine approach with dependent cigarette smokers to investigate if (1) overnight nicotine abstinence, compared with satiety, will produce greater attentional bias (AB), higher pleasantness ratings of cigarette-related stimuli and increased craving and withdrawal; and (2) CBD in comparison to placebo, would attenuate AB, pleasantness of cigarette-related stimuli, craving and withdrawal and not produce any side effects. **Design** Randomized, double-blind cross-over study with a fixed satiated session followed by two overnight abstinent sessions. **Setting** UK laboratory. **Participants** Thirty non-treatment-seeking, dependent cigarette smokers recruited from the community. **Intervention and comparator** 800 mg oral CBD, or matched placebo (PBO) in a counterbalanced order. **Measurements** AB to pictorial tobacco cues was recorded using a visual probe task and an explicit rating task. Withdrawal, craving, side effects, heart rate and blood pressure were assessed repeatedly. **Findings** When participants received PBO, tobacco abstinence increased AB ($P = 0.001$, $d = 0.789$) compared with satiety. However, CBD reversed this effect, such that automatic AB was directed away from cigarette cues ($P = 0.007$, $d = 0.704$) and no longer differed from satiety ($P = 0.82$). Compared with PBO, CBD also reduced explicit pleasantness of cigarette images ($P = 0.011$; $d = 0.514$). Craving (Bayes factor = 7.08) and withdrawal (Bayes factor = 6.95) were unaffected by CBD, but greater in abstinence compared with satiety. Systolic blood pressure decreased under CBD during abstinence. **Conclusions** A single 800-mg oral dose of cannabidiol reduced the salience and pleasantness of cigarette cues, compared with placebo, after overnight cigarette abstinence in dependent smokers. Cannabidiol did not influence tobacco craving or withdrawal or any subjectively rated side effects.

Keywords Abstinence, attentional bias, cannabidiol, cigarette dependence, craving, withdrawal.

Correspondence to: Chandni Hindocha, Clinical Psychopharmacology Unit, University College London, 1–19 Torrington Place, London WC1E 7HB, UK.
E-mail: c.hindocha@ucl.ac.uk

Submitted 4 December 2017; initial review completed 15 January 2018; final version accepted 6 April 2018

INTRODUCTION

More than 1.1 billion people smoke world-wide [1]. A primary addictive driver of cigarette smoking is nicotine withdrawal. Withdrawal occurs upon cessation and includes physiological symptoms (headaches, nausea), affective symptoms (anxiety, depression and irritability) and impaired cognitive performance (delay discounting, response inhibition) [2], which peak within the first few days [3]. Some evidence suggests withdrawal severity predicts

relapse [3–6], prevention of which is a major challenge in the treatment of addiction [7]. Even when using the currently most effective smoking cessation drug (varenicline), a majority still fail to maintain long-term abstinence [8]. Nicotinic medications may also have unpleasant side effects, e.g. nausea [9].

There is mounting evidence that the endogenous cannabinoid (eCB) system is involved in motivation for rewards, including modulating the rewarding effects of drugs [10–15]. In relation to nicotine dependence,

cannabinoid receptor 1 (CB1R) antagonists, such as rimonabant, decrease nicotine conditioned place preference and self-administration in pre-clinical models of addiction [16,17]. In human clinical trials, rimonabant increased smoking abstinence rates 1.6-fold [18,19]. Although potentially effective, rimonabant was withdrawn from the market due to serious neuropsychological side effects.

Cannabidiol (CBD) is the second most abundant cannabinoid in cannabis. It has been shown to have broad therapeutic benefits [20,21] and is showing initial promise as a treatment for addiction, anxiety and schizophrenia. The psychological properties of CBD are suggestive of a potentially ideal drug for smoking cessation. These include its lack of intoxicating and subjective effects [22–24], alongside its anxiolytic [25,26] effects in humans. Its anxiolytic properties are particularly relevant, as anxiety is a primary symptom of tobacco withdrawal [27]. The first human pilot study to investigate CBD as a treatment for nicotine dependence randomized participants to either 1 week of *ad-hoc* CBD or placebo inhaler to be used when they had the urge to smoke. CBD reduced the number of cigarettes reportedly smoked by almost 40%, in comparison to placebo, but did not affect craving [28]. No neurocognitive mechanisms through which CBD may assist with the treatment of smoking cessation were investigated. On the basis of previous findings [29], the authors proposed that a reduction in the salience of drug cues could be one candidate mechanism.

Attentional bias is a potentially important in-laboratory predictive marker of the salience of drug cues. It is heightened, as indexed by dot-probe tasks, during acute abstinence [2]; predicts short-term relapse [30]; and is thought to play a causal role in maintaining addiction [31]. Attentional bias to tobacco stimuli at a short (compared to longer) exposure interval is particularly important, as tobacco abstainers show greater bias to these cues only at short exposure [32]. CBD may reduce the salience of smoking cues, which would be consistent with pre-clinical, human experimental and neuroimaging research. In human naturalistic research, cannabis with high, in comparison to low, levels of CBD reduced cue salience to cannabis-related stimuli in a visual probe task [29]. This was again only observed at the short stimulus exposure interval which taps 'automatic' bias, i.e. that which is not subject to conscious cognitive control. As such, CBD may target an important implicit process involved in relapse. In a pre-clinical rat model of addiction, Ren *et al.* [33] showed that CBD (5–20 mg/kg) attenuated cue-induced heroin-seeking behaviour and relapse, which was maintained for 2 weeks after CBD administration. Furthermore, human translational pilot research showed that a single dose of CBD can attenuate cue-induced craving in heroin users during a 24-hour period and this

was maintained for 7 days [34]. One neuroimaging study suggests that CBD modulates activity of areas in the brain associated highly with salience attribution, including the striatum, hippocampus and prefrontal cortex [35]. Taken together, the experimental evidence provides a strong rationale to hypothesize that CBD is a potential treatment for substance use disorders where the salience of drug cues is key.

This is the first study, to our knowledge, to investigate the effects of CBD during nicotine withdrawal in humans. We employ an experimental medicine approach to investigate CBD's potential to target processes relevant to smoking cessation. Human laboratory studies of smoking abstinence provide an efficient, cost-effective, mechanistic evaluation of medications for smoking behaviour [36], which may facilitate translational research. Specifically, we hypothesized that: (1) overnight nicotine abstinence, compared with satiety, will produce a range of nicotine withdrawal symptoms in dependent cigarette smokers which include greater attentional bias (short stimulus exposure), higher pleasantness of cigarette-related stimuli and increased craving and withdrawal; (2) CBD in comparison to placebo, would attenuate attentional bias and pleasantness of cigarette-related stimuli, craving and withdrawal symptomology relative to pre-drug scores; and (3) CBD in comparison to placebo, will not produce any significant cardiovascular or side effects.

MATERIAL AND METHODS

Design and participants

Thirty participants attended three sessions [mean = 7.85, standard deviation (SD) = 2.77 days between sessions]. Participants smoked as normal before their first (baseline) session, verified with expired carbon monoxide (CO) ≥ 10 parts per million (p.p.m.) (Bedfont Scientific, Harrietsham, UK). Participants then attended two sessions after overnight (~12-hour) abstinence, verified by CO ≤ 10 p.p.m. [37]. A double-blind, placebo-controlled, cross-over design was used to compare the effects of 800 mg oral CBD with matched placebo (PBO) after overnight smoking abstinence. Treatment order for abstinent sessions was randomized and counterbalanced. Participants received the drug based on a randomization code, balanced for gender (www.random.org), which was concealed from experimenters until all data were collected and entered. Drug concealment occurred through participant-numbered, opaque, sealed envelopes. There was a minimum washout period of 1 week between drug sessions to preclude potential CBD carry-over effects following previous research [23,24].

Dependent cigarette smokers were recruited from the community through on-line message boards. Inclusion criteria were: (i) age 18–50 years; (ii) smoking ≥ 10

cigarettes a day for at least the last year; (iii) Fagerström Test for Nicotine Dependence (FTND) score ≥ 4 (moderate dependence) [38]; (iv) smoking first cigarette within an hour of waking; and (v) negative drug urine screen for all major drugs of abuse at baseline. Exclusion criteria were: (i) use of nicotine replacement therapy/cessation pharmacotherapy; (ii) self-reported recent use of cannabis or other illicit drugs; (iii) recent (past 4 weeks) or ongoing use of e-cigarettes; (iv) current mental or physical health issues or learning impairments; (v) pregnancy or breastfeeding; and (vi) allergies to CBD, gelatine, lactose, microcrystalline cellulose or chocolate.

Power calculation

We calculated that $n = 20$ would be necessary to have power of 95% at an alpha of 5% to detect a large effect size of $d = 0.78$ ($F = 0.38$). This was based on the difference in the number of cigarettes smoked pre–post 1 week of CBD inhaler versus placebo (23.25 cigarettes) in Morgan *et al.* [28]. This sample size was increased by 50%, yielding a final sample of 30 to adjust for ‘winner’s curse’ [39], i.e. over-inflation of effect sizes from initial positive studies.

Drug administration

Participants were administered 800 mg oral CBD [pure synthetic (–) CBD, STI Pharmaceuticals, Brentwood, UK] or matched placebo (lactose powder) in identical, opaque capsules on each testing occasion. 800 mg was chosen, as it produces an increase in plasma concentrations after acute administration [$C_{\max} = 77.9$, standard error = 25 ng/ml, $T_{\max} = 180$ minutes [23]), is well tolerated in humans, is efficacious for schizophrenia [40], increases extracellular anandamide levels [40] and should be sufficient to influence salience attribution after a single dose [35].

Assessments

Visual probe task (Fig. 1)

This task was implemented as a measure of attentional bias [41]. Thirty smoking (target) and composition-matched neutral (non-target) images were shown [42]. Each trial began with a fixation point (500 ms). A pair of images then appeared on the left and right of the screen for either a short (200 ms) or long (500 ms) duration to assess automatic orientating and controlled attention processing, respectively. Image pairs were replaced by a probe (an arrow pointing upwards or downwards) in the location of either the neutral or smoking-related image. The probe remained on screen until the participant responded to identify the probe orientation (upwards or downwards) by pressing one of two appropriate response keys as quickly and accurately as possible (defined as a ‘correct trial’ if a correct response was made). Probes replaced the cigarette-related and neutral images equally often. The position of image type, probe location and stimulus duration was counterbalanced. Trials were displayed in a single block with each pair presented eight times, producing 80 critical trials and 32 neutral trials. The task began with four buffer trials. Trial order was randomized each time the task was run. The task was programmed with Experiment Builder (SR Research, Kanata, ON, Canada).

Pleasantness rating task (PRT)

Each trial began with a fixation cross of 500 ms, followed by either a cigarette or neutral cue, presented in a randomized order for 3000 ms. Stimuli were matched on brightness and complexity. Cigarette stimuli involved smoking-related scenes and were the same as the visual probe. Participants rated the pleasantness of each image on a scale of –3 (very unpleasant) to +3 (very pleasant). Valence was

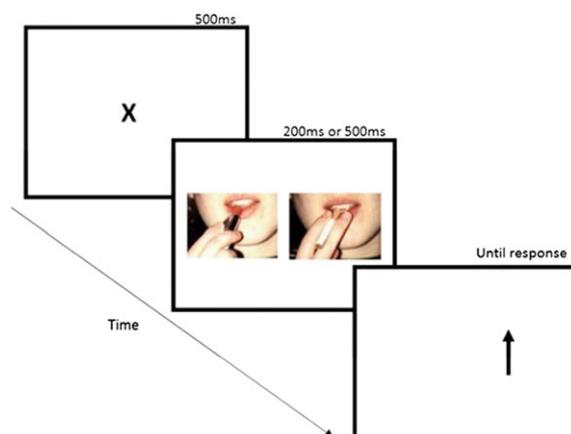


Figure 1 Trial structure for the visual probe task. Example of cigarette (right) and matched neutral stimuli (left) provided. [Colour figure can be viewed at wileyonlinelibrary.com]

recorded. Three versions were available for counterbalancing. The experiment was conducted using Psychopy [43,44].

State questionnaires

Withdrawal was assessed with the Mood and Physical Symptoms Scale (MPSS) [45]. Craving was assessed with Questionnaire of Smoking Urges–Brief (QSU-B) [46]. Participants completed a six-item side-effect form with items: ‘strong drug effect’, ‘good drug effect’, ‘willing to take drug again’, ‘like drug effect’, ‘I have an upset stomach’ and ‘I have a headache’. Each item was rated on a 10-point visual analogue scale (VAS) from ‘not at all’ to ‘extremely’.

Trait questionnaires

The FTND was used to assess nicotine dependence [38]. Anxiety was assessed with the State–Trait Anxiety Inventory (STAI) [47] and depression with the Beck Depression Inventory (BDI) [48]. A comprehensive drug history was taken [49]. Pre-morbid verbal intelligence was indexed by the Spot the Word task [50].

Procedure

After telephone screening eligible participants attended a baseline ‘satiated session’, prior to which they smoked as normal. This involved further screening assessments (CO, urine test, pregnancy test, Spot the Word) as well as the same assessments as on the abstinent days. On the satiated day, participants completed state measures of craving (QSU-B) and withdrawal (MPSS) after they were deemed eligible (T1; +12 minutes), were asked to smoke a cigarette (Marlboro Gold) to ensure satiety (+30 minutes), then completed a second measure of craving and withdrawal (T2; +35 minutes), the visual probe task (+60 minutes), PRT (+68 minutes) and a final measure of craving and withdrawal (T3; +75 minutes). On abstinent sessions, participants attended two ~3.5-hour sessions, separated by 1 week, after overnight abstinence. They provided a CO reading, then completed state questionnaires and cardiovascular measures [QSU-B, MPSS, heart rate (HR), blood pressure (BP) (T1, +5 minutes)]. CBD or matched placebo was then administered orally (+10 minutes). After drug administration, participants completed half the trait questionnaires in each session. At 70 minutes (T2) and 130 (T3) minutes they again completed the MPSS, QSU-B, HR and BP. Participants then completed the visual probe (+180 minutes) and PRT (+188 minutes). At 200 minutes, participants completed a final measure of craving and withdrawal (T4). A detailed schedule of assessments can be found in Supporting information, Table S1. Other assessments are reported elsewhere [51]. All participants

provided written informed consent. Ethical approval was given by UCL Ethics Committee. Participants were reimbursed £10 per hour.

Statistical analysis

Statistical analyses were performed in the Statistical Package for Social Scientists (SPSS version 24; IBM, Chicago, IL, USA). Visual inspection of diagnostic plots was used to check for normality. Where the assumption of sphericity was violated, the Greenhouse–Geisser correction was used and rounded to the nearest integer; η^2_p denotes partial eta-squared. Outliers $> 1.5 \times$ the interquartile range (IQR) were Winsorized to the next highest/lowest value. For the PRT, 4.2% of the data were missing due to technical issues and were replaced with the means of the condition. Sensitivity analysis showed that Winsorization or mean imputation did not modify any result.

Only correct trials (99.97% of the data) were analysed for the visual probe and responses > 2000 and < 200 ms were removed. Following Mogg *et al.* [52], bias scores were calculated for the visual probe and PRT, such that a positive score indicates a bias towards cigarette cues. This was calculated as the difference in RT between when the probe replaced the neutral, in comparison to cigarette, stimulus ($RT_{\text{neutral}} - RT_{\text{cigarette}}$) for the visual probe task; and $\text{cigarette_valence} - \text{neutral_valence}$ for the PRT.

The visual probe and PRT were analysed using repeated-measures analysis of variance (ANOVA) with two *a priori* orthogonal Helmert contrasts to investigate main effects. The first describes the main effect of abstinence, i.e. satiated (SAT) versus abstinent (CBD). The second describes the main effect of drug, i.e. CBD versus PBO. For the visual probe task, an additional task-specific factor of exposure time was included to investigate automatic (short) in comparison to strategic (long) processing. Interactions between condition and exposure were explored via pairwise *post-hoc* comparisons, Bonferroni-corrected locally within each omnibus term.

Craving (QSU) and withdrawal (MPSS) symptomology were analysed with two repeated-measures ANOVAs because of the difference in timing between sessions and number of assessments of craving and withdrawal. The first investigated satiation (T2: immediately after a cigarette) versus abstinence (T1: pre-drug administration). The second compared CBD in comparison to PBO across all time-points [T1 (pre-drug), T2, T3, T4]. Interactions between condition and time were assessed with *post-hoc* comparisons, Bonferroni-corrected locally within each omnibus term.

Side effects, HR and BP were measured three times on abstinent sessions, therefore these data were analysed with a 2 [CBD, PBO] \times 3 T1 (pre-drug), T2, T3 ANOVA. Interactions between condition and time were assessed

Table 1 Participants' demographic and trait variables. Results are displayed as mean (standard deviation).

<i>n</i>	30
Age (years)	28.07 (8.66)
FTND score	5.56 (1.13) range 4–8
Cigarettes per day	13.5 (2.39) range 10–20
Time to first cigarette (mins)	25.5 (15.87)
Years smoked	9.55 (7.36)
Years smoking > 10+ cigarettes/day	8.17 (7.08)
Life-time quit attempts (<i>n</i> = 25)	3.2 (3.91)
Most successful quit attempt (days)	100.48 (163.47)
Body mass index	23.98 (7.78)
Spot the Word	48.03 (4.15)
STAI	40.53 (9.4)
BDI	10.36 (7.54)

FTND = Fagerström Test for Nicotine Dependence; STAI = Stait–Trait Inventory; BDI = Beck Depression Inventory.

with *post-hoc* comparisons, Bonferroni-corrected locally within each omnibus term.

Scaled Jeffreys–Zellner–Siow (JZS) Bayes factors (BF) were calculated when the main effect of drug (CBD versus PBO) was not significant according to frequentist statistics ($P > 0.05$). We used a scaled-information prior of $r = 1$ [53].

Carry-over effects were assessed using an additional between-subjects factor of 'order'. No order effects were found for the main analyses (as evidenced by no interactions or main effects involving treatment order). Therefore, we report results without accounting for order. As we did not have any specific a priori hypotheses regarding covariates, we did not include any, as per Kraemer [54].

RESULTS

Participant characteristics (Tables 1 & 2)

Thirty participants (14 female) took part. The sample had a mean (SD) age of 28.07 (8.66) years, with an FTND score of 5.56 (1.13) demonstrating moderate dependence. They smoked 13.5 (2.39) cigarettes per day, which is slightly more than the national adult average of 11.5 [55]. Further demographics, trait scores and cigarette smoking

information can be found in Table 1. Use of other drugs was minimal in this population (Table 2). For confirmation of both self-reported and CO level indexed abstinence; see Supporting information.

Attentional bias

Visual probe task (Fig. 2)

There was a main effect of abstinence ($F_{(1,29)} = 9.52$, $P = 0.004$, $\eta^2_p = 0.27$), which showed that there was a greater attentional bias under abstinence versus satiation. There was a main effect of drug, which was subsumed under the condition \times exposure interaction ($F_{(2,58)} = 4.66$, $P = 0.013$, $\eta^2_p = 0.14$). The interaction showed that under the short stimulus exposure, there was greater attentional bias to cigarette cues in the PBO condition, in comparison to SAT (45.15 ms, 95% CI = 71.77, 18.54, $P = 0.001$, $d = 0.789$), as well as greater attentional bias in the PBO condition in comparison to CBD (36.47 ms, 95% CI = 64.18, 8.77, $P = 0.007$, $d = 0.704$), but not between SAT and CBD (−8.68 ms, 95% CI = −28.43, 11.07, $P = 0.82$). Under the long stimulus exposure, none of these comparisons were significant. Additionally, AB was greater to cigarette cues under the long, in comparison to short, exposure time for CBD (20.94 ms, 95% CI = 40.29, 5.15, $P = 0.015$), but not under SAT ($P = 0.263$) or PBO ($P = 0.155$). There was no main effect of exposure time ($F_{(1,29)} = 2.14$, $P = 0.155$, $\eta^2_p = 0.07$).

Pleasantness rating task

Valence (Fig. 3)

There was no main effect of abstinence ($F_{(1,29)} = 0.53$, $P = 0.47$, $\eta^2_p = 0.02$). There was a significant main effect of drug ($F_{(1,29)} = 7.41$, $P = 0.011$, $\eta^2_p = 0.20$), indicating less bias towards cigarette stimuli on CBD compared to PBO (−0.51, 95% CI = −0.99, −0.03); $d = 0.514$).

Craving (Fig. 4)

Pre-drug QSU scores were greater in abstinent conditions versus satiation ($F_{(1,29)} = 99.75$, $P < 0.001$, $\eta^2_p = 0.78$).

Table 2 Drug use history (*n* = the number of people who used the drug in the past year). Results are displayed as mean (standard deviation).

	Alcohol	Cannabis	MDMA	Cocaine
<i>n</i>	26	17	9	9
Days since last use	6.39 (10.13)	100 (68.30)	84.66 (82.22)	100 (56.12)
Number of years used	13.08 (8.68)	8.29 (4.61)	4.55 (1.59)	3.33 (2.12)
Days per month	11.43 (8.85)	0.75 (1.30)	0.67 (1.32)	0.5 (1.15)
Typical amount per session	7.1 units (3.23)	0.87 joints (0.69)	258.33 mg (144.70)	800 mg (0.83)

MDMA = 3,4-methylenedioxymethamphetamine.

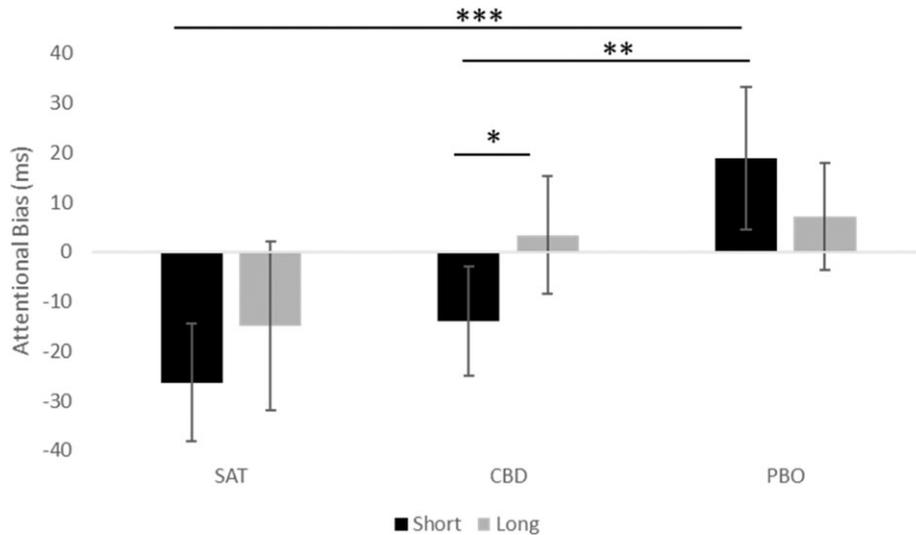


Figure 2 Attentional bias across satiated (30 min post-cigarette) and abstinent (180 min post-drug administration) for both short and long exposure times. Estimated marginal means are presented with 95% confidence interval error bars. * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$. SAT=satiated; CBD=cannabidiol; PBO=placebo

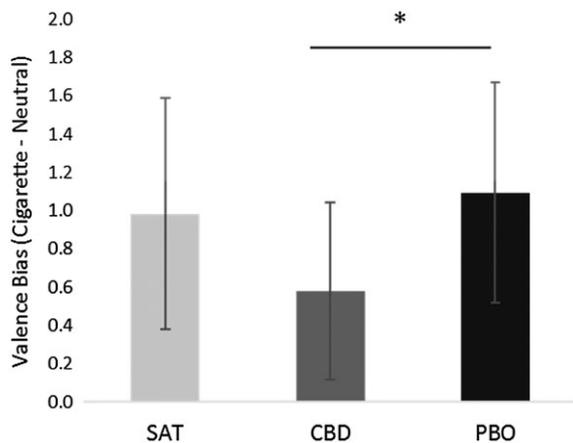


Figure 3 Bias in pleasantness rating (calculated as cigarette valence minus neutral valence) for satiated (38 min post-cigarette) and abstinent (188 min post-drug administration) conditions. Estimated marginal means are presented with 95% confidence interval error bars. * $P \leq 0.05$

There was no difference between CBD and PBO, pre-drug administration ($P = 0.99$) confirmed by a Bayesian analysis, showing that the null was 7.08 more likely than the alternative given the data (JZS BF = 7.08). To investigate if CBD attenuated craving in comparison to PBO on abstinent sessions, we conducted an ANOVA that showed a main effect of time ($F_{(2,54)} = 8.34, P < 0.001, \eta^2 p = 0.22$); however, there was no main effect of drug ($P = 0.81$) confirmed by a Bayesian analysis (JZS BF = 6.87) or drug \times time interaction, suggesting no difference between CBD and PBO.

Withdrawal (Fig. 5)

Pre-drug MPSS scores were greater under abstinent conditions versus satiation ($F_{(1,29)} = 29.88, P < 0.001, \eta^2 p = 0.51$), suggesting that abstinence increased withdrawal. There was no difference between CBD and PBO,

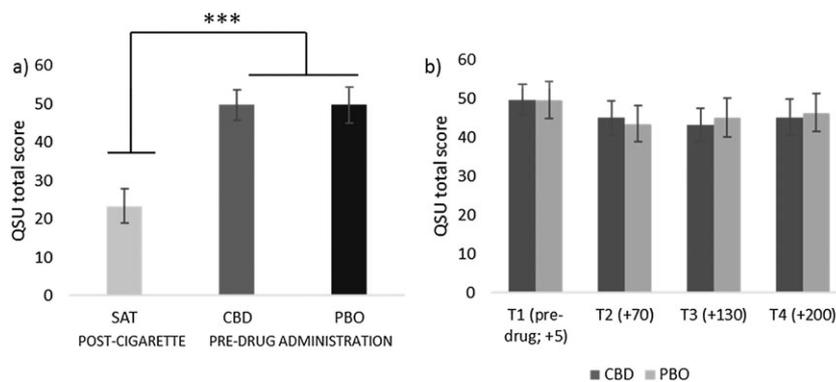


Figure 4 Scores for the Questionnaire of Smoking Urges–Brief (QSU-B) (craving). Left panel (a) shows significantly greater craving on abstinent sessions before drug administration, in comparison to satiation scores after a cigarette. Right panel (b) compares cannabidiol (CBD) and matched placebo (PBO) across all time-points pre- and post-drug administration (T2 onwards). See Supporting information, Table S1 for details on timing. Estimated marginal means with 95% confidence interval are presented. *** $P \leq 0.001$

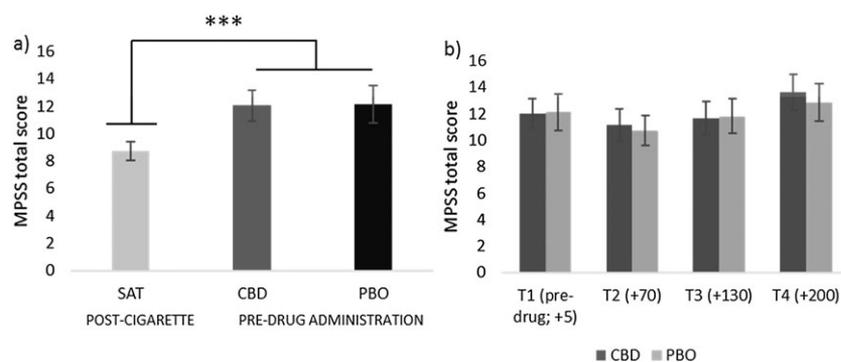


Figure 5 Scores for the Mood and Physical Symptoms Scale (MPSS) (withdrawal symptoms). Left panel (a) shows significantly greater withdrawal on abstinent sessions before drug administration, in comparison to satiation scores after a cigarette. Right panel (b) compares cannabidiol (CBD) and matched placebo (PBO) across all time points pre- and post-drug administration (T2 onwards). See Supporting information, Table S1 for details on timing. Estimated marginal means with 95% confidence interval are presented. *** $P \leq 0.001$

pre-drug administration ($P = 0.85$) confirmed by Bayesian analysis showing the null was 6.95 more likely than the alternative given the data (JZS BF = 6.95). To investigate if CBD attenuated withdrawal in comparison to PBO on abstinent sessions, we conducted an ANOVA that showed a main effect of time ($F_{(2,69)} = 8.98$, $P < 0.001$, $\eta^2_p = 0.24$); however, there was no effect of drug ($F_{(1,29)} = 0.22$, $P = 0.64$, $\eta^2_p = 0.01$) confirmed by a Bayesian analysis (JZS BF = 6.35) or drug \times time interaction.

Analysis of the additional MPSS questions (amount of time spent with urges and strength of urges) can be found in Supporting information.

Cardiovascular effects

Heart rate (HR)

There was a main effect of time ($F_{(1,39)} = 33.73$, $P < 0.001$, $\eta^2_p = 0.54$) which showed that HR decreased over time. There was no main effect of drug ($P = 0.30$) confirmed by a Bayesian analysis (JZS BF = 4.17) and no interaction between drug and time.

Blood pressure (BP)

A main effect of drug ($F_{(1,29)} = 6.72$, $P = 0.015$, $\eta^2_p = 0.19$) showed higher systolic BP after PBO than after CBD (+3.40, 95% CI = 0.72–6.08). There was a main effect of time ($F_{(2,58)} = 13.24$, $P < 0.001$, $\eta^2_p = 0.31$), which showed that systolic BP decreased over time. There were no main effects or interactions for diastolic BP.

Side effects

One interaction between drug and time was found for 'headache', but no significant pairwise comparisons emerged. No other main effects of drug or interactions were found between drug and time. See Supporting information for more details.

DISCUSSION

This study employed an experimental medicine approach to investigate the effects of a single 800-mg oral dose of CBD on nicotine withdrawal. We found evidence that, compared to placebo, CBD reversed attentional bias to cigarette cues in abstinent smokers, such that it was no longer significantly different from attentional bias when they were satiated. Simultaneously, we observed a reduction in explicit pleasantness during abstinence, such that cigarette stimuli were rated as less pleasant after CBD than placebo. These neurocognitive effects occurred in the absence of any changes in subjective states of craving and withdrawal between CBD and placebo. This suggests that CBD may have specific effects on the evaluative and motivational salience-reducing properties of drug cues, which is consistent with clinical [29,34] and pre-clinical research [33]. Moreover, no significant psychoactive or side effects were observed. These results therefore support the potential of CBD in targeting specific neurocognitive processes in nicotine addiction.

To be specific, a reduction in the implicit salience of drug cues of a large effect size was observed in the CBD condition (versus placebo) after overnight abstinence in dependent cigarette smokers. That is to say that participants were over 40 ms faster to detect probes replacing smoking (versus neutral) cues under placebo than under CBD. This was observed in the short exposure time only, consistent with our initial hypothesis and with previous findings regarding attentional bias [32] and CBD [29]. The short exposure time is related to implicit automatic processing and initial orientation to cues, which occur outside the individual's explicit awareness [32,56].

These results suggest that one potential candidate mechanism by which CBD may exert anti-addictive effects is by normalizing the salience of drug cues. This is in line with the incentive salience model of drug addiction [57]. Given that attentional bias may predict smoking cessation

outcomes [30], CBD may be useful in aiding early abstinence by reducing the salience of drug-related cues. However, it is unlikely that attentional bias is the only driver of nicotine addiction, and other mechanisms require investigation.

As well as effects of CBD on implicit attentional bias, a reduction in explicit pleasantness for cigarettes under CBD compared to placebo was also observed. Explicit pleasantness is important with regard to addiction because it partly indexes the reinforcing value of a drug. In humans, users of high, in comparison to low CBD : THC ratio cannabis showed lower self-reported pleasantness of cannabis stimuli, which follows the same pattern as the present study [29] and may be related to endocannabinoid involvement in hedonic experiences [58]. However, there was no difference between abstinence and satiated sessions, which was unexpected, as it was hypothesized and has been shown previously [59].

The absence of CBD effects on withdrawal and craving are surprising because, theoretically, the incentive salience model of Robinson & Berridge [57] would suggest that a reduction in attentional bias would be accompanied by a reduction in craving. Moreover, Hurd *et al.* [34] found that CBD reduced cue-induced craving and anxiety which was maintained for 24 hours in heroin users (however, a different paradigm was used). It is notable that both Morgan *et al.* [28] and the present study did not find effects on tonic craving, therefore CBD may not be effective for all smokers but only those suffering from heightened attentional bias to drug cues. The incentive salience model equates craving with wanting a drug, not liking a drug, and argues that craving reflects the attribution of intense incentive salience to reward-associated stimuli. In the present research, CBD reduced attentional bias, arguably an index of incentive salience, but had no impact on craving. Given that craving and attentional bias are dissociated here, with CBD specifically attenuating attentional bias, this research seems to be inconsistent with the model. It may be the observed reduction in attentional bias is a result of a general motivational effect in that CBD may be reducing general orienting to salient cues, thus explaining the observed dissociation. Future research should investigate whether CBD also modifies orientating to other salient stimuli such as food cues. This has been investigated with street cannabis, where individuals smoking cannabis high (in comparison to low) in CBD had significantly lower attentional bias to both cannabis and food-related cues [29].

The neurobiological mechanism by which CBD may exert these effects is unclear; however, a promising candidate is through normalization of extracellular anandamide, via inhibition of fatty acid amide hydrolase (FAAH). FAAH inhibitors have been shown to reduce nicotine self-administration and conditioned place preference (CPP) in rats and monkeys as well as nicotine-induced dopamine

release in the nucleus accumbens [60–63]. Here, we were unable to measure anandamide levels; however, this putative mechanism requires further research, as more potent FAAH inhibitors may provide more anti-addictive effects than CBD. This may also be the mechanism by which CBD may alleviate psychotic symptoms in people with schizophrenia [40].

Limitations

First, we used an experimental medicine approach to investigate mechanistic effects of single-dose CBD during overnight tobacco withdrawal, therefore it is unclear whether these effects will translate to the clinic and how long they might last. The visual probe task provides only a cross-sectional snapshot of attentional bias in a laboratory setting, and may suffer from low internal reliability [64]. In this case, ecological momentary assessment may be more indicative of attentional bias in actual drug-taking environments. Additionally, use of eye tracking, functional magnetic resonance imaging (fMRI) or electroencephalogram (EEG) would provide additional information on the time-course and neural correlates of attentional bias. Moreover, only a single dose of CBD was given; future research needs to investigate repeated dosing and a range of doses [65]. Finally, compliance with tobacco smoking abstinence instructions was verified with breath CO, but abstinence from other nicotine products was based on self-report, therefore we could not verify objectively that participants had not used other nicotine products. However, craving and withdrawal scores were markedly higher under abstinence than satiation, suggesting that self-report was reliable.

CONCLUSIONS

This is the first study, to our knowledge, to investigate effects of CBD on nicotine withdrawal. After overnight tobacco abstinence, cigarette smokers administered 800 mg CBD, in comparison to placebo, show a reduced salience and pleasantness of cigarette cues, in the absence of any reductions in withdrawal or craving. This study highlights the potential utility of CBD as a treatment for specific neurocognitive components of tobacco use disorder, and suggests that one potential mechanism by which CBD may exert its effects on addiction is via a reduction in the salience of drug cues. These results support the growing literature regarding CBD in the treatment of addictive disorders.

Declaration of interests

None.

Acknowledgements

This research was funded by a PhD Studentship from the Medical Research Council (MRC) to C.H. and an MRC DPFS award (MR/K015524/1) to H.V.C. and C.J.A.M. T.P.F. is funded by a Senior Academic Fellowship from the Society for the Study of Addiction.

References

- World Health Organisation. *WHO global report on trends in prevalence of tobacco smoking 2015*. Geneva, Switzerland: WHO Press; 2015.
- Grabski M., Curran H. V., Nutt D. J., Husbands S. M., Freeman T. P., Fluharty M. *et al.* Behavioral tasks sensitive to acute abstinence and predictive of smoking cessation success: a systematic review and meta-analysis. *Addiction* 2016; **111**: 2134–44.
- Hughes J. R. Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tob Res* 2007; **9**: 315–27.
- Killen J. D., Fortmann S. P. Craving is associated with smoking relapse: findings from three prospective studies. *Exp Clin Psychopharmacol* 1997; **5**: 137–42.
- Piasecki T. M., Jorenby D. E., Smith S. S., Fiore M. C., Baker T. B. Smoking withdrawal dynamics: I. Abstinence distress in lapsers and abstainers. *J Abnorm Psychol* 2003; **112**: 3–13.
- Patterson E., Jepson C., Loughhead J., Perkins K., Strasser A. A., Siegel S. *et al.* Working memory deficits predict short-term smoking resumption following brief abstinence. *Drug Alcohol Depend* 2010; **106**: 61–4.
- Potenza Marc N., Sofuoglu M., Carroll Kathleen M., Rounsaville Bruce J. Neuroscience of behavioral and pharmacological treatments for addictions. *Neuron* 2011; **69**: 695–712.
- Schnoll R. A., Lerman C. Current and emerging pharmacotherapies for treating tobacco dependence. *Expert Opin Emerg Drugs* 2006; **11**: 429–44.
- Cahill K., Lindson-Hawley N., Thomas K. H., Fanshawe T. R., Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2016; Issue 5 Art. No.: CD006103. <https://doi.org/10.1002/14651858.CD006103.pub7>.
- Parsons L. H., Hurd Y. L. Endocannabinoid signalling in reward and addiction. *Nat Rev Neurosci* 2015; **16**: 579–94.
- Lawn W., Freeman T. P., Pope R. A., Joye A., Harvey L., Hindocha C. *et al.* Acute and chronic effects of cannabinoids on effort-related decision-making and reward learning: an evaluation of the cannabis 'amotivational' hypothesis. *Psychopharmacology (Berl)* 2016; **233**: 3537–52.
- Zlebnik N. E., Cheer J. F. Beyond the CB1 receptor: is cannabidiol the answer for disorders of motivation? *Annu Rev Neurosci* 2016; **39**: 1–17.
- Prud'homme M., Cata R., Jutras-Aswad D. Cannabidiol as an intervention for addictive behaviors: a systematic review of the evidence. *Subst Abuse Res Treat* 2015; **9**: 33–8.
- Hindocha C., Lawn W., Freeman T. P., Curran H. V. Individual and combined effects of cannabis and tobacco on drug reward processing in non-dependent users. *Psychopharmacology (Berl)* 2017; **234**: 3153–63.
- Viudez-Martínez A., García-Gutiérrez M. S., Navarrón C. M., Morales-Calero M. I., Navarrete F., Torres-Suárez A. I. *et al.* Cannabidiol reduces ethanol consumption, motivation and relapse in mice. *Addict Biol* 2018; **23**: 154–64.
- Le Foll B., Goldberg S. R. Rimonabant, a CB1 antagonist, blocks nicotine-conditioned place preferences. *Neuroreport* 2004; **15**: 2139–43.
- Forget B., Hamon M., Thiébot M.-H. Cannabinoid CB1 receptors are involved in motivational effects of nicotine in rats. *Psychopharmacology (Berl)* 2005; **181**: 722–34.
- Cahill K., Ussher M. H. Cannabinoid type 1 receptor antagonists for smoking cessation. *Cochrane Database Syst Rev* 2011; Issue 3 Art. No.: CD005353. <https://doi.org/10.1002/14651858.CD005353.pub4>.
- Robinson J. D., Cinciripini P. M., Karam-Hage M., Aubin H. J., Dale L. C., Niaura R. *et al.* Pooled analysis of three randomized, double-blind, placebo controlled trials with rimonabant for smoking cessation. *Addict Biol* 2017; **23**: 291–303.
- Pertwee R. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ 9-tetrahydrocannabinol, cannabidiol and Δ 9-tetrahydrocannabivarin. *Br J Pharmacol* 2008; **153**: 199–215.
- Russo E. B. Beyond cannabis: plants and the endocannabinoid system. *Trends Pharmacol Sci* 2016; **37**: 594–605.
- Hindocha C., Freeman T. P., Schafer G., Gardener C., Das R. K., Morgan C. J. *et al.* Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users. *Eur Neuropsychopharmacol* 2015; **25**: 325–34.
- Babalonis S., Haney M., Malcolm R. J., Lofwall M. R., Votaw V. R., Sparenborg S. *et al.* Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug Alcohol Depend* 2016; **172**: 9–13.
- Haney M., Malcolm R. J., Babalonis S., Nuzzo P. A., Cooper Z. D., Bedi G. *et al.* Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis. *Neuropsychopharmacology* 2015; **41**: 1974–82.
- Fusar-Poli P., Crippa J. A., Bhattacharyya S., Borgwardt S. J., Allen P., Martin-Santos R. *et al.* Distinct effects of Δ 9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Arch Gen Psychiatry* 2009; **66**: 95–105.
- Bergamaschi M. M., Queiroz R. H. C., Chagas M. H. N., de Oliveira D. C. G., De Martinis B. S., Kapczinski F. *et al.* Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. *Neuropsychopharmacology* 2011; **36**: 1219–26.
- Hughes J. R. Tobacco withdrawal in self-quitters. *J Consult Clin Psychol* 1992; **60**: 689–97.
- Morgan C. J., Das R. K., Joye A., Curran H. V., Kamboj S. K. Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. *Addict Behav* 2013; **38**: 2433–6.
- Morgan C. J., Freeman T. P., Schafer G. L., Curran H. V. Cannabidiol attenuates the appetitive effects of Δ 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology* 2010; **35**: 1879–85.
- Waters A. J., Shiffman S., Sayette M. A., Paty J. A., Gwaltney C. J., Balabanis M. H. Attentional bias predicts outcome in smoking cessation. *Health Psychol* 2003; **22**: 378–87.
- Franken I. H. Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; **27**: 563–79.
- Freeman T., Morgan C., Beesley T., Curran H. Drug cue induced overshadowing: selective disruption of natural reward processing by cigarette cues amongst abstinent but not satiated smokers. *Psychol Med* 2012; **42**: 161–71.

33. Ren Y., Whittard J., Higuera-Matas A., Morris C. V., Hurd Y. L. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. *J Neurosci* 2009; **29**: 14764–9.
34. Hurd Y. L., Yoon M., Manini A. F., Hernandez S., Olmedo R., Ostman M. *et al.* Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage. *Neurotherapeutics* 2015; **12**: 807–15.
35. Bhattacharyya S., Falkenberg I., Martin-Santos R., Atakan Z., Crippa J. A., Giampietro V. *et al.* Cannabinoid modulation of functional connectivity within regions processing attentional salience. *Neuropsychopharmacology* 2015; **40**: 1343–52.
36. Lerman C., LeSage M. G., Perkins K. A., O'Malley S. S., Siegel S. J., Benowitz N. L. *et al.* Translational research in medication development for nicotine dependence. *Nat Rev Drug Discov* 2007; **6**: 746–62.
37. Benowitz N. L., Jacob P. III, Ahijevych K., Jarvis M. J., Hall S., LeHouezec J. *et al.* Biochemical verification of tobacco use and cessation. *Nicotine Tob Res* 2002; **4**: 149–59.
38. Heatherton T. F., Kozlowski L. T., Frecker R. C., Fagerstrom K. O. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 1991; **86**: 1119–27.
39. Button K. S., Ioannidis J. P., Mokrysz C., Nosek B. A., Flint J., Robinson E. S. *et al.* Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci* 2013; **14**: 365–76.
40. Leweke F., Piomelli D., Pahlisch F., Muhl D., Gerth C., Hoyer C. *et al.* Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2012; **2**: e94.
41. Charles M., Wellington C., Mokrysz C., Freeman T., O'Ryan D., Curran H. Attentional bias and treatment adherence in substitute-prescribed opiate users. *Addict Behav* 2015; **46**: 100–5.
42. Mogg K., Bradley B. P., Field M., De Houwer J. Eye movements to smoking-related pictures in smokers: relationship between attentional biases and implicit and explicit measures of stimulus valence. *Addiction* 2003; **98**: 825–36.
43. Peirce J. W. PsychoPy—psychophysics software in Python. *J Neurosci Methods* 2007; **162**: 8–13.
44. Peirce J. W. Generating stimuli for neuroscience using PsychoPy. *Front Neuroinform* 2009; **2**: 10.
45. West R., Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology (Berl)* 2004; **177**: 195–9.
46. Tiffany S. T., Drobes D. J. The development and initial validation of a questionnaire on smoking urges. *Br J Addict* 1991; **86**: 1467–76.
47. Spielberger C. D., Gorsuch R. L., Lushene R. E., Vagg P. R. State-trait anxiety inventory (STAI). *BiB* 2010; **1970**: 180.
48. Beck A. T., Ward C., Mendelson M. Beck Depression Inventory (BDI). *Arch Gen Psychiatry* 1961; **4**: 561–71.
49. Hindocha C., Freeman T. P., Xia J. X., Shaban N. D. C., Curran H. V. Acute memory and psychotomimetic effects of cannabis and tobacco both 'joint' and individually: a placebo-controlled trial. *Psychol Med* 2017; **47**: 2708–19.
50. Baddeley A., Emslie H., Nimmo-Smith I. The Spot-the-Word test: a robust estimate of verbal intelligence based on lexical decision. *Br J Clin Psychol* 1993; **32**: 55–65.
51. Hindocha C., Freeman T. P., Grabski M., Crudgington H., Davies A. C., Stroud J. B. *et al.* The effects of cannabidiol on impulsivity and memory during abstinence in cigarette dependent smokers. *Sci Rep* 2018; <https://doi.org/10.1038/s41598-018-25846-2>.
52. Mogg K., Field M., Bradley B. P. Attentional and approach biases for smoking cues in smokers: an investigation of competing theoretical views of addiction. *Psychopharmacology (Berl)* 2005; **180**: 333–41.
53. Rouder J. N., Speckman P. L., Sun D., Morey R. D., Iverson G. Bayesian t-tests for accepting and rejecting the null hypothesis. *Psychon Bull Rev* 2009; **16**: 225–37.
54. Kraemer H. A source of false findings in published research studies: adjusting for covariates. *JAMA Psychiatry* 2015; **72**: 961–2.
55. NHS-Digital. Statistics on smoking, England—2016. 2016. Available at: <https://digital.nhs.uk/catalogue/PUB20781> (accessed 8 May 2018) (Archived at <http://www.webcitation.org/6zfx6WpkL>).
56. Field M., Cox W. M. Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug Alcohol Depend* 2008; **97**: 1–20.
57. Robinson T. E., Berridge K. C. Incentive-sensitization and addiction. *Addiction* 2001; **96**: 103–14.
58. Mahler S. V., Smith K. S., Berridge K. C. Endocannabinoid hedonic hotspot for sensory pleasure: anandamide in nucleus accumbens shell enhances 'liking' of a sweet reward. *Neuropsychopharmacology* 2007; **32**: 2267–78.
59. Field M., Mogg K., Bradley B. P. Eye movements to smoking-related cues: effects of nicotine deprivation. *Psychopharmacology (Berl)* 2004; **173**: 116–23.
60. Justinova Z., Panlilio L. V., Moreno-Sanz G., Redhi G. H., Auber A., Secci M. E. *et al.* Effects of fatty acid amide hydrolase (FAAH) inhibitors in non-human primate models of nicotine reward and relapse. *Neuropsychopharmacology* 2015; **40**: 2185–97.
61. Panlilio L. V., Justinova Z., Goldberg S. R. Inhibition of FAAH and activation of PPAR: new approaches to the treatment of cognitive dysfunction and drug addiction. *Pharmacol Ther* 2013; **138**: 84–102.
62. Scherma M., Panlilio L. V., Fadda P., Fattore L., Gamaledin I., Le Foll B. *et al.* Inhibition of anandamide hydrolysis by cyclohexyl carbamic acid 3'-carbamoyl-3-yl ester (URB597) reverses abuse-related behavioral and neurochemical effects of nicotine in rats. *J Pharmacol Exp Ther* 2008; **327**: 482–90.
63. Forget B., Coen K. M., Le Foll B. Inhibition of fatty acid amide hydrolase reduces reinstatement of nicotine seeking but not break point for nicotine self-administration—comparison with CB(1) receptor blockade. *Psychopharmacology (Berl)* 2009; **205**: 613–24.
64. Ataya A. E., Adams S., Mullings E., Cooper R. M., Attwood A. S., Munafò M. R. Internal reliability of measures of substance-related cognitive bias. *Drug Alcohol Depend* 2012; **121**: 148–51.
65. Zuairi A. W., Rodrigues N. P., Silva A. L., Bernardo S. A., Hallak J. E. C., Guimaraes F. S. *et al.* Inverted U-shaped dose-response curve of the anxiolytic effect of cannabidiol during public speaking in real life. *Front Pharmacol* 2017; **8**: 259.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure S1 Flow diagram for study recruitment and assessments. The final sample included 30 participants who completed all three sessions.

Table S1 Schedule of assessments on the satiated and abstinence sessions.