



The acute effects of cannabidiol on emotional processing and anxiety: a neurocognitive imaging study

Michael A. P. Bloomfield^{1,2,3,4,5,6} · Yumeya Yamamori^{1,7} · Chandni Hindocha^{1,2,4} · Augustus P. M. Jones^{1,8} · Jocelyn L. L. Yim^{1,7,9} · Hannah R. Walker¹ · Ben Statton¹⁰ · Matthew B. Wall¹¹ · Rachel H. Lees¹² · Oliver D. Howes^{3,13} · Valerie H. Curran^{2,4} · Jonathan P. Roiser⁷ · Tom P. Freeman^{1,2,12,14}

Received: 8 February 2021 / Accepted: 21 January 2022 / Published online: 21 April 2022
© The Author(s) 2022

Abstract

Rationale There is growing interest in the therapeutic potential of cannabidiol (CBD) across a range of psychiatric disorders. CBD has been found to reduce anxiety during experimentally induced stress in anxious individuals and healthy controls. However, the mechanisms underlying the putative anxiolytic effects of CBD are unknown.

Objectives We sought to investigate the behavioural and neural effects of a single dose of CBD vs. placebo on a range of emotion-related measures to test cognitive-mechanistic models of its effects on anxiety.

Methods We conducted a randomised, double-blind, placebo-controlled, crossover, acute oral challenge of 600 mg of CBD in 24 healthy participants on emotional processing, with neuroimaging (viewing emotional faces during functional magnetic resonance imaging) and cognitive (emotional appraisal) measures as well as subjective response to experimentally induced anxiety.

Results CBD did not produce effects on brain responses to emotional faces and cognitive measures of emotional processing, or modulate experimentally induced anxiety, relative to placebo.

Conclusions Given the rising popularity of CBD for its putative medical benefits, these findings question whether further research is warranted to investigate the clinical potential of CBD for the treatment of anxiety disorders.

Keywords Cannabidiol · Cannabinoids · Anxiety · Emotional processing · fMRI · Neuroimaging

Introduction

Anxiety disorders constitute a leading global cause of morbidity (World Health Organization 2017) and are associated with considerable economic burden (Revicki et al. 2012). In the search for novel treatments, cannabidiol (CBD) is a cannabinoid that has been proposed to possess anxiolytic effects which may be clinically promising across a range of anxiety disorders (Blessing et al. 2015). Research into CBD's potential anxiolytic properties has been much needed to stimulate

progress in novel pharmacological approaches to treatment, given only moderate response rates of around 50–60% (for example in cognitive behavioural therapies (Loerinc et al. 2015) and serotonin reuptake-inhibitors (Baldwin et al. 2011)), and major cutbacks in psychiatric drug development (Abbott 2011; Miller 2010).

CBD elicits anxiolytic effects comparable to those of classical anxiolytic drugs (e.g. diazepam) in animal anxiety models, including the marble-burying test (Casarotto et al. 2010), the Vogel conflict test (Moreira et al. 2006) and the elevated plus maze (Guimaraes et al. 1990). Despite this, and in contrast with standard drugs, CBD's effects are not dependent on serotonergic or GABAergic signalling as CBD's anxiolytic effects were blocked by neither a 5HT_{1A} receptor antagonist (Casarotto et al. 2010) nor a benzodiazepine antagonist (Moreira et al. 2006). However, CBD's effects on fear learning were blocked by the endocannabinoid receptor type 1 (CB₁R) antagonist SR141716A (Bitencourt et al. 2008), which suggests

Michael AP Bloomfield and Yumeya Yamamori contributed jointly to the research (for joint first authorship).

This article belongs to a Special Issue on Cannabis and Cannabinoids

✉ Michael A. P. Bloomfield
m.bloomfield@ucl.ac.uk

Extended author information available on the last page of the article

that anxiolysis is attributable to the endocannabinoid system. This endocannabinoid pathway has been proposed as a novel pharmacological target for anxiety (Hill and Gorzalka 2009; Lutz et al. 2015; Ruehle et al. 2012), and therefore, cannabinoid research may provide new means to treat these disorders.

In humans, the anxiolytic effects of CBD have been supported through tasks involving anxiogenic public speech paradigms in healthy individuals (Linares et al. 2019; Zuardi et al. 1993), in social anxiety (Bergamaschi et al. 2011), in clinical high risk of psychosis (Appiah-Kusi et al. 2020) and in Parkinson's disease (de Faria et al. 2020). Further, CBD also reduced drug cue-induced anxiety in heroin-abstinent individuals (Hurd et al. 2019). The effects of CBD on emotional processing, i.e. the cognitive processing of emotion-related information, have also been investigated. CBD appears to facilitate extinction learning of fear memories in humans (Das et al. 2013), improve performance in the recognition of ambiguous emotional facial expressions (Hindocha et al. 2015) and shift attention away from emotional stimuli to more neutral stimuli (Arndt and Wit 2017). Functional magnetic resonance imaging (fMRI) studies have shown attenuated amygdala and anterior cingulate responses (as well as attenuated connectivity between these regions) to fearful faces following CBD administration (Fusar-Poli et al. 2010, 2009), and this effect was correlated with reduced subjective anxiety (Bhattacharyya et al. 2010). One finding complicates this general trend as CBD produced a non-significant increase in anxiety ratings in a paranoid sample during virtual reality (Hundal et al. 2018). Yet, the majority of these results support the anxiolytic hypothesis of CBD, which may be mediated by the neurocognitive effects of CBD on emotional processing.

Despite recent research into the anxiolytic role of CBD, little attention has been given to the neurocognitive mechanisms underlying CBD's effects on anxiety—that is, whether emotional processing modulation and associated neural effects constitute mechanisms of this anxiolytic effect. Thus, we sought to assess CBD-induced anxiolysis from a neurocognitive perspective to investigate candidate mechanisms. Firstly, we measured CBD's effect on the neural correlates of emotional processing in an fMRI emotion viewing task, with a region-of-interest in the amygdala. Secondly, we measured CBD's behavioural effects on emotional appraisal using a task adapted from a previous study which was sensitive to the effects of CBD in reward processing (Hindocha et al. 2018). Thirdly, we measured CBD's effects on anxiety responses to experimentally induced stress. Lastly, we explored the relationship between these measures to assess the link between CBD's effects on neurocognitive mechanisms of emotional processing and its effects on subjective anxiety. Specifically, we hypothesised that, compared to placebo, CBD would (i) attenuate automatic responses of the amygdala

to negative emotions; (ii) lower valence and arousal scores in appraising negative facial expressions; and lastly (iii) attenuate experimentally induced anxiety in the stress task.

Methods

We used a double-blind, placebo-controlled, crossover design to assess the effects of acute CBD challenge in healthy participants. The order of CBD and placebo administration was randomised and balanced for sex. The research procedure was approved by the UCL Research Ethics Committee (reference: 3325/002) and conducted in accordance with the Helsinki Declaration of 1975.

Participants

Twenty-four healthy participants (12 M, 12F) were recruited. Inclusion criteria were (i) healthy volunteer; (ii) English-speaking; (iii) age 18–70 years and (iv) right-handed. Primary exclusion criteria included lifetime CBD use, psychiatric history and fMRI contraindications (see the supplementary methods for full exclusion criteria). All participants gave written informed consent. A sensitivity analysis was conducted with G*Power 3.1.9.2. Faul et al. (2007) indicated that our sample size provided 84% power to detect a significant difference ($p < 0.05$, two-tailed) between CBD and placebo with an estimated effect size of $d = 0.5$, based on previous findings of acute CBD on subjective ratings of drug-related stimuli ($d = 0.5$; Hindocha et al., 2018).

Drugs

Participants were administered 600 mg of oral CBD (pure synthetic (-)-CBD, STI Pharmaceuticals, Essex, UK) or matched placebo (lactose powder) in 12 identical and opaque capsules in each testing session. The dose of 600 mg was selected given previous evidence of CBD's anxiolytic effect at this dose (Bergamaschi et al. 2011), and a waiting period of 2.5 h before testing was chosen based on evidence for peak plasma CBD around this time (Haney et al. 2016). To measure blood CBD concentrations, we collected blood samples via venepuncture 4 h post-drug administration (after MRI) in EDTA vacutainers for immediate centrifugation. Plasma samples were stored at -80°C and analysed using gas chromatography and mass spectrometry with a lower limit of quantification of 0.5 ng/ml.

Behavioural measures

Subjective/physiological measures We recorded state measures of mood ('happy', 'anxious') at 5 timepoints across each session, using 11-point VAS anchored at 0 ('not at all') to 10 ('extremely'). Heart rate (HR) and systolic and diastolic blood

pressure (SBP, DBP) were also measured. Measurements were made 10 min before drug administration (baseline) and subsequently at 0.5 h, 2 h, 4 h and 6 h post-drug administration. We used the Beck Anxiety Inventory (Beck et al. 1988) to measure trait anxiety symptoms over the previous week.

Face rating task This task measured subjective emotion appraisal (based on the pleasantness rating task in Hindocha et al. 2018). Stimuli were male and female adult open-mouth happy/angry/neutral expressions from the NimStim set of facial expressions (Tottenham et al. 2009). The actors were changed across sessions. Participants viewed the faces in randomised order and made valence and arousal judgments on each face. The valence judgment was described through the question: ‘How positive or negative does the image look to you?’ and rated along a 7-point VAS from ‘−3: very negative’ to ‘3: very positive’. The arousal judgment was described through the question: ‘How aroused does the image make you feel?’ and rated along a 7-point VAS from ‘0: not at all aroused’ to ‘+6: extremely aroused’. Faces remained on the screen until both rating judgments were made. Participants were instructed to respond as quickly and accurately as possible and that arousal referred to emotional reaction rather than sexual arousal.

Mental arithmetic task A mental arithmetic task (Constantinou et al. 2010) was implemented to measure emotional responses to stress. The task was comprised of two parts: a “no-stress” (control) condition and a “stress” condition, in fixed order (no-stress, stress) to avoid carry-over stress effects to the no-stress condition:

Part 1: No-stress condition. Participants were given a paper handout consisting of a series of arithmetic additions and subtractions. They were asked to simply circle the character ‘3’ every time it appeared for 3 min. Participants were told that speed and accuracy were not important.

Part 2: Stress condition (stress task). Participants were asked to verbally and serially subtract 13’s from 6022 (session 1) or 6021 (session 2) as quickly and as accurately as they could for 3 min. Participants were prompted on incorrect responses and reminded of the importance of accuracy and speed after the 1st and 2nd minute to promote stress regardless of performance.

Verbal responses were recorded using an external microphone held before the participant, although these recordings were not analysed. HR, SBP, DBP and VAS scores of ‘anxious’, ‘stressed’, ‘calm’, and ‘relaxed’ were recorded four times throughout the task: immediately after the control task instructions, immediately after completing the control task, immediately after the stress task instructions and immediately after completing the stress task (pre-control, post-control, pre-stress and post-stress, respectively).

Neuroimaging measures

fMRI paradigm The task was based on a previous incidental emotional processing task (O’Nions et al. 2011). The participants were shown a series of faces and asked to categorise them on the basis of sex (male/female) by key-press. There were eight cycles of three 16-s blocks (happy, fearful and neutral) in fixed order. Each block was composed of eight faces representing one emotion, with each face presented for 1500 ms followed by a central fixation cross of 500 ms. There was a 2-s interval between each block, and 16-s interval of rest following each cycle of three blocks. The stimuli were 42 faces also obtained from the NimStim set of facial expressions (Tottenham et al. 2009). Faces were presented in pseudo-random order such that there were equal numbers of male and female faces. As task performance was irrelevant to the main measure of automatic emotional processing, the behavioural data are not discussed further (see supplementary information for MRI acquisition and pre-processing procedures).

Procedure

Participants attended two sessions with at least 7 days between sessions to minimise carry-over drug effects (Haney et al. 2016; Hindocha et al. 2018). We asked participants to fast from midnight (12 am) on the night before each session, based on a previous study (Haney et al. 2016). Water was permitted anytime thereafter and a caffeinated drink for participants routinely consuming caffeine was also permitted to avoid caffeine withdrawal. We also asked participants to avoid alcohol for 24 h before sessions and to avoid smoking on the morning of sessions. Pre-drug checks consisted of breath tests for alcohol and tobacco (via carbon monoxide) use, drug urine screens and pregnancy tests for female participants. Drug administration (0 h) was followed by the waiting period, after which fMRI scanning occurred (2 h 30 min post-drug). Participants were then provided a standard meal consisting of a sandwich, snack and drink (4 h). Finally, the behavioural tasks were administered (5 h 30 min post-drug). Other measures were recorded as part of the procedure; however, these are reported elsewhere (Bloomfield et al. 2020; Lawn et al. 2020). The procedure for the present study lasted approximately 7 h (Table 1).

Statistical analyses

Behavioural data analyses were performed with frequentist analysis via Statistical Package for the Social Sciences 25

Table 1 Timeline for each testing session

Time from drug administration	Measure
– 10 min	Physiological and subjective measures (baseline)
+ 0 h	Drug administration—cannabidiol or placebo
+ 30 min	Physiological and subjective measures (T1)
+ 2 h	Physiological and subjective measures (T2)
+ 2 h 30 min	fMRI scanning (emotional processing task)
+ 4 h	Blood samples, physiological and subjective measures (T3)
+ 5 h 30 min	Behavioural tasks (face rating, mental arithmetic)
+ 6 h	Physiological and subjective measures (T4)

We recorded physiological and subjective measures including subjective anxiety at 5 timepoints over the course of a single testing session (baseline, T1–T4). All procedures were time-locked to the time of drug administration. Other neuroimaging and behavioural measures were employed as part of the study; however, these are reported elsewhere

(SPSS Inc. Released 2020) and Bayesian analysis via JASP (JASP Team 2020). Frequentist and Bayesian repeated-measures analyses of variance (ANOVAs) were performed, comparing the effect of drug (CBD, placebo) and other task factors (e.g. emotion, time) on each task's dependent variables. Bayes factors were computed from the Bayesian repeated-measures ANOVAs, which measure the relative predictive performance of the null and alternative hypotheses, which in turn allowed us to evaluate the strength of evidence in favour of the null hypothesis (which is assumed to be true, but not tested, in frequentist analyses). Post hoc tests were conducted through a priori orthogonal contrasts relevant to the task variables: contrasting happy vs. neutral and angry vs. neutral in the face rating task, and as Helmert contrasts in the mental arithmetic task and the periodic subjective/physiological measures. Outliers, defined as data points which were more than three times the interquartile range from the nearest quartile, were winsorised to the nearest non-outlier value. We re-tested all statistical models with drug administration order as a between-subjects factor to account for practice/familiarity effects. A significance threshold of $\alpha = 0.05$ (2-tailed) was adopted for the frequentist analyses. For the Bayesian analyses, we followed standard guidelines for interpreting the Bayes factors in accordance with Jeffreys (1998).

The neuroimaging (MRI) statistical model was specified as a blocked design by creating 16-s duration box-car regressors each for happy, fearful and neutral affect. Realignment motion parameters were included as covariates-of-no-interest. A high-pass filter of 128 s was applied. Neural responses to positive and negative emotion were modelled by contrasts of happy vs. neutral faces and fearful vs. neutral faces, respectively. Task and drug effects were analysed across the whole brain at a cluster-level threshold of $\alpha = 0.05$ (FWE-corrected), and through an anatomically defined amygdala region-of-interest (ROI) at a within-ROI voxel-level threshold of $\alpha = 0.05$ (FWE-corrected). A voxel-based ROI analysis was preferred

over single-parameter extraction, as multiple amygdala sub-regions were used to produce the ROI with potentially distinct sensitivities for positive and negative emotion. The ROI was built using the SPM Anatomy Toolbox (Eickhoff et al. 2005), by conglomerating masks of the basolateral, centromedial and superficial sub-regions (Amunts et al. 2005) into a single mask of the bilateral amygdala. The SPM Anatomy Toolbox was used to localise activation maps.

Results

The inclusion of order as a between-subjects factor did not affect any drug-related findings, so this was not included in the final models.

Sample characteristics

Four participants were excluded due to aversion to MRI ($n = 2$), gastro-intestinal discomfort following lunch ($n = 1$) and positive test for tricyclic antidepressant use ($n = 1$). The final sample consisted of 24 participants (12 male, 12 female) and had a mean age of 23.6 years ($SD = 4.12$), BMI of 22.3 kg/m² ($SD = 3.48$) and low BAI score of 2.6 ($SD = 3.23$) which is in the range of 'normal to no anxiety' (Julian 2011). All participants had a Fagerström Test for Nicotine Dependence score (Heatherton et al. 1991) of 0, whilst the mean score on the Alcohol Use Disorders Identification Test (Saunders et al. 1993) was 2 ($SD = 2.1$). The mean interval between sessions was 9.5 days ($SD = 4.25$).

Blood plasma CBD concentration

Analysis of plasma CBD levels via Wilcoxon signed-rank test revealed higher CBD plasma concentrations in CBD sessions (median = 6.01 ng/ml, IQR = 4.24) compared to

placebo (median = 0 ng/ml, IQR = 0) sessions ($z = 4.10$, $p < 0.001$, $r = 0.88$).

Neuroimaging results

Effect of task For the happy vs. neutral faces contrast, we found significantly increased BOLD response in the right calcarine gyrus ($p_{\text{FWE-corrected}} < 0.001$; Fig. 1A, Table 2a). For the fearful vs. neutral faces contrast, we found significantly increased response in the left lingual gyrus ($p_{\text{FWE-corrected}} < 0.001$; Fig. 1B, Table 2b). We did not find any significant reductions in BOLD response across the whole brain for either contrast. Within the amygdala ROI, we found a non-significant trend of the fear vs. neutral faces contrast in the right basolateral amygdala (greater BOLD response for fearful vs. neutral faces; $p_{\text{FWE-corrected}} = 0.057$; Fig. 1C, Table 2b*).

Effect of drug We did not find significant drug effects for either the happy vs. neutral faces or the fearful vs. neutral faces contrasts across the whole brain and within the ROI.

Behavioural results

Drug-relevant behavioural effects (main effects of drug and drug-related interactions) are reported below (see supplementary results for full statistical analyses).

Face rating task (Fig. 2) We did not find significant drug-related effects for valence (drug: $F_{1,23} = 0.54$, $p = 0.468$, $\text{BF}_{10} = 0.180$; drug \times emotion: $F_{1.39,31.93} = 0.16$, $p = 0.771$, $\text{BF}_{10} = 0.118$) and arousal (drug: $F_{1,23} = 0.29$, $p = 0.597$, $\text{BF}_{10} = 0.183$; drug \times emotion: $F_{1.26,29.01} < 0.01$, $p = 0.975$, $\text{BF}_{10} = 0.115$) judgments, and similarly for valence (drug: $F_{1,23} = 0.98$, $p = 0.333$, $\text{BF}_{10} = 0.504$; drug \times emotion: $F_{2,46} = 2.67$, $p = 0.080$, $\text{BF}_{10} = 0.220$) and arousal (drug: $F_{1,23} = 0.26$, $p = 0.617$, $\text{BF}_{10} = 0.228$; drug \times emotion: $F_{1.43,32.81} = 1.13$, $p = 0.318$, $\text{BF}_{10} = 0.181$) RTs.

Mental arithmetic task (Fig. 3) We did not find a main effect of drug for self-reports of anxiety ($F_{1,23} = 0.07$, $p = 0.799$, $\text{BF}_{10} = 0.155$). Frequentist analysis showed a significant interaction effect of drug and time ($F_{2,14,49.29} = 3.17$,

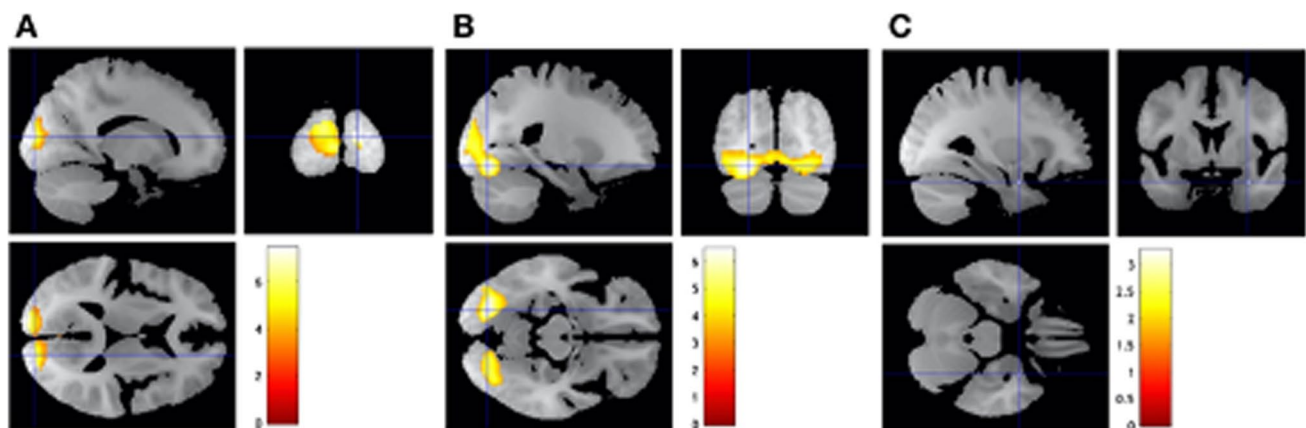


Fig. 1 **A** Happy faces, relative to neutral faces, increased BOLD responses in the right calcarine gyrus. **B** Fearful faces, relative to neutral faces, increased BOLD responses in the left lingual gyrus. **C** There was a non-significant effect within the a priori amygdala region-of-interest. Statistical maps are overlaid on the sample mean

structural image. A voxel-based threshold of $\alpha = .001$ (uncorrected) was used to form the beta clusters, after which a cluster-level threshold of $\alpha = .05$ (FWE-corrected) was applied. Coloured bars indicate t -values ($n = 24$)

Table 2 Regions with significant increases in BOLD response during the fMRI emotional processing task across the whole brain and *a non-significant finding within the amygdala region-of-interest (ROI)

Contrast	Region	MNI coordinates (mm)			Cluster size (mm ³)	Z-score
		x	y	z		
a. Happy vs. neutral	Right calcarine gyrus	16	-92	11	13,776	6.02
b. Fearful vs. neutral	Left lingual gyrus	-22	-78	-13	24,468	5.45
	*Right amygdala	30	2	-25	12	3.10

A voxel-based threshold of $\alpha = .001$ (uncorrected) was used to form the beta clusters, after which a cluster-level threshold of $\alpha = .05$ (FWE-corrected) was applied. *This finding was under the FWE-corrected threshold of $\alpha = .05$ at $p_{\text{FWE-corrected}} = .057$

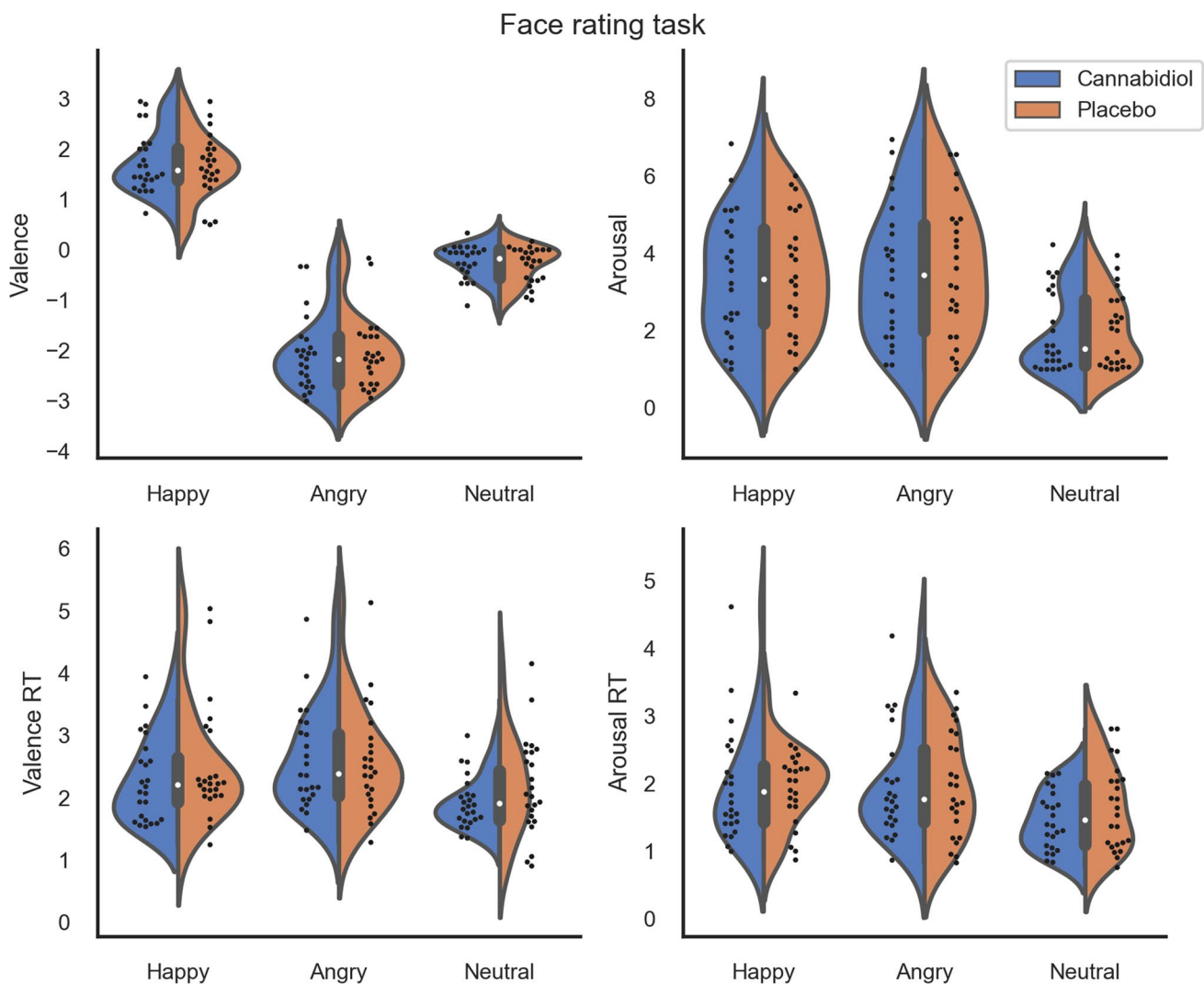


Fig. 2 Subjective valence and arousal scores from the face rating task and their reaction times ($n=24$). There was no evidence for differences across drug (cannabidiol vs. placebo)

$p=0.048$, $\eta^2p=0.12$), driven by a greater increase in anxiety from pre- to post-stress for CBD (mean = 1.17, SE = 0.40) compared to placebo (mean = 0.29, SD = 0.36). However, this was not supported by Bayesian analysis ($BF_{10}=0.387$) which rather suggested anecdotal evidence in favour of the null hypothesis, and suggests that the frequentist finding represents a type I error. We did not find significant drug-related effects for self-reports of stress (drug: $F_{1,23}=0.06$, $p=0.802$, $BF_{10}=0.157$; drug \times time: $F_{2,09,48,11}=0.11$, $p=0.904$, $BF_{10}=0.062$). We also note that on average, the stress condition in this task did not induce high scores of self-reported anxiety (mean = 2.64, SD = 2.56) and stress (mean = 2.90, SD = 2.48), in the stress condition of this task.

We did not find significant drug-related effects for self-reports of calm (drug: $F_{1,23}=0.04$, $p=0.846$, $BF_{10}=0.164$; drug \times time: $F_{2,04,46,91}=0.36$, $p=0.705$, $BF_{10}=0.070$) and self-reports of relaxed (drug: $F_{1,23}=0.02$, $p=0.899$, $BF_{10}=0.154$; drug \times time: $F_{1,91,43,92}=1.14$, $p=0.327$, $BF_{10}=0.115$) ratings. Similarly, we did not find significant drug-related effects for heart rate (drug: $F_{1,23}=0.02$, $p=0.901$, $BF_{10}=0.156$; drug \times time: $F_{3,69}=2.26$, $p=0.089$, $BF_{10}=0.212$), systolic blood pressure (drug: $F_{1,23}=0.48$, $p=0.496$, $BF_{10}=0.247$; drug \times time: $F_{3,69}=0.79$, $p=0.503$, $BF_{10}=0.108$) or diastolic blood pressure (drug: $F_{1,23}=0.02$, $p=0.887$, $BF_{10}=0.158$; drug \times time: $F_{3,69}=1.18$, $p=0.322$, $BF_{10}=0.107$).

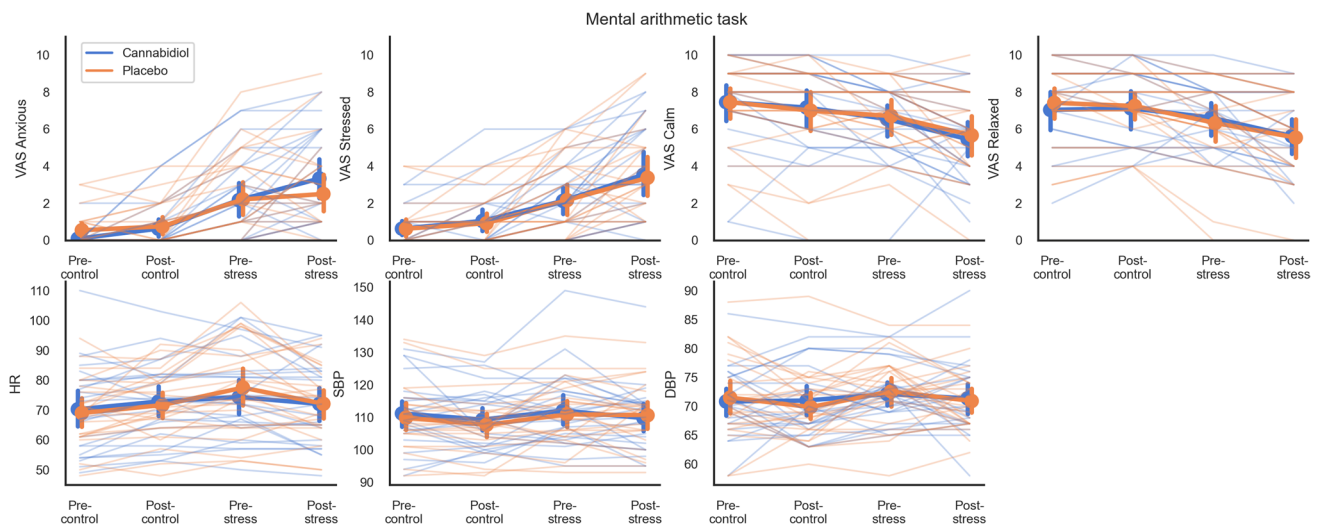


Fig. 3 Subjective and physiological responses during the mental arithmetic task ($n=24$). Frequentist analyses suggested an interaction effect of drug and time on subjective anxiety ($p=.048$) where the increase in pre-stress to post-stress was greater for cannabidiol

vs. placebo; however, this was contradicted by Bayesian analysis ($BF_{10}=0.387$). No other effects were evident. Error bars represent 95% confidence intervals

Subjective and physiological measures across the experiment (Time from drug administration)

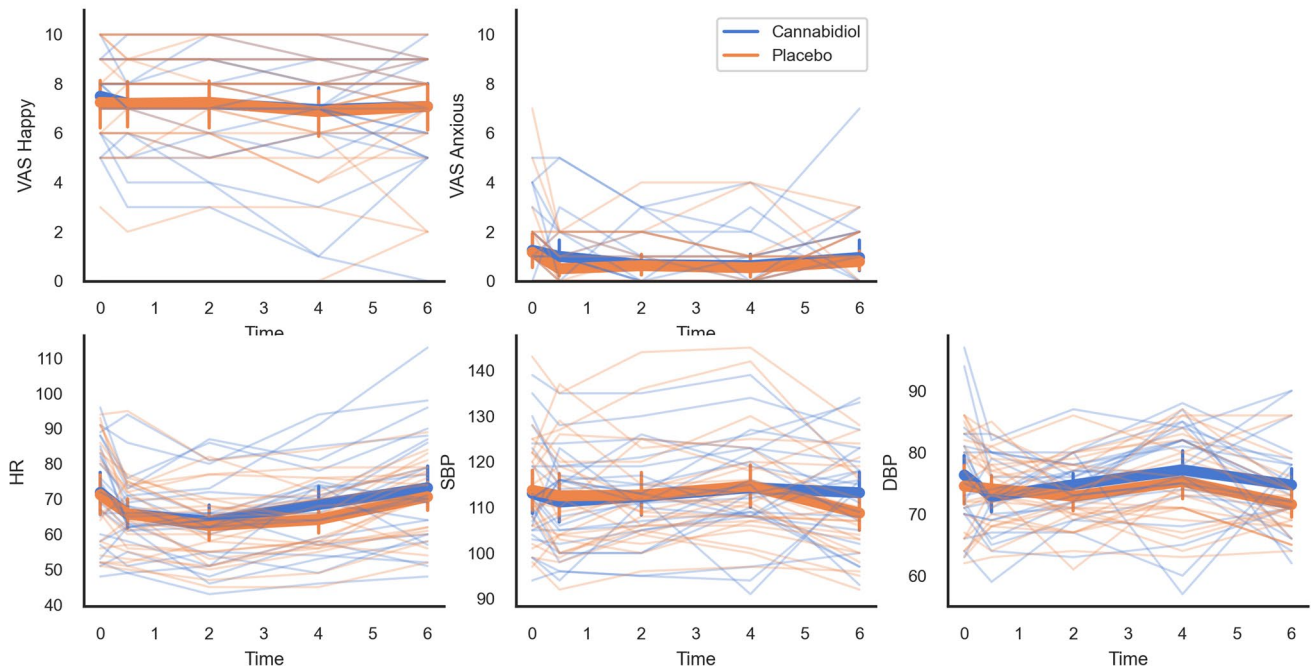


Fig. 4 Subjective and physiological measures across the duration of the experiment (time from drug administration; $n=24$). There was no evidence for differences across drug (cannabidiol vs. placebo). Error bars represent 95% confidence intervals

Subjective and physiological measures(Fig.4)

We did not find significant drug-related effects for subjective anxiety (drug: $F_{1,23}=0.69$, $p=0.416$, $BF_{10}=0.318$;

drug \times time: $F_{2.74,63.08}=0.54$, $p=0.639$, $BF_{10}=0.054$) or happiness (drug: $F_{1,23}=0.08$, $p=0.785$, $BF_{10}=0.163$; drug \times time: $F_{2.21,50.82}=0.24$, $p=0.805$, $BF_{10}=0.037$) across the experiment. Similarly, we did not find significant

drug-related effects for heart rate (drug: $F_{1,23} = 2.45$, $p = 0.128$, $BF_{10} = 0.610$; drug \times time: $F_{2,46,56.58} = 1.09$, $p = 0.354$, $BF_{10} = 0.094$), systolic blood pressure (drug: $F_{1,23} = 0.14$, $p = 0.717$, $BF_{10} = 0.151$; drug \times time: $F_{3,05,70.15} = 1.98$, $p = 0.124$, $BF_{10} = 0.328$) or diastolic blood pressure (drug: $F_{1,23} = 2.77$, $p = 0.110$, $BF_{10} = 1.640$; drug \times time: $F_{4,92} = 1.51$, $p = 0.204$, $BF_{10} = 0.187$).

Discussion

The results suggest that CBD did not have any effects on our measures relating to anxiety. Whilst we confirmed that CBD was absorbed into blood plasma, contrary to our hypothesis, CBD did not modulate neural or behavioural correlates of emotional processing via incidental emotion viewing, or emotion appraisal, and had no effect on subjective and cardiovascular responses to experimentally induced stress. These null findings follow those of other studies reporting minimal behavioural effects of CBD (Arndt and Wit 2017; Babalonis et al. 2017; Haney et al. 2016).

We may have observed our negative findings as a result of a lack of sensitivity of our measures to CBD's effects. Evidence against this possibility is that we selected our measures on the basis of their previous sensitivity to drug-related effects (Hindocha et al. 2018; Selvaraj et al. 2018) and that each of our measures elicited significant task effects (e.g. differentiation of valence and arousal responses to positive and negative emotional stimuli in the face rating task, increased subjective and cardiovascular stress responses in the mental arithmetic task, see the supplementary materials for full statistical results). This pattern of results mirror those of Arndt and Wit (2017) who also found no effects of CBD on a range of emotion-related measures despite significant task effects.

Critically, our null findings for the effect of CBD on experimentally induced stress are in contrast to previous findings reporting that CBD attenuated task-induced anxiety (Bergamaschi et al. 2011; Zuardi et al. 1993, 2017), and these discrepant findings may be due to the potentially dose-dependent nature of CBD's effects. Recent work suggests that CBD may have an inverted U-shaped dose–response curve (Campos and Guimaraes 2008; Freeman et al. 2020; Hsiao et al. 2012; Linares et al. 2019; Zuardi et al. 2017) with best efficacy for human anxiety at 300 mg (Linares et al. 2019; Zuardi et al. 1993, 2017) compared to our dose of 600 mg. However, the finding that CBD was able to reduce drug cue-induced craving and anxiety at single doses of 400 mg and 800 mg (Hurd et al. 2019) suggests that our dose of 600 mg still falls within the effective range. More research will be needed to determine the optimal dose strategy in human anxiety and indeed other symptom domains using a variety of behavioural paradigms.

Lastly, three previous studies have found that chronic administration of CBD was anxiolytic: a 21-day treatment of 600 mg of CBD was effective at reducing psychosis-related anxiety in patients at high risk of psychosis, compared to placebo (Bhattacharyya et al. 2018), and a 4-week treatment of oil with 300 mg of CBD significantly reduced anxiety in a socially anxious sample, compared to placebo (Masataka 2019). Additionally, 4-week treatment with 800 mg CBD reduced anxiety in people with a cannabis use disorder compared to placebo (Freeman et al. 2020). Therefore, repeated dosing of CBD may be necessary to produce anxiolytic effects.

Strengths and limitations

There are several strengths of the present study. Our experimental design allowed for a simultaneous test of CBD's effects across neurocognitive and subjective levels of emotional processing. We used previously validated measures (Constantinou et al. 2010; O'Nions et al. 2011), especially with respect to the cognitive tasks which were sensitive to the effects of CBD in a reward processing context (Hindocha et al. 2018). Further, the measures tested for both positive and negative emotional processing, whereas previous studies have only focused on the latter, especially in neuroimaging studies.

The limitations of the study are that the oral route of CBD administration is slow and associated with variable bioavailability. For example, Haney et al. (2016) reported that oral administration of 800 mg resulted in a wide spread of peak concentrations of CBD in plasma from 1.6 to 271.9 ng/ml, and the times of peaks of CBD plasma varied from 120 to 360 min. We also employed a relatively long fasting time compared to other studies (overnight vs. 2 h) and did not use an oil buffer, which may have led to insufficient absorption of CBD, especially as a previous study has suggested that co-administering CBD with food can increase oral bioavailability (Taylor et al. 2018). However, our plasma measures showed that there was significant absorption of CBD. Additionally, the stimuli employed across tasks were inconsistent; the fMRI task used fearful faces to represent negative emotion, whilst the face rating task used angry faces.

Finally, the mental arithmetic task was novel in the context of CBD research, whereas previous studies have employed public speaking (Appiah-Kusi et al. 2020; Bergamaschi et al. 2011; Zuardi et al. 1993, 2017) and virtual reality (Hundal et al. 2018) paradigms. Importantly, unlike the public speaking task, an advantage of this mental arithmetic task is its suitability for use in a repeated-measures design. However, we note that the mental arithmetic task did not induce large increases in anxiety, and thus may not have been sufficiently anxiogenic to observe an effect on CBD.

Conclusions

The present study found no effect of a single dose of 600 mg CBD on a range of emotional processing measures in a healthy sample, despite multiple previous reports of anxiolytic effects of CBD and effects of CBD on emotional processing. These findings warrant further investigation in light of increasing popularity of CBD and its potential use for treating anxiety disorders.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00213-022-06070-3>.

Funding This study was funded by a British Medical Association Foundation for Medical Research Margaret Temple Award to Dr Bloomfield. Dr Bloomfield was funded by a UCL Excellence Fellowship and is funded by a UKRI Future Leaders Fellowship. Drs. Bloomfield and Hindocha and Professor Curran are supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. Mr. Yamamori is funded by a 4-year PhD Studentship in Science from the Wellcome Trust. Dr Freeman was funded by a senior academic fellowship from the Society for the Study of Addiction.

Data Availability The data are available upon request to the corresponding author.

Declarations

Conflict of interest Dr Bloomfield has participated at an advisory board for Makara Health. Otherwise, the authors declare that there is no conflict of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Abbott A (2011) Novartis to shut brain research facility. *Nature* 480:161–162. <https://doi.org/10.1038/480161a>
- Amunts K et al (2005) Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps. *Anat Embryol (Berl)* 210:343–352. <https://doi.org/10.1007/s00429-005-0025-5>
- Appiah-Kusi E et al (2020) Effects of short-term cannabidiol treatment on response to social stress in subjects at clinical high risk of developing psychosis. *Psychopharmacology* 237:1121–1130. <https://doi.org/10.1007/s00213-019-05442-6>
- Arndt DL, de Wit H (2017) Cannabidiol does not dampen responses to emotional stimuli in healthy adults. *Cannabis Cannabinoid Res* 2:105–113. <https://doi.org/10.1089/can.2017.0014>
- Babalonis S, Haney M, Malcolm RJ, Lofwall MR, Votaw VR, Sparenborg S, Walsh SL (2017) Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug Alcohol Depend* 172:9–13. <https://doi.org/10.1016/j.drugalcdep.2016.11.030>
- Baldwin D, Woods R, Lawson R, Taylor D (2011) Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. *BMJ* 342:d1199. <https://doi.org/10.1136/bmj.d1199>
- Beck AT, Epstein N, Brown G, Steer RA (1988) An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 56:893–897. <https://doi.org/10.1037//0022-006x.56.6.893>
- Bergamaschi MM et al (2011) Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology* 36:1219–1226. <https://doi.org/10.1038/npp.2011.6>
- Bhattacharyya S et al (2010) Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology* 35:764–774. <https://doi.org/10.1038/npp.2009.184>
- Bhattacharyya S et al (2018) Effect of cannabidiol on medial temporal, midbrain, and striatal dysfunction in people at clinical high risk of psychosis: a randomized clinical trial. *JAMA Psychiatry* 75:1107–1117. <https://doi.org/10.1001/jamapsychiatry.2018.2309>
- Bitencourt RM, Pamplona FA, Takahashi RN (2008) Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. *Eur Neuropsychopharmacol* 18:849–859. <https://doi.org/10.1016/j.euroneuro.2008.07.001>
- Blessing EM, Steenkamp MM, Manzanares J, Marmar CR (2015) Cannabidiol as a potential treatment for anxiety disorders. *Neurotherapeutics* 12:825–836. <https://doi.org/10.1007/s13311-015-0387-1>
- Bloomfield MAP et al (2020) The effects of acute cannabidiol on cerebral blood flow and its relationship to memory: an arterial spin labelling magnetic resonance imaging study. *J Psychopharmacol* 34:981–989. <https://doi.org/10.1177/0269881120936419>
- Campos AC, Guimaraes FS (2008) Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. *Psychopharmacology (Berl)* 199:223–230. <https://doi.org/10.1007/s00213-008-1168-x>
- Casarotto PC, Gomes FV, Resstel LB, Guimaraes FS (2010) Cannabidiol inhibitory effect on marble-burying behaviour: involvement of CB1 receptors. *Behav Pharmacol* 21:353–358. <https://doi.org/10.1097/fbp.0b013e32833b33c5>
- Constantinou N, Morgan CJ, Battistella S, O’Ryan D, Davis P, Curran HV (2010) Attentional bias, inhibitory control and acute stress in current and former opiate addicts. *Drug Alcohol Depend* 109:220–225. <https://doi.org/10.1016/j.drugalcdep.2010.01.012>
- Das RK et al (2013) Cannabidiol enhances consolidation of explicit fear extinction in humans. *Psychopharmacology* 226:781–792. <https://doi.org/10.1007/s00213-012-2955-y>
- de Faria SM et al (2020) Effects of acute cannabidiol administration on anxiety and tremors induced by a simulated public speaking test in patients with Parkinson’s disease. *J Psychopharmacol* 34:189–196. <https://doi.org/10.1177/0269881119895536>
- Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K (2005) A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage* 25:1325–1335. <https://doi.org/10.1016/j.neuroimage.2004.12.034>
- Faul F, Erdfelder E, Lang AG, Buchner A (2007) G*Power 3: a flexible statistical power analysis program for the social, behavioral, and

- biomedical sciences. *Behav Res Methods* 39:175–191. <https://doi.org/10.3758/bf03193146>
- Freeman TP et al (2020) Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *Lancet Psychiatry* 7:865–874. [https://doi.org/10.1016/S2215-0366\(20\)30290-X](https://doi.org/10.1016/S2215-0366(20)30290-X)
- Fusar-Poli P et al (2010) Modulation of effective connectivity during emotional processing by delta 9-tetrahydrocannabinol and cannabidiol. *Int J Neuropsychopharmacol* 13:421–432. <https://doi.org/10.1017/S1461145709990617>
- Fusar-Poli P et al (2009) Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Arch Gen Psychiatry* 66:95–105. <https://doi.org/10.1001/archgenpsychiatry.2008.519>
- Guimaraes FS, Chiaretti TM, Graeff FG, Zuardi AW (1990) Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology* 100:558–559. <https://doi.org/10.1007/BF02244012>
- Haney M et al (2016) Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis. *Neuropsychopharmacology* 41:1974–1982. <https://doi.org/10.1038/npp.2015.367>
- Heatherington TF, Kozlowski LT, Frecker RC, Fagerstrom KO (1991) The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 86:1119–1127. <https://doi.org/10.1111/j.1360-0443.1991.tb01879.x>
- Hill MN, Gorzalka BB (2009) The endocannabinoid system and the treatment of mood and anxiety disorders. *CNS Neurol Disord Drug Targets* 8:451–458. <https://doi.org/10.2174/187152709789824624>
- Hindocha C et al (2018) Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal. *Addiction*. <https://doi.org/10.1111/add.14243>
- Hindocha C, Freeman TP, Schafer G, Gardener C, Das RK, Morgan CJ, Curran HV (2015) 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* 25:325–334. <https://doi.org/10.1016/j.euroneuro.2014.11.014>
- Hsiao YT, Yi PL, Li CL, Chang FC (2012) Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. *Neuropharmacology* 62:373–384. <https://doi.org/10.1016/j.neuropharm.2011.08.013>
- Hundal H et al (2018) The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group. *J Psychopharmacol* 32:276–282. <https://doi.org/10.1177/0269881117737400>
- Hurd YL et al (2019) Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial. *Am J Psychiatry* 176:911–922. <https://doi.org/10.1176/appi.ajp.2019.18101191>
- Inc. S (Released 2020.) IBM SPSS Statistics for Macintosh, Version 27.0
- Jeffreys H (1998) *The theory of probability*. OUP Oxford,
- Julian LJ (2011) Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res (Hoboken)* 63(Suppl 11):S467–472. <https://doi.org/10.1002/acr.20561>
- Lawn W et al (2020) The acute effects of cannabidiol on the neural correlates of reward anticipation and feedback in healthy volunteers. *J Psychopharmacol* 34:969–980. <https://doi.org/10.1177/026981120944148>
- Linares IM, Zuardi AW, Pereira LC, Queiroz RH, Mechoulam R, Guimaraes FS, Crippa JA (2019) Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. *Braz J Psychiatry* 41:9–14. <https://doi.org/10.1590/1516-4446-2017-0015>
- Loerinc AG, Meuret AE, Twohig MP, Rosenfield D, Bluett EJ, Craske MG (2015) Response rates for CBT for anxiety disorders: need for standardized criteria. *Clin Psychol Rev* 42:72–82. <https://doi.org/10.1016/j.cpr.2015.08.004>
- Lutz B, Marsicano G, Maldonado R, Hillard CJ (2015) The endocannabinoid system in guarding against fear, anxiety and stress. *Nat Rev Neurosci* 16:705–718. <https://doi.org/10.1038/nrn4036>
- Masataka N (2019) Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. *Front Psychol* 10:2466. <https://doi.org/10.3389/fpsyg.2019.02466>
- Miller G (2010) Is pharma running out of brainy ideas? *Science* 329:502–504. <https://doi.org/10.1126/science.329.5991.502>
- Moreira FA, Aguiar DC, Guimaraes FS (2006) Anxiolytic-like effect of cannabidiol in the rat Vogel conflict test. *Prog Neuropsychopharmacol Biol Psychiatry* 30:1466–1471. <https://doi.org/10.1016/j.pnpbp.2006.06.004>
- O’Nions EJ, Dolan RJ, Roiser JP (2011) Serotonin transporter genotype modulates subgenual response to fearful faces using an incidental task. *J Cogn Neurosci* 23:3681–3693. https://doi.org/10.1162/jocn_a_00055
- Organization WH (2017) Depression and other common mental disorders: global health estimates. <https://apps.who.int/iris/handle/10665/254610>
- Revicki DA et al (2012) Humanistic and economic burden of generalized anxiety disorder in North America and Europe. *J Affect Disord* 140:103–112. <https://doi.org/10.1016/j.jad.2011.11.014>
- Ruehle S, Rey AA, Remmers F, Lutz B (2012) The endocannabinoid system in anxiety, fear memory and habituation. *J Psychopharmacol* 26:23–39. <https://doi.org/10.1177/0269881111408958>
- Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M (1993) Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption—II. *Addiction* 88:791–804. <https://doi.org/10.1111/j.1360-0443.1993.tb02093.x>
- Selvaraj S et al (2018) Effect of citalopram on emotion processing in humans: a combined 5-HT1A [(11)C]CUMI-101 PET and functional MRI study. *Neuropsychopharmacology* 43:655–664. <https://doi.org/10.1038/npp.2017.166>
- Taylor L, Gidal B, Blakey G, Tayo B, Morrison G (2018) A phase I, randomized, double-blind, placebo-controlled, single ascending dose, multiple dose, and food effect trial of the safety, tolerability and pharmacokinetics of highly purified cannabidiol in healthy subjects. *CNS Drugs* 32:1053–1067. <https://doi.org/10.1007/s40263-018-0578-5>
- Team J (2020) JASP (Version 0.14)[Computer software].
- Tottenham N et al (2009) The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res* 168:242–249. <https://doi.org/10.1016/j.psychres.2008.05.006>
- Zuardi AW, Cosme RA, Graeff FG, Guimaraes FS (1993) Effects of ipsapirone and cannabidiol on human experimental anxiety. *J Psychopharmacol* 7:82–88. <https://doi.org/10.1177/026988119300700112>
- Zuardi AW, Rodrigues NP, Silva AL, Bernardo SA, Hallak JEC, Guimaraes FS, Crippa JAS (2017) Inverted u-shaped dose-response curve of the anxiolytic effect of cannabidiol during public speaking in real life. *Front Pharmacol* 8:259. <https://doi.org/10.3389/fphar.2017.00259>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Michael A. P. Bloomfield^{1,2,3,4,5,6} · Yumeya Yamamori^{1,7} · Chandni Hindocha^{1,2,4} · Augustus P. M. Jones^{1,8} · Jocelyn L. L. Yim^{1,7,9} · Hannah R. Walker¹ · Ben Statton¹⁰ · Matthew B. Wall¹¹ · Rachel H. Lees¹² · Oliver D. Howes^{3,13} · Valerie H. Curran^{2,4} · Jonathan P. Roiser⁷ · Tom P. Freeman^{1,2,12,14}

- ¹ Translational Psychiatry Research Group, Research Department of Mental Health Neuroscience, Division of Psychiatry, University College London, Maple House, Tottenham Court Road, London W1T 7NF, UK
- ² Clinical Psychopharmacology Unit, Research Department of Clinical, Educational and Health Psychology, University College London, London, UK
- ³ Psychiatric Imaging Group, Medical Research Council, London Institute of Medical Sciences, Imperial College London, Hammersmith Hospital, London, UK
- ⁴ NIHR University College Hospitals London Biomedical Research Centre, University College London, London, UK
- ⁵ The Traumatic Stress Clinic, St Pancras Hospital, Camden and Islington NHS Foundation Trust, London, UK
- ⁶ National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK

- ⁷ Institute of Cognitive Neuroscience, University College London, London, UK
- ⁸ Medical Sciences Division, University of Oxford, Oxford, UK
- ⁹ King's Clinical Trials Unit, King's College London, London, UK
- ¹⁰ Medical Research Council, London Institute of Medical Sciences, Imperial College London, Hammersmith Hospital, London, UK
- ¹¹ Invicro, Hammersmith Hospital, London, UK
- ¹² Addiction and Mental Health Group (AIM), Department of Psychology, University of Bath, Bath, UK
- ¹³ Psychosis Studies, King's College London, London, UK
- ¹⁴ National Addiction Centre, King's College London, London, UK