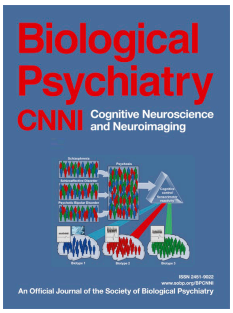

The effects of acute cannabis with and without cannabidiol on neural reward anticipation in adults and adolescents

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Title: The effects of acute cannabis with and without cannabidiol on neural reward anticipation in adults and adolescents

Running title: Acute effects of cannabis on neural reward anticipation

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Abstract

Background. Adolescents may respond differently to cannabis than adults, yet no functional magnetic resonance imaging (fMRI) study has examined acute cannabis effects in this age-group. We investigated the neural correlates of reward anticipation after acute exposure to cannabis in adolescents and adults.

Methods. This was a double-blind, placebo-controlled, randomized, crossover experiment. Forty-seven adolescents (n=24, 12 females, 16-17 years) and adults (n=23, 11 females, 26-29 years), matched on cannabis use frequency (0.5-3 days/week), completed the Monetary Incentive Delay task during fMRI after inhaled cannabis with 0.107 mg/kg THC ('THC') (8 mg THC for a 75 kg person) or THC plus 0.320 mg/kg CBD ('THC+CBD') (24 mg CBD for a 75 kg person), or placebo cannabis ('PLA'). We investigated reward anticipation activity with whole-brain analyses and region of interest (ROI) analyses in right and left ventral striatum, right and left anterior cingulate cortex, and right insula.

Results. THC reduced anticipation activity compared to placebo in the right (P=.005, d=0.49) and left (P=.003, d=0.50) ventral striatum, and right insula (P=.01, d=0.42). THC+CBD reduced activity compared to placebo in the right ventral striatum (P=.01, d=0.41) and right insula (P=.002, d=0.49). There were no differences between 'THC' and 'THC+CBD' and no significant Drug*Age-Group effect, supported by Bayesian analyses. There were no significant effects in the whole-brain analyses.

Conclusions. In weekly cannabis users, cannabis suppresses the brain's anticipatory reward response to money and CBD does not moderate this effect. Furthermore, the adolescent reward circuitry is not differentially sensitive to acute effects of cannabis on reward anticipation.

Introduction

Cannabis is the third most commonly used controlled substance worldwide, after alcohol and nicotine (1). With the currently changing legal landscape, it is crucial to know how cannabis use affects the brain and cognition of both adolescents and adults.

The major psychoactive effects of cannabis are ascribed to Δ^9-tetrahydrocannabinol (THC), which acts as a partial agonist of CB_1 cannabinoid receptors (CB_1Rs). Acute THC has widespread effects on brain activity and neurocognitive function mediated by CB_1Rs on gamma-aminobutyric acid (GABA)ergic and glutamatergic neurons in the cortex, hippocampus, basal ganglia, and cerebellum (2-5). Cannabidiol (CBD), typically the second most abundant phytocannabinoid, has low affinity for CB_1Rs but may attenuate CB_1R agonist effects as a negative allosteric modulator. There is some evidence that CBD can attenuate the acute anxiogenic and psychotomimetic effects of THC, though findings are not consistent (6).

Cannabis use typically starts in adolescence and is more prevalent among adolescents and young adults than other age-groups (7). In 2021, the annual prevalence was estimated at 16% among 15-year-olds in England (8), down from 19% in 2018 (9), and 17% of 15-16-year-olds in the United States (10), down from 28% in 2020 (11). Adolescence is an important period of socio-emotional, cognitive, and neural development, including maturation of the endocannabinoid system (12-17). As such, adolescents may respond differently to acute cannabis compared with adults. However, only two previous controlled experiments have compared the acute effects of cannabis in these two age-groups. Mokrysz et al. (18) found that twenty 16-17-year-old male cannabis users (median use 11 days/month) showed weaker subjective, memory, and psychotomimetic effects, along with reduced satiety and impaired inhibition, compared to twenty 24-28-year-old male users (8 days/month) after 0.107 mg/kg inhaled THC. Using an older sample with less cannabis use (1-20 total days/lifetime), Murray

et al. (19) found increased sensitivity to the effects of 7.5 and 15 mg oral THC on reaction time, stop-signal response accuracy, and time perception in twelve 18-20-year-olds compared with twelve 30-40-year-olds. There were no age-group differences in the effect of THC on working memory, response inhibition, cardiovascular measures, or subjective effects. They also found that THC decreased the amplitude of the event-related potential (ERP) P300 component during an auditory oddball task in the adolescents but not the adults, during electroencephalography (EEG).

In another recent investigation from the same study, Murray et al. (20) examined the effect of oral THC on ERPs during an EEG-adapted Monetary Incentive Delay (MID) task. Both doses of THC reduced the amplitude of a component related to outcome evaluation (RewP) during reward feedback, and the high dose (15 mg) reduced the P300 component as well as a component related to affective processing (LPP) during hits compared with misses. There were no effects on reward anticipation. Only two functional magnetic resonance imaging (fMRI) studies have assessed neural reward anticipation after acute THC exposure (21). Both administered 6 mg inhaled THC or placebo to young adult male cannabis users (4-52 days/year) and examined reward anticipation with the MID task. While Van Hell et al. (22) found no effect of THC on neural anticipation activity in 11 participants, Jansma et al. (23) found that THC decreased activity in the nucleus accumbens (NAc) – a key reward processing region (24) – in 10 nicotine dependent participants, but not in 11 participants who were not nicotine dependent. Crucially, none of these studies included adolescents below 18 years of age. One previous study has explored adolescent vulnerability to the long-term effects of cannabis on reward processing, and found that adolescents were neither more or less vulnerable to cannabis-related differences in neural reward anticipation or feedback on the MID task (25). However, the differential effects of acute cannabis in adolescents and adults have never been investigated.

Notably, both previous fMRI studies investigating the effect of acute cannabis on reward anticipation had small samples and consequently low power, and neither included female participants (22,23). The effects of acute cannabis on reward processing therefore remain unclear. Additionally, neither of these studies explored the potential modulatory effects of CBD. CBD is available as an over-the-counter health supplement in many countries, yet its effects on brain and cognition are poorly understood. In one previous study, 600 mg of oral CBD did not alter the neural correlates of reward anticipation (26). However, 10 mg inhaled CBD has been found to partially modulate the impact of THC on effort expenditure for reward (27), neural responses to music (28), and connectivity in the limbic striatum (29). Finally, and most crucially, no previous controlled experiments have investigated the effects of acute cannabis in adolescents using fMRI (2,21). Considering that adolescents use cannabis at higher rates than adults (7,8,30), and may show resilience or vulnerability to the acute and non-acute effects of cannabis (12,17-19), this is a critical gap in the research base.

In the current study we compared reward anticipation on the MID task during fMRI in 24 adolescent and 23 adult cannabis users (0.5-3 days/week) after acute exposure to THC with CBD ('THC+CBD'), THC without CBD ('THC'), and placebo ('PLA'). We performed whole-brain analyses and region of interest (ROI) analyses in key reward regions. We proposed the following, pre-registered (31) hypotheses:

1. Both active cannabis conditions will reduce reward anticipation activity in all ROIs compared to placebo.
2. CBD will attenuate the effect of THC, such that there will be lower reward anticipation activity in all ROIs during 'THC' than 'THC+CBD'.
3. There will be an interaction between drug and age-group, with a greater difference between 'THC' and 'PLA' for adults compared to adolescents. This hypothesis was

based on the previously published results by Mokrysz et al. (18) demonstrating adolescent resilience to some acute effects of THC.

Methods and Materials

We present data from the CannTeen-Acute study. Full details on trial procedures and outcomes are found in the study protocol (32). This study was categorized as not a clinical trial by the UK Medicines & Healthcare products Regulatory Agency, as it is not attempting to research the diagnosis, prevention, or treatment of a disease. Nonetheless, it was registered on clinicaltrials.gov 20/04/2021, ID NCT04851392.

Participants

Participants were 24 adults (26-29 years, mean=27.8 years, 12 females) and 24 adolescents (16-17 years, mean=17.2 years, 12 females), recruited from the greater London area using online advertisements and word-of-mouth. This was a per-protocol analysis; thus drop-outs were replaced and recruitment continued until 48 participants had completed all three study sessions (Figure 1). Participants had to use cannabis between 0.5 and 3 days per week, averaged over the past three months, and use frequency was matched between the two age-groups. The range of 0.5-3 days/week was to ensure that participants were likely to tolerate the drug well without unexpected adverse events, whilst minimizing potential tolerance effects. Adult users were excluded if they had used cannabis regularly prior to the age of 18, to ensure they had not used cannabis during this key developmental window that might confer vulnerability to the harmful effects of cannabis. Participants also had to be physically healthy and not receiving treatment for any mental health condition. Inclusion and exclusion criteria are presented in

Table S1 in the Supplement. Ethical approval was obtained from the University College London (UCL) ethics committee, project ID 5929/005. The study was conducted in line with the Declaration of Helsinki, and all participants provided written informed consent to participating.

Design

We employed a double-blind, placebo-controlled, randomized, crossover design, with three drug conditions: 'PLA', 'THC', and 'THC+CBD'. Drug order was balanced for all participants, and within both age-groups and genders. Within these groups participants were randomly allocated to drug order using blocked randomization written by TPF and HVC, with blocks of 12 participants.

Materials

Reward anticipation was assessed with the Monetary Incentive Delay (MID) task (33). The current version of the task included win and neutral trials, but no loss trials. Details are presented in Supplemental Methods. Additional measures and covariates are presented in Supplemental Methods.

Procedure

The drug administration sessions were completed at the Invicro clinical imaging facility, Hammersmith Hospital, London, between 11th March 2019 and 16th June 2021. Participants completed an instant saliva drugs test (Alere DDSV 703 or ALLTEST DSD-867MET/C) and a Lion Alcometer 500 breathalyser and self-reported abstinence at the start of all sessions, to

confirm no recent use of alcohol (≥24 hours cut-off), or cannabis or other illicit drugs (all ≥72 hours cut-off). Additional details are in the Supplemental Methods and the full drug administration session schedule is presented in Figure S1.

Dried medical cannabis flower was obtained from Bedrocan, The Netherlands, and imported under a UK Home Office License. Three cannabis products were used: "Bedrocan" (20.2% THC, 0.1% CBD), "Bedrolite" (0.4% THC, 8.5% CBD), and "Bedrobinol" (no THC or CBD). Participants inhaled vaporized active cannabis containing 0.107 mg/kg THC during 'THC' (e.g., 8 mg THC/1.6 standard THC units (34) for a person weighing 75 kg) or 0.107 mg/kg THC plus 0.320 mg/kg CBD during 'THC+CBD' (e.g., 24 mg CBD for a person weighing 75 kg), or placebo cannabis. The cannabis was vaporised using a Volcano Medic Vaporiser (Storz and Bickel, Tuttlingen, Germany) at 210°C. Participants inhaled two "balloons" within nine minutes each, using standardised timings. The balloon was covered in an opaque bag so the contents were not visible. This method has been shown to be safe (18,35) and produce similar pulmonary and plasma cannabinoid levels to smoked cannabis, but with lower expired carbon monoxide levels (36-38).

Unmasked staff blinded the drugs. The placebo cannabis matched the active cannabis in appearance and smell, and all experimental researchers and participants were blinded to treatment allocation. The minimum washout period between drug sessions was 72 hours, the mode was 7 days, and the maximum was 51 days (39,40). Blood samples were taken from participants to quantify plasma levels of THC and CBD (see Supplemental Methods).

MRI Data Acquisition

MRI data were collected with 3.0 T Siemens Verio and Trio scanners (the Verio scanner was decommissioned part-way through data collection). Participants always completed all three

sessions on the same scanner, and an equal number of participants in each gender and age-group were scanned with each scanner (n=36 on Verio, n=12 on Trio). T_2* images were acquired using a multiband gradient echo Echo-Planar Imaging (EPI) sequence (41). T_1-weighted structural images were acquired using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (42). The acquisition sequences and all other aspects of the set-up (behavioral task, response boxes, etc.) were identical for both scanners. Full MRI acquisition parameters are in Supplemental Methods.

MRI Data Pre-processing and First-level Analysis

Pre-processing and first-level fMRI analyses were performed in FSL (43), with the fMRI Expert Analysis Tool (FEAT) (44,45). Structural high-resolution images were pre-processed using the fsl_anat script provided with FSL. Functional images were realigned with MCFLIRT (motion correction FMRIB linear image registration tool) (46) and normalised to MNI-152 (Montreal Neurological Institute) space with FNIRT (FMRIB's nonlinear registration tool), using a 10 mm warp resolution and 12 degrees of freedom. Spatial smoothing was carried out using a 6 mm full-width at half-maximum Gaussian kernel. Raw functional image series, movement estimates, and registration were carefully inspected for each participant.

There were two explanatory variables (EVs): Anticipation of win outcomes (Anticipate-win; EV1) and anticipation of neutral outcomes (Anticipate-neutral; EV2). These were implemented in a General Linear Model, by convolving their respective onsets with a gamma function model of the hemodynamic response. Motion parameters (standard + temporal derivatives + squared + quadratic) and temporal derivatives were included as regressors-of-no-interest. The FILM pre-whitening procedure was used to account for temporal autocorrelation,

and a high-pass filter (100 s cut-off) was used to remove low-frequency noise. Reward anticipation was examined with the Anticipate-win > Anticipate-neutral contrast [1 -1 0 0 0 0].

Statistical Analyses

Analyses and hypotheses were pre-registered to the Open Science Framework (31). Power calculations are presented in Supplemental Methods. Behavioral and ROI analyses were performed with R 3.6.2 (47), using the rstatix and BayesianFactor packages (48,49). One adult female did not complete the MID task during 'THC+CBD' and was excluded from analyses, leaving 23 adults.

The main behavioral outcome on the MID task was mean reaction times (RTs) for win and neutral trials. This was analyzed in a linear mixed model with Trial-Type (win, neutral) and Drug ('PLA', 'THC', 'THC+CBD') as within-subjects factors, Age-Group (adult, adolescent) as the between-subjects factor, and mean-centered covariates weekly cigarette/roll-up tobacco use (yes/no), depression, and scanner (Supplemental Methods). These covariates were chosen *a priori* due to their putative interaction with cannabis use and reward processing (50-53). In fact, tobacco/nicotine use has been shown to influence the association between cannabis use and neural reward anticipation both acutely (23) and non-acutely (25). An unstructured covariance structure was used. As hit rates (% hit targets) were calibrated to 50% these were not analyzed.

Group-level fMRI analyses were performed with FMRIBs local analysis of mixed effects (FLAME). Cluster-level statistics were used, with a cluster-defining threshold of Z=3.1 (p=0.001) and a multiple test corrected cluster-extent threshold of a=0.05. Mean blood-oxygen-level-dependent responses during reward anticipation were examined in separate whole-brain one-sample *t*-tests for 'PLA', 'THC', and 'THC+CBD'. The main effect of Drug and the

Drug*Age-Group interaction were investigated with a 3X2 mixed measures analyses of variance (ANOVA). The design setup in FSL does not allow for a between-subjects main effect to be examined simultaneously, as this causes rank deficiency of the design matrix. Therefore, we performed subject-level fixed effects analyses averaging the three drug conditions for each participant, and then passed these results up to a separate group-level FLAME independent-samples *t*-test analysis with Age-Group as a factor.

ROIs were the right and left ventral striatum, right and left anterior cingulate cortex (ACC), and right insula. These were selected based on a large meta-analysis of the MID task (24) and a previous study of MID reward processing in adult and adolescent cannabis users and controls (25). Six mm radius spheres were constructed around coordinates with peak *Z*-values or activation likelihood estimates (Table S2), and unstandardized *b*-values were extracted from the lower-level contrasts. Separate 2X3 mixed measures analyses of covariance (ANCOVAs) were performed for each ROI with Drug, Age-Group, and mean-centered covariates cigarette/roll-up tobacco use, depression, and scanner. All two-way Drug interactions were included. Null Drug main effects were followed up with paired-samples Bayesian tests of 'PLA' vs. 'THC' and 'THC' vs. 'THC+CBD'. Null Drug*Age-Group interactions were followed up with independent-samples Bayesian tests comparing adults and adolescents on difference scores for 'THC' vs. 'PLA'. A scaled-information prior of r=.707 was used, and Jeffreys-Zellner-Siow Bayes factors (BF_{01}) above 3 were interpreted as meaningful (54). Finally, correlations between 'THC' minus 'PLA' difference scores for reward anticipation responses in every ROI and days/week of cannabis use, lifetime days of use, and dependence were computed.

Results

Participant characteristics are displayed in Table 1. Plasma concentrations of THC and CBD are displayed in Figure 2. Full trial results on primary outcome measures, blinding, and adverse events will be reported elsewhere.

Descriptive statistics and full results of the behavioral analyses are presented in tables S3 and S4. There was a significant effect of Trial-Type, with higher lower RTs (mean difference 6 ms, $P<.001$) for win trials than neutral trials. There were no significant effects of Drug and Age-Group.

Brain regions were labelled using the Harvard-Oxford cortical and subcortical structural atlases (55-57). The whole-brain analysis revealed reward anticipation activity in a large network comprising the striatum, insula, thalamus, anterior cingulate and paracingulate cortex, and prefrontal cortex (Figure S2 and Table S5). There were no significant effects of Drug, Age-Group, or Drug*Age-Group. Exploratory paired-samples *t*-tests were performed with $Z=2.3$ ($p<0.05$, cluster-corrected) to compare the drug conditions. These showed lower activity during 'THC' and 'THC+CBD' compared to 'PLA' in a network comprising the dorsal and ventral striatum, paracingulate cortex, insula, frontal pole, and orbitofrontal cortex (Figure 3 and Table S6). There were no significant differences between 'THC' and 'THC+CBD'.

Results of the ROI analyses are displayed in Figure 4 and Table S7. Unadjusted models are presented in Table S8. There was a significant main effect of Drug for right ventral striatum ($P=.009$, $\eta_p^2=.11$), left ventral striatum ($P=.02$, $\eta_p^2=.09$), and right insula ($P=.003$, $\eta_p^2=.13$). *Post hoc* paired samples *t*-tests showed significantly greater activity during 'PLA' than 'THC' for right ventral striatum ($P=.005$, $d=0.49$), left ventral striatum ($P=.003$, $d=0.50$), and right insula ($P=.01$, $d=0.42$). There was significantly greater activity during 'PLA' than 'THC+CBD' for right ventral striatum ($P=.01$, $d=0.41$) and right insula ($P=.002$, $d=0.49$), but

not left ventral striatum (*P*=.17, *d*=0.24). There were no significant differences between 'THC' and 'THC+CBD', and no significant Drug effects in the ACC. These findings were supported by Bayesian analyses (Table S9).

There was a significant main effect of Age-Group for all ROIs except left ACC, with adolescents activating more than adults (Figure 4 and Table S7). However, there were no significant Drug*Age-Group effects. This was supported by Bayesian analyses for 'THC' minus 'PLA' in all ROIs (Table S9). None of the correlations were significant (Table S10).

Discussion

This is the first fMRI study to investigate the effects of acute cannabis in adolescents, and consequently also the first to compare adults and adolescents after acute cannabis administration. We found that active cannabis, in comparison to placebo, attenuated reward anticipation brain activity in key reward-related regions, including the ventral striatum, in people who used cannabis 0.5-3 days/week. Age-group did not moderate the effect of cannabis on the neural correlates of reward anticipation. Finally, CBD did not modulate the effect of THC.

THC Reduces Activity in the Brain's Reward System

The current results are partially consistent with those of Jansma et al. (23) who found that THC attenuated reward anticipation activity in the NAc in nicotine dependent participants. This effect was not found in non-nicotine dependent participants or by van Hell et al. (22), although both these studies had markedly smaller samples relative to the current study. THC has also been found to acutely attenuate ERPs during the feedback phase of the MID task (20), ventral

striatal responses to music listening (28), and functional connectivity in the limbic striatum (29), relative to placebo. Thus, our results along with some previous evidence suggest that acute THC reduces activity in the brain's reward system.

Notably, our participants used cannabis roughly twice as frequently as those of van Hell et al. (22) and Jansma et al. (23) (roughly 1.5-2 days/month), and much more frequently than those of Murray et al. (20) (1-20 days/life). Level of cannabis use is important given that repeated exposure can increase the tolerance to acute effects (58,59). However, we found no correlation between days per week of use and 'THC' minus 'PLA' difference scores in any ROI (Table S10). Moreover, as we did find an acute effect of cannabis in this study, 0.5-3 days per week of cannabis use cannot fully attenuate acute effects of THC on the reward system through a putative tolerance mechanism.

Lastly, it is not known whether the present acute effects persist into abstinence. In one longitudinal investigation, Martz et al. found that cannabis use predicted attenuated reward anticipation activity in the NAc in 108 young adults after ≥48 hours of abstinence (60), indicating some convergence between acute and long-term effects. This is also similar to what has been found in other substance use and gambling disorders (50,61). However, Skumlien et al. did not find an association between cannabis use and reward anticipation in a recent cross-sectional study of 125 adults and adolescents after ≥12 hours of abstinence (25). More longitudinal research is needed to unpack long-term, chronic associations while users are not intoxicated.

CBD Does Not Modulate the Effect of THC

There were no differences between 'THC' and 'THC+CBD' on any outcome, which was supported by Bayesian analyses, confirming that CBD did not modulate the effect of THC.

Thus, although high dose pre-administration of CBD has been previously shown to attenuate anxiogenic and psychotomimetic effects of THC (6,62,63), the present study did not find an effect neural reward anticipation. Of note, both THC and CBD were successfully absorbed and observed in plasma. Moreover, cannabinoid levels did not differ between adolescents and adults in the 'THC' condition, which contrasts with some previous findings from preclinical studies in rodents (64,65). However, adults did have slightly higher CBD levels in the 'THC+CBD' condition. Additionally, in line with some (66), but not all existing research (67), THC concentrations were higher in the 'THC+CBD' condition than in the 'THC' condition (Figure 2). This deserves further exploration in future studies.

Adolescents Are Not Differentially Sensitive to the Acute Effects of THC on Reward Anticipation

Crucially, this is the first controlled experiment to examine the acute effects of cannabis in adolescents using fMRI. Adolescents had higher reward anticipation activity across Drug conditions in all but one ROI (left ACC), which converges with some previous studies showing striatal hyperactivity in adolescents during reward processing (68-70). However, adolescents and adults did not differ in their neural responses to active cannabis in any ROI, which was confirmed by Bayesian analyses. Thus, our results suggest that the reward system is not more or less sensitive to disruption by a moderate dose of acute cannabis at age 16-17 years than at age 26-29 years. Previous research in the CannTeen study has also not revealed different associations between chronic cannabis use and reward processing in adolescents and adults (25,71). Nonetheless, other cognitive or psychological processes could still be differently affected by acute cannabis in these two age-groups, and should be explored in future studies.

Of note, the age-group comparison is somewhat limited by the significantly higher number of lifetime days of cannabis use in the adults compared with the adolescents (Table 1). Prolonged cannabis use may lead to increased tolerance to the acute effects of THC (58,59), which could have cancelled out the hypothesized greater vulnerability to these effects in the adult age-group. This limitation is difficult to avoid as adults typically have a longer history of cannabis use than adolescents, although we did restrict the adult group to people who had not used cannabis regularly prior to age 18. Relatedly, adolescents had significantly higher scores on the Cannabis Use Disorder Identification Test - Revised (CUDIT-R) than the adults, suggesting greater levels of cannabis use problems in this group. Adolescent cannabis users are consistently found to have greater risk of developing dependence than adult users, even with similar levels of use (72-77). Crucially, the two age-groups were matched on days per week of cannabis use. Moreover, we did not find a significant correlation between lifetime days of use or CUDIT-R scores and 'THC' minus 'PLA' difference scores in any ROI (Table S10), suggesting that neither were associated with the impact of THC on reward function.

Limitations

One limitation of this study concerned the restricted age range of participants. It is possible that younger adolescents with less developed reward systems respond differently to THC than adults. However, ethical considerations prevent controlled experiments of acute drug effects in this age-group. Future work should also further examine the effect of acute cannabis on the consummatory phase of reward processing, which could include the feedback phase of the MID task (20,22,23). Finally, although our sample size greatly exceeds that of previous studies with similar aims, this study was not powered to detect small effects.

Conclusions

In this placebo-controlled, randomized, crossover trial, we found blunted reward anticipation activity in key reward regions after acute active cannabis compared to placebo. Adolescents and adults did not show different neural responses to acute cannabis. There was also no evidence of a modulatory effect of CBD. These findings demonstrate that cannabis suppresses the brain's anticipatory reward response to money, CBD does not modulate this effect, and adolescents are neither more sensitive nor more resilient to the acute effects of cannabis on neural reward anticipation.

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Disclosures

B.J.S. consults for Cambridge Cognition. HVC has consulted for Janssen Research and Development. MBW's primary employer is Invicro LLC, a contract research organization which performs commercial research for the pharmaceutical and biotechnology industries. Remaining authors report no biomedical financial interests or potential conflicts of interest.

Data Sharing Statement

The data are not available.

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Tables

Table 1. Participant characteristics

	Adolescents (*n* = 24)	**Adults** (*n* = 23)	**Group differences**	**Test statistic**
Demographics and covariates				
Sex				
Female	12 (50%)	11 (48%)		
Male	12 (50%)	12 (52%)		
Age in years	17.17 (0.43), 16.50-17.92	27.78 (1.06), 26.33-29.58	Adolescents < Adults	$t_{28.67}$=44.51, *P*<.001
Ethnicity				
White	17 (71%)	18 (78%)		
Mixed	4 (17%)	1 (4%)		
Asian	1 (4%)	2 (9%)		
Black	0	2 (9%)		
Other	1 (4%)	0		
Prefer not to say	1 (4%)	0		
Maternal education				
Below undergraduate degree	8 (33%)	8 (35%)		
Undergraduate degree or above	16 (67%)	15 (65%)		
BDI	10.38 (8.55), 0-28	5.43 (6.56), 0-22	Adolescents > Adults	t_{45}=2.22, *P*=.03
SUPPS-P	48.17 (7.51), 34-61	42.57 (9.02), 30-64	Adolescents > Adults	t_{45}=2.32, *P*=.03
Alcohol use, days/week	0.56 (0.62), 0-2.50	2.10 (1.72), 0-6	Adolescents < Adults	$t_{27.39}$=4.04, *P*<.001
Alcohol units/week	5.39 (8.24), 0-35.50	12.58 (9.89), 0-31.99	Adolescents < Adults	t_{45}=2.71, *P*=.009
Tobacco use, days/week	2.33 (2.05), 0-7	1.20 (1.56), 0-6.25	Adolescents > Adults	t_{45}=2.13, *P*=.04
Hours since last nicotine use[a]				
'PLA'	36.73 (41.04), 1-146, n=16	80.75 (34.71), 32-154, n=10	Adolescents < Adults	t_{24}=2.82, *P*=.01
'THC'	24.90 (30.75), 0.1-93, n=15	52.78 (36.48), 12-130, n=9		t_{22}=2.01, *P*=.06
'THC+CBD'	37.46 (45.81), 0.5-169, n=17	52.54 (37.94), 1.5-141, n=12		t_{27}=0.94, *P*=.36
Other illicit drug use, monthly use				
Yes	2 (8%)	2 (9%)		
No	22 (92%)	21 (91%)		

Cannabis use				
Days/week of use	1.41 (0.77), 0.25-3.50	1.50 (0.75), 0.50-2.75		t_{45}=0.42, P=.67
Grams used on a day of use	0.81 (0.56), 0.25-2.50	0.52 (0.52), 0.10-2.00		t_{45}=1.84, P=.07
Days since last use				
'PLA'	6.04 (8.06), 2.90-43.00	5.13 (3.47), 3.00-19.00		t_{45}=0.50, P=.62
'THC'	8.01 (9.72), 3.00-51.00	7.41 (4.31), 3.33-18.00		t_{45}=0.27, P=.79
'THC+CBD'	5.46 (2.48), 3.10-12.00	6.91 (5.34), 2.88-26.00		t_{45}=1.21, P=.24
Age of first ever use	14.55 (1.03), 11.92-16.08	18.30 (2.60), 14.00-24.42	Adolescents < Adults	$t_{28.51}$=6.47, P<.001
Lifetime days of use	153.67 (89.97), 11-418	560.35 (640.27), 136-3172	Adolescents < Adults	$t_{22.83}$=3.02, P=.006
CUDIT-R	10.17 (3.14), 5-16	7.35 (3.31), 3-15	Adolescents > Adults	t_{45}=2.99, P=.004

[a]Includes participants who reported having used nicotine in the past week.

Abbreviations: BDI, Beck Depression Inventory; CBD, cannabidiol; CUD, Cannabis Use Disorder; CUDIT-R, Cannabis Use Disorder Identification Test – Revised; DSM, Diagnostic and Statistical Manual of Mental Disorders; PLA, placebo; SUPPS-P, Short UPPS-P Impulsive Behavior Scale; THC, Δ^9-tetrahydrocannabinol.

Note. For continuous data mean (SD) and range are shown. For categorical data, n (%) is shown. Age-group differences were investigated with independent samples t-tests. Two participants had used cannabis <72 hours prior to a drug administration session, in breach of abstinence rules. However, as they were unable to reschedule their sessions, lead experimenters made the decision to continue with the session considering the abstinence requirement was not severely violated (<3 hours).

Figure legends

Figure 1. Trial profile.

Other reasons for dropping out included scheduling conflicts, personal reasons, and no reason given. COVID-related restrictions were primarily due to lockdowns in March 2020 (after which the study was paused for seven months) and restrictions from January 2021.

Figure 2. Plasma concentrations of THC and CBD by Drug and Age-Group.

A, Δ^9-tetrahydrocannabinol (THC) plasma levels ($ng.ml^{-1}$). B, cannabidiol (CBD) plasma levels ($ng.ml^{-1}$).

The blood sample was taken 30 minutes after the start of drug administration, immediately before scanning. Bars represent means with dots indicating individual participant values, and error bars represent standard errors. Differences in THC and CBD levels for placebo, 'THC', and 'THC+CBD' conditions were investigated with paired samples *t*-tests. Differences between adolescents and adults within each Drug condition were investigated with independent-samples *t*-tests. Data were missing for four adolescents and one adult for the placebo condition, four adolescents for the 'THC' condition, and two adolescents and one adult for the 'THC+CBD' condition.

Figure 3. Differences in reward anticipation between drug conditions

Significant differences in reward anticipation between the placebo ('PLA'), Δ^9-tetrahydrocannabinol ('THC'), and Δ^9-tetrahydrocannabinol + cannabidiol ('THC+CBD') conditions in whole-brain paired-samples *t*-tests across Age-Group (n=47). Cluster-defining threshold was 2.3. Images are presented in radiological orientation, such that left on the image is the right hemisphere.

Figure 4. Region of interest reward anticipation activity by Drug and Age-Group

Abbreviations: ACC, anterior cingulate cortex; R, right; L, left.

Bars represent mean beta-values with dots indicating individual participant values, and error bars represent standard errors.