

LAWN WILL (ORCID ID: 0000-0002-0143-2724)

MOKRYSZ CLAIRE (ORCID ID: 0000-0002-1970-8530)

PETRILLI KAT (ORCID ID: 0000-0001-9801-1442)

FREEMAN TOM (ORCID ID: 0000-0002-5667-507X)

THE ACUTE EFFECTS OF CANNABIS WITH AND WITHOUT CANNABIDIOL IN ADULTS AND ADOLESCENTS: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER EXPERIMENT

Authors

Will Lawn^{*1,2,3}, Katie Trinci^{*3}, Claire Mokrysz³, Anna Borissova^{4,5}, Shelan Ofori³, Kat Petrilli⁶, Michael Bloomfield^{3,5,7}, Zarah R Haniff³, Daniel Hall³, Natalia Fernandez-Vinson³, Simiao Wang^{3,2}, Amir Englund^{2,8}, Edward Chesney^{2,8}, Matthew B Wall^{3,9}, Tom P Freeman^{3,6}, and H Valerie Curran³

*Joint first authors

Affiliations

1 Department of Psychology, Institute of Psychiatry Psychology and Neuroscience, King's College London, London, UK

2 Department of Addictions, Institute of Psychiatry Psychology and Neuroscience, King's College London, London, UK

3 Clinical Psychopharmacology Unit, Clinical Educational and Health Psychology, University College London, London, UK

4 Department of Neuroimaging, Institute of Psychiatry Psychology and Neuroscience, King's College London, London, UK

5 NIHR University College London Hospitals Biomedical Research Centre, University College Hospital, London, United Kingdom.

6 Addiction and Mental Health Group (AIM), Department of Psychology, University of Bath, Bath, United Kingdom

7 Translational Psychiatry Research Group, Research Department of Mental Health Neuroscience, Division of Psychiatry, University College London, London, United Kingdom.

8 Department of Psychosis Studies, Institute of Psychiatry Psychology and Neuroscience, King's College London, London, UK

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9 Invicro London, Burlington Danes Building, Hammersmith Hospital, Du Cane Road, London, United Kingdom.

Running head

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Corresponding author

Dr Will Lawn; will.lawn@kcl.ac.uk

Department of Psychology,

Institute of Psychology Psychiatry and Neuroscience,

King's College London,

Guy's Campus,

Great Maze Pond,

SE1 1UL

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Clinical trial registration details

Although not deemed to be a clinical trial by the UK Medicines and Healthcare products Regulatory Agency, given international variations in defining a clinical trial, this study was registered on ClinicalTrials.gov (NCT04851392).

Protocol and analysis pre-registration

<https://osf.io/z638r/>

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ABSTRACT

Background and aims

Long-term harms of cannabis may be exacerbated in adolescence, but little is known about the acute effects of cannabis in adolescents. We aimed to: (1) compare the acute effects of cannabis in adolescent and adult cannabis users, and (2) determine if cannabidiol (CBD) acutely modulates the effects of delta-9-tetrahydrocannabinol (THC).

Design

Randomised, double-blind, placebo-controlled, crossover experiment. The experiment was registered on ClinicalTrials.gov (NCT04851392).

Setting

Laboratory in London, United Kingdom.

Participants

Twenty-four adolescents (12 women, 16-17 year-olds) and 24 adults (12 women, 26-29 year-olds) who used cannabis 0.5-3 days/week and were matched on cannabis use frequency (mean=1.5 days/week).

Intervention

We administered three weight-adjusted vaporised cannabis flower preparations: 'THC' (8mg THC for 75kg person); 'THC+CBD' (8mg THC and 24mg CBD for 75kg person); and 'PLA' (matched placebo).

Measurements

Primary outcomes were: i) subjective 'feel drug effect'; ii) verbal episodic memory (delayed prose recall); and iii) psychotomimetic effect (Psychotomimetic States Inventory).

Findings

Compared with 'PLA', 'THC' and 'THC+CBD' significantly ($p < 0.001$) increased 'feel drug effect' (mean difference (MD)=6.3, 95% confidence interval (CI) 5.3 to 7.2; MD=6.8, 95% CI 6.0 to 7.7), impaired verbal memory (MD=-2.7, 95% CI -4.1 to -1.4; MD=-2.9, 95% CI -4.1 to -1.7), and increased psychotomimetic effects (MD=7.8, 95% CI 2.8 to 12.7; MD=10.8, 95% CI 6.2 to 15.4). There was no evidence that adolescents differed from adults in their responses to cannabis (interaction $p \geq 0.4$). Bayesian analyses supported equivalent effects of cannabis in adolescents and adults ($BF_{01} > 3$). There was no evidence that CBD significantly modulated the acute effects of THC.

Conclusions

Adolescent cannabis users are neither more resilient nor more vulnerable than adult cannabis users to the acute psychotomimetic, memory-impairing, or subjective effects of cannabis. Furthermore, in adolescents and adults, vaporised cannabidiol does not mitigate the acute harms caused by delta-9-tetrahydrocannabinol.

INTRODUCTION

Cannabis is the most commonly used internationally controlled drug in the world and is particularly popular amongst adolescents. Between 15–20% of English 15 year-olds (1,2) and 28% of American 15–16 year-olds (3) report using cannabis in the last year. Globally, roughly half of those who try cannabis do so aged 18.5 years or younger (4). Adolescents are approximately three times more likely than adults to develop cannabis addiction in the years immediately after initiating cannabis use (5–7). Meanwhile, cannabis laws are rapidly evolving across the world (8), which is likely to have profound impacts on young people (9–11). Accordingly, there is an urgent need to understand the acute psychopharmacological effects of cannabis in teenagers.

Adolescence is a period during which important biological, neural, psychological, social, and personal changes occur (12–15). Crucially, the endocannabinoid (eCB) system continues to develop, with changing levels of cannabinoid receptors and endocannabinoids (16,17). It is also a time when mental health problems typically begin to emerge (18), with 14 years being the average age-of-onset of mental illness (19). In epidemiological studies, long-term cannabis use in adolescence has been associated with an increased likelihood of psychosis (20), mood disorders (21), and poorer cognitive function and educational achievement (22). Therefore, there is concern that the potential harms of cannabis use may be accentuated in adolescents who are at a critical neurodevelopmental stage (23). However, the acute effects of cannabis intoxication in adolescents have rarely been studied in controlled settings.

Acutely, cannabis reliably produces an array of transient and dose-dependent effects including intoxication, euphoria, memory impairment, psychotomimetic effects, anxiogenic effects, attention deficits, and tachycardia (24–27). Notably, there is wide interindividual variation (27). The major psychoactive effects of cannabis arise from delta-9-tetrahydrocannabinol (THC), which is a partial cannabinoid-1 receptor (CB1R) agonist. Cannabidiol (CBD), which is the second most abundant phytocannabinoid (28), has a complex pharmacology (29), including inhibition of anandamide metabolism (27), agonism of the serotonin-1A receptor (30), and negative allosteric modulation of CB1 receptors (31). CBD may moderate some of the acute effects of THC (32); however, findings are inconsistent with CBD sometimes attenuating harmful effects of THC (33) and sometimes not (34), which may be related to CBD dose, route of administration, and user characteristics. High-dose oral (600mg) and intravenous (5mg) CBD attenuated the psychotomimetic effects (35,36) and episodic memory impairing effects of THC (36), but 8mg of vaporised CBD did not (37,38). The moderating influence of CBD co-administration on the acute effects of cannabis in adolescents is unknown.

Despite the pervasiveness of adolescent cannabis use, only one controlled human experiment has compared the acute effects of cannabis in adolescents under the age of 18 years and adults (39). Participants were 20 adolescent males (aged 16-17 years) and 20 adult males (aged 24-28 years) who used cannabis an average of 2.4 and 1.8 days/week, respectively. Participants inhaled vapourised cannabis (8mg THC for a 75kg person) or placebo cannabis. Notably, adolescents reported less intense subjective effects, fewer psychotomimetic symptoms, and exhibited less episodic memory impairment than adults. However, in this study, adolescents used cannabis significantly more frequently than adults and weighed less than adults, so received a lower absolute dose of THC.

More recently, one placebo-controlled study compared the impact of oral THC (7.5mg and 15mg) in young people aged 18-20 years and adults aged 30-40 with limited cannabis experience (40). They found similar responses on all subjective effects, cardiovascular measures, working memory, and response inhibition; however the 18-20 year-olds experienced stronger electroencephalography and psychomotor changes compared with adults (40). One observational, ecological momentary assessment study examined the associations between age and subjective response in 15–24 year-old frequent cannabis users (41). Contrastingly, they reported that being older was associated with diminished self-reported stimulatory response and subjective 'high'. Moreover, non-human animal research has found mixed results; acute cannabinoid agonists elicited stronger anxiogenic effects in adults (42), but provoked greater impairments in learning in adolescents (43).

In sum, no studies have investigated the combined effects of CBD and THC in adolescents, in whom the impact may be different from adults. Only one controlled experiment to date has compared the acute effects of cannabis in human adolescents under the age of 18 years with adults (39), which had the following limitations: (i) no female participants; (ii) the adolescents used cannabis more frequently than the adults; (iii) the modulatory impact of CBD was not studied; and (iv) no pharmacokinetic data was collected.

To address these limitations, we tested equal numbers of female and male participants, included a combined THC and CBD ('THC+CBD') condition as well as THC-only ('THC') and placebo ('PLA') conditions, carefully matched cannabis use frequency between the groups, and collected pharmacokinetic data. In the largest study of its kind, we aimed to replicate the adolescent vs. adult difference in acute effects of cannabis and to explore the modulatory impact of CBD co-administration in these age-groups.

First, we hypothesised that, across age-group, there would be a main effect of drug, such that (i) subjective 'feel drug effect', (ii) verbal episodic memory impairment, and (iii) psychotomimetic effects,

would be greater on 'THC' and 'THC+CBD' than placebo. Second, we hypothesised that CBD in 'THC+CBD' would reduce the (i) verbal episodic memory impairing, and (ii) psychotomimetic effects, relative to 'THC', but (iii) subjective 'feel drug effect' would be similar on 'THC' and 'THC+CBD'. Third, we hypothesised there would be an interaction between age-group and drug, such that the expected difference between the 'THC' and 'PLA' conditions on measures (i)-(iii) would be greater for adults than for adolescents.

METHODS

Study design and participants

The experiment was registered on ClinicalTrials.gov (NCT04851392) and the protocol was uploaded to the Open Science Framework (OSF) (44)

We conducted a randomised, double-blind, placebo-controlled, crossover experiment on the acute effects of cannabis in adolescents and adults. The experiment had a between-subjects factor of age-group (adolescent and adult) and a within-subjects factor of drug ('THC', 'THC+CBD', 'PLA').

This was a single-centre study conducted at University College London and Invicro (Hammersmith Hospital, UK). We recruited healthy participants from the community in London, UK. The study received full ethical approval from UCL Ethics Committee (project code: 5929/005). This study was registered on ClinicalTrials.gov (NCT04851392). All participants provided written, informed consent and provided verbal ongoing consent at the beginning of each study session.

We continued recruitment until we reached our target sample size of 48 completed participants, comprising 24 adolescents (50% female; aged 16-17 years) and 24 adults (50% female; aged 26-29 years). Participants who did not complete all sessions were replaced. Key inclusion criteria were: self-reported use of cannabis 0.5, 1, 2 or 3 days/week; healthy or overweight body mass index (BMI); and right-handed. Key exclusion criteria were: DSM-5 severe cannabis use disorder; currently receiving treatment for a mental health disorder; history of personal or familial psychosis; pregnant or breast-feeding; use of any illicit drug (apart from cannabis) more than two days per month; nicotine dependence as defined by a Heaviness of Smoking score >1 (45); currently taking a psychotropic medication that interacts with cannabis or directly affects outcome variables; magnetic resonance imaging (MRI) contraindications; and if an adult, cannabis use at a frequency \geq one day/week before turning 18 years old. For full eligibility criteria, see Table S1. Cannabis use frequency (days per week) was purposefully matched between the adolescents and adults.

Randomisation and Blinding

There were six drug orders. Each order was used with eight participants (one sixth of total sample), to ensure that drug order was balanced. Drug order was balanced within age-group and gender. Within these groups, participants were randomly allocated to drug order using a blocked randomisation sequence. All experimental researchers and participants were blinded to treatment allocation. At the end of each session, participants were asked to guess which drug they thought they had received that day.

Procedures

Participants were screened online and via telephone. Potentially eligible participants attended an in-person (pre-COVID) or virtual (post-COVID) baseline session. In-person eligibility criteria were confirmed at either the in-person baseline or first drug administration session.

Eligible participants then completed three drug administration sessions. At the start of each session, recent alcohol and illicit drug use were checked to ensure abstinence via an alcohol breathalyser, a saliva drugs test and self-report. Female participants completed a urine pregnancy test. Drug administration sessions lasted 5-6 hours in total. Participants completed assessments before and after cannabis inhalation (Table 1 and Figure S1). MRI data, other neurocognitive task data, and detailed pharmacokinetic and physiological data will be reported elsewhere, as these results are beyond the scope of this manuscript.

Dried medical cannabis flower was procured from Bedrocan (<https://bedrocan.com/>) in the Netherlands and imported under HVC's UK Home Office licence. Cannabis types used were 'Bedrocan' (20.2% THC; 0.1% CBD), 'Bedrolite' (0.4% THC; 8.5% CBD), and 'Bedrobinol Placebo'. Dose was weight-adjusted (39): the 'THC' condition contained 0.107mg/kg THC (8mg THC for a 75kg person); the 'THC+CBD' condition contained 0.107mg/kg THC and 0.320mg/kg CBD (8mg THC and 24mg CBD for a 75kg person); and the 'PLA' condition contained no THC or CBD and was matched in appearance and smell to the other conditions. This dose of THC corresponds to approximately one quarter of a typical 'joint' (46,47), or 1.6 standard THC units (48). The total weight of cannabis flower material was kept constant across the conditions through the addition of placebo cannabis. Cannabis was vaporised into a 'balloon' using a Volcano Medic Vaporiser (Storz and Bickel, Tuttlingen, Germany) and participants inhaled the contents of the balloon according to a standardised, timed procedure. The minimum washout period was three days (72 hours) between drug sessions (49); the elimination half-life of THC is 21.5 hours (50,51), giving adequate time for THC elimination.

Outcomes

The registered primary outcome variables were: (i) strength of the subjective drug effect, as measured by self-reported 'feel drug effect' (39) 20 minutes after the start of cannabis inhalation (i.e. almost immediately after inhalation completion) (T2); (ii) verbal episodic memory, as measured by delayed prose recall (52) two hours after the start of cannabis inhalation (T4); and (iii) psychotomimetic effect, as measured by the total Psychotomimetic States Inventory (PSI) score (53) two hours after the start of cannabis inhalation (T4).

The subjective 'feel drug effect' visual analogue scale (VAS) is a single-item scale rated from 0 ('not at all') to 10 ('extremely'). The prose recall task requires participants to listen to a 30-second story presented via headphones, immediately write down as much as they can remember, and then again write down as much as they can remember 100 minutes later. The PSI is a 48-item self-report questionnaire assessing psychotic-like symptoms.

Secondary variables were: (1) psychotomimetic effect, as measured by the Positive and Negative Syndrome Scale (PANSS) positive and negative subscales (54) three hours after the start of cannabis inhalation, when the participant is sober and reflects on their experiences; (2) psychotomimetic effect measured via PSI subscales, including delusory thinking, perceptual distortion, cognitive disorganisation, anhedonia, mania and paranoia, two hours after the start of drug inhalation (T4); (3) subjective effects of 'anxious', 'paranoid', 'want cannabis', 'feel drug effect', 'like drug effect', 'dislike drug effect' and 'happy' measured via 10-point visual analogue scales (VAS; 0 'not at all' to 10 'extremely') at five minutes pre-cannabis (T1), 20 minutes (T2), 30 minutes (T3), 120 minutes (T4), and 160 minutes (T5) after the start of cannabis inhalation; (4) THC and CBD plasma levels 20 minutes after the start of cannabis inhalation (T2); and (5) heart rate 20 minutes after the start of cannabis inhalation (T2). See supplementary materials for a detailed description of all measures.

Statistical Analyses

The study was powered to replicate our previous finding that adolescents experienced a weaker psychotomimetic effect of cannabis than adults (39). We found an effect size of Cohen's $f=0.33$ for the age-group (adolescent, adult) by drug (THC, placebo) interaction on total PSI score. To obtain 80% power in our current experiment to replicate this 2 by 2 interactive result, with $\alpha=0.05$, number of groups=2, number of repeated measures=2 ('THC' and 'PLA'), and a conservative repeated-measures correlation=0.2, 32 participants were required. We therefore recruited 48 participants to complete the study and account for winner's curse (+50%) (55). For other analyses, with our set $n=48$, three repeated measures, $\alpha = 0.05$, we had an estimated 80% power to detect a within-subjects main effect (drug) and a within-between interaction (age-group by drug) with effect sizes of Cohen's $f \geq 0.24$.

The analysis followed our OSF analysis plan (56)., which was published before data collection was completed and before data were unblinded. A per-protocol analysis was used; only participants who completed all three experimental sessions were included. Data were first pre-processed and assumptions were examined (see supplementary materials). For each of the three primary outcome variables, a 2x3 mixed ANOVA with a between-subjects factor of age-group (adolescent, adult) and a within-subjects factor of drug ('PLA', 'THC', 'THC+CBD') was conducted. The main effect of drug ('PLA' vs. 'THC' vs. 'THC+CBD') and the interaction between drug and age-group were first examined. Where significant main effects or interactions were detected (alpha cut-off of 0.05), these were explored with post-hoc pairwise Bonferroni-corrected t-tests which compared all conditions against one another. We corrected for multiple comparisons within each primary outcome variable, but not across all primary outcome variables. If a Greenhouse-Geisser correction was implemented, we report uncorrected degrees of freedom. Where data violated assumptions for parametric analyses, we proceeded with parametric tests, but non-parametric analyses were also conducted to support findings. We re-ran all primary analyses with drug-order included as a between-subjects covariate to test whether drug-order altered the pattern of results.

Post-hoc Bayesian t-tests were conducted to support null differences. Bayes factors (BF_{01})>3 were interpreted as evidence in favour of no difference. For primary outcome variables, differences between 'THC' and 'PLA' ('THC minus PLA') were calculated and underwent Bayesian independent t-tests to test for equivalence in response to cannabis in adolescents and adults. Across age-group, Bayesian paired t-tests were used to test for equivalence in 'THC+CBD' and 'THC' conditions. All analyses were conducted using SPSS (Version 25).

Secondary outcome variables were primarily analysed via two-way or three-way mixed ANOVAs similar to the ANOVAs described above. Three-way ANOVAs included a within-subject factor of time. For subjective effect VASs, time had levels: T1/T2 to T5, and separately area-under-the-curve and peak effects were analysed. For prose recall, time had levels: immediate and delayed. For THC and CBD plasma results at T2, mixed effects models were performed to account for 8 missing datapoints out of 144. Positive and negative PANSS scores were analysed using mixed ANOVAs and supported with generalised estimating equations (GEE) models and chi-square and McNemar's tests. See supplementary materials for full details.

RESULTS

Data collection started on 11th March 2019 and concluded on 16th June 2021 when 48 participants (n=24 adolescents, 50% female and n=24 adults, 50% female) had completed all three drug administration sessions, as planned (CONSORT diagram, Figure S3). Data collection was suspended from March 2020 until November 2020 due to the COVID-19 pandemic, after which the experiment resumed in a safe way according to government and local regulations.

After weight-adjustment by participants' actual weight, adolescents received a mean THC dose of 6.8mg (SD=0.9, range: 5.4-8.7mg), and adults received a mean THC dose of 7.4mg (SD=1.4, range: 5.4-10.7mg) on both 'THC' and 'THC+CBD' conditions. On 'THC+CBD' adolescents received a mean CBD dose of 20.3mg (SD=2.6, range: 16.3-26.1mg) and adults received a mean CBD dose of 22.2mg (SD=4.3, range: 16.3-32.2mg) of CBD. These differences were not statistically significant (THC: $t(46)=1.760$, $p=0.085$; CBD: $t(46)=1.762$, $p=0.085$).

For a summary of participant characteristics see Table 2 (for full details see Tables S4-S8). Adolescents had a mean age of 17.17 years (SD=0.43) and adults had a mean age of 27.77 years (SD=1.04). Cannabis use frequency was purposefully matched between adolescents (1.41 days/week, SD=0.77) and adults (1.45 days/week, SD=0.77). Adolescents and adults had similar SES, ethnicity, problematic alcohol consumption levels, cigarette/roll-up use, and other illicit drug use. However, adolescents had higher depression, anxiety, and impulsiveness scores and adults had higher verbal IQ, and alcohol use frequency.

Pre-drug administration (T1) minimal THC was detected in plasma. Across the three conditions, four participants had a plasma THC level >0.5 ng/ml; all other participants had plasma THC levels that were zero. The non-zero levels were all <1.25 ng/ml. Pre-drug administration, at T1, across the three conditions, all participants had a zero plasma CBD level (Table S17a).

Primary outcomes

For subjective 'feel drug effect' (at T2, 20 mins; Table S9; Figure 1a-b), a Greenhouse-Geisser correction was implemented. There was no significant interaction between drug and age-group ($F(2,92)=0.557$, $p=0.547$, $\eta^2_p=0.012$). There was a main effect of both drug ($F(2,92)=262.214$, $p<0.001$, $\eta^2_p=0.851$) and age-group ($F(1,46)=8.190$, $p=0.006$, $\eta^2_p=0.151$). 'THC' led to greater ratings than 'PLA' ($MD=6.292$, 95% CI 5.343–7.240, $t(47)=16.480$, $p<0.001$) and 'THC+CBD' led to greater ratings than 'PLA' ($MD=6.813$, 95% CI 5.964–7.661, $t(47)=19.957$, $p<0.001$); there was no significant difference between 'THC' and 'THC+CBD' ($MD=0.521$, 95% CI -0.121–1.163, $t(47)=2.017$, $p=0.149$). Overall, across the three drug conditions (including 'PLA'), adults had larger 'feel drug effect' ratings than adolescents ($MD=0.847$, 95% CI 0.251–1.443, $t(46)=2.862$, $p=0.006$). However, null age-group differences in the 'THC minus PLA' value were supported by Bayesian analysis ($BF_{01}=3.591$), providing evidence that adolescents and adults responded similarly. When comparing 'THC' and 'THC+CBD', Bayesian results were inconclusive ($BF_{01}=1.328$), thus there was no evidence that CBD moderated THC's effects in either direction. These results did not significantly change when controlling for drug-order, or when removing participants with outlying subjective or plasma data.

For prose recall delayed scores (Table S9, Figure 1c-d), there was no significant interaction between drug and age-group ($F(2,92)=0.727$, $p=0.486$, $\eta^2_p=0.016$). There was a main effect of drug ($F(2,92)=20.616$, $p<0.001$, $\eta^2_p=0.309$), but not of age-group ($F(1,46)=0.073$, $p=0.789$, $\eta^2_p=0.002$). 'THC' led to lower (delayed) prose recall scores than 'PLA' ($MD=-2.740$, 95% CI -4.059– -1.420, $t(47)=5.158$, $p<0.001$). 'THC+CBD' also led to lower scores than 'PLA' ($MD=-2.896$, 95% CI -4.130– -1.662, $t(47)=5.830$, $p<0.001$). Furthermore, there was no significant difference between scores during 'THC' and 'THC+CBD' ($MD=0.156$, 95% CI -1.069–1.381, $t(47)=0.317$, $p=1.00$). Null age-group differences in 'THC minus PLA' were supported by Bayesian analysis ($BF_{01}=3.192$), providing evidence that adolescents and adults responded similarly. Additionally, Bayesian analysis provided evidence that CBD did not impact THC effects on prose recall ($BF_{01}=8.423$). These results did not significantly change when controlling for drug-order, or when removing participants with outlying subjective or plasma data.

For psychotomimetic effects (PSI total score; Table S9, Figure 1e-f), there was no significant interaction between drug and age-group ($F(2,92)=0.932$, $p=0.398$, $\eta^2_p=0.020$). There was a main effect of drug ($F(2,92)=18.796$, $p<0.001$, $\eta^2_p=0.290$), but not of age-group ($F(1,46)=1.582$, $p=0.215$, $\eta^2_p=0.033$). Across age-group, 'THC' led to greater PSI ratings than 'PLA' ($MD=7.771$, 95% CI 2.844–12.698, $t(47)=3.919$, $p=0.001$) and 'THC+CBD' led to greater ratings than 'PLA' ($MD=10.792$, 95% CI 6.172–15.411, $t(47)=5.805$, $p<0.001$); there was no significant difference between 'THC' and 'THC+CBD'

(MD=-3.021, 95% CI -6.954–0.912, $t(47)=1.908$, $p=0.188$). Null age-group differences for PSI ratings in ‘THC minus PLA’ were supported by Bayesian analysis ($BF_{01}=4.385$), providing evidence that adolescents and adults responded similarly. When comparing ‘THC’ and ‘THC+CBD’, Bayesian results were inconclusive ($BF_{01}=1.589$), thus there was no evidence that CBD moderated THC’s effects in either direction. These results did not significantly change when controlling for drug-order, or when removing participants with outlying subjective or plasma results.

Secondary outcomes

Across secondary outcomes, the results generally followed a similar pattern (see Table 3 for summary) such that there were typically no drug by age-group interactions and there were main effects of drug. Post-hoc pairwise drug comparisons generally showed significant differences between ‘PLA’ compared with ‘THC’ and ‘THC+CBD’, and occasionally differences between outcomes during ‘THC’ and ‘THC+CBD’.

Exceptions to this pattern included the following results. There were drug by age-group interactions for ‘happy’ (across T1-T5; Figure S5g-i) and CBD plasma levels (T2; Figure S7 & Table S17b). There were significant differences between active drug conditions (‘THC+CBD’ > ‘THC’) for: ‘feel drug effect’ (across T2-T5; Figure S4a-c), PSI subscale cognitive disorganisation (Table S14), heart rate (Figure S7e-f), and THC and CBD plasma levels (at T2) (Figure S7a-d; Table S17b). Notably, T2 plasma THC levels were greater on ‘THC’ (14.88ng/ml, SD=7.15) than ‘THC+CBD’ (27.86ng/ml, SD=14.20) ($t(90.514)=7.760$, $p<0.001$).

For subjective effects over time, there were no drug by age-group by time interactions for any secondary outcome (Tables S10-11). For peak subjective effects and are-under-the-curve data, there were no drug by age-group interactions and the pattern of results was mainly consistent with the previous analyses. Detailed results for all secondary outcomes are presented in the supplementary materials.

DISCUSSION

We carried out the first controlled experiment testing the acute effects of vaporised cannabis with and without cannabidiol in both adolescents and adults. On our three primary outcomes, subjective 'feel drug effect', verbal episodic memory, and psychotomimetic effect, we found no evidence that age-group moderated the impact of cannabis. Furthermore, Bayesian analyses supported these null results. Additionally, we found no evidence that vaporised CBD (24mg for a 75kg person) modulated the acute impact of vaporised THC (8mg for a 75kg person) on our primary outcome variables. Our results were supported by analysis of our secondary outcome variables, which showed, almost unanimously, that there were null moderating effects of age-group and CBD. The mostly consistent pattern of results was: (1) 'THC' and 'THC+CBD' produced expected changes from 'PLA'; (2) 'THC' and 'THC+CBD' did not differ from one another; and (3) the impact of cannabis did not differ in adolescents and adults.

Based on Mokrysz et al (2016), we hypothesised that adolescents would be more resilient to the acute effects of cannabis than adults (57). We did not find evidence for this; indeed, our Bayesian analyses supported equivalence of the impact of cannabis on adolescents and adults in all three of our primary outcome variables. This partially supports Murray et al. (2022), which reported no differences in the impact of oral THC (fixed 7.5mg and 15mg doses) on 18-20 year-olds and 30-40 year-olds on all subjective effects recorded, cardiovascular measures, working memory, and response inhibition (58). In comparison to Mokrysz et al. (2016), in which adolescents used cannabis significantly more frequently (median 2.4 days/week) than adults (median 1.8 days/week), our adolescent and adult participants were matched on cannabis use frequency. The discrepancy in our findings may have been partially due to the greater frequency of cannabis use in the adolescent group in the previous experiment, thus contributing to a higher tolerance to THC's effects (59). Furthermore, in the experiment conducted by Mokrysz et al. (2016), adolescents weighed significantly less and received an absolutely lower dose of THC than adults.

On our primary outcome variables, CBD did not moderate the acute effects of THC. This is in line with previous controlled cannabis vaporisation experiments (37,38,60). Significant modulation of THC's acute effects may require pre-dosing with larger oral (36) or intravenous (35) CBD. Additionally, stronger THC-induced psychotomimetic effects may be necessary before the protective effect of CBD is observed (61).

However, there were some notable exceptions to the primarily null findings. Firstly, there was some limited evidence that 'THC+CBD' produced stronger effects than 'THC': 'feel drug effect' was half a point greater on 'THC+CBD' compared to 'THC', when collapsing across all timepoints, and this was

supported by an area-under-the-curve difference too; the PSI cognitive disorganisation subscale was greater by approximately 2 points on 'THC+CBD' compared to 'THC'; and heart rate was greater on 'THC+CBD' than 'THC' by 8 beats/min. To contextualise these differences, the 'THC' vs. 'PLA' conditions gave differences of 4.5 points, 4 points, and 18 beats/min, respectively. Notably, these were secondary outcome variables. They should also be considered against a backdrop of null CBD moderation effects on 'like drug', 'dislike drug', 'paranoid', 'want cannabis', all other PSI subscales, prose recall performance, and both positive and negative PANSS scores. The supplementary analyses of area-under-the-curve and peak subjective effects (supplementary materials 3.5.2) confirmed there was no significant moderation by CBD, apart from on 'feel drug effect'. On the whole, CBD did not appear to moderate THC's acute effects.

Mean THC plasma concentrations at T2 for 'THC' (15ng/ml) and 'THC+CBD' (28ng/ml) conditions (Table S17b) are in line with some previous THC vaporisation studies (62,63) but slightly lower than other studies (64,65). Mean plasma CBD concentration at T2 for the 'THC+CBD' condition was 55ng/ml, with zero or trace levels in the 'THC' condition. Some (63,65,66), but not all (67,68), previous research has reported that CBD co-administration enhances THC plasma levels. It is unclear why THC levels were greater under the 'THC+CBD' condition relative to the 'THC' condition. A pharmacokinetic explanation, whereby CBD augments THC levels by inhibiting the metabolism of THC (69), is possible. However, another possible explanation is the difference in inhalation time. Participants took significantly longer to inhale the 'THC+CBD' vapour and coughed significantly more during 'THC+CBD' compared with 'THC'. Our supplementary analysis (Table S21) demonstrated that those who took longer to complete the second balloon had higher plasma THC levels at T2, thus partially explaining the impact of CBD on plasma THC levels. Future, detailed analyses of our pharmacokinetic data may shed light on this, but this is beyond the scope of the current manuscript. Despite the greater plasma THC levels in the 'THC+CBD' condition, we did not observe stronger effects on our primary outcome variables. Speculatively, this could be because CBD pharmacokinetically increases THC levels but partially pharmacodynamically blocks THC's effects. Alternatively, there may not be a simple linear relationship between plasma THC levels and subjective, psychological effects (70–72). Additional research into the pharmacokinetics of co-administered THC and CBD is required.

We also detected an age-group by drug interaction for CBD plasma level, in which adults had greater CBD levels than adolescents ($p < 0.001$, mean difference = 21ng/ml). Adults weighed slightly more than the adolescents, and therefore received more CBD (20mg vs. 22mg), though that difference was not statistically significant. The two age-groups took similar times to inhale the balloons. The variance in CBD plasma levels was much greater in adults than adolescents, with many adults surpassing 100ng/ml, but no adolescents surpassing 80ng/ml. The reason for this difference is unknown. This age-

difference in CBD absorption appears not to have meaningfully altered our psychological outcomes. We only found one significant drug by age-group interaction, on 'happy'. This unhypothesised interaction was driven by adults being slightly happier on placebo than active drug, whilst adolescents were slightly happier on active drugs than on placebo.

Our study has numerous strengths. In addition to its novelty, we biochemically verified drug abstinence; we improved on previous work by matching adolescent and adult users on cannabis use; including equal numbers of men and women; and we powered our study to detect an age-group by drug interaction and took account of winner's curse (73). One limitation is the absence of a CBD-only condition. A further limitation is that our results may not generalise beyond adolescents aged 16-17 years and adults aged 26-29 years, who use cannabis 0.5-3 days/week. It is possible that younger adolescents or older adults could respond differently to the administration of cannabis. Moreover, it is possible that some age differences may be apparent in less frequent (40) or more frequent cannabis users.

Our findings have important scientific, policy, and educational implications. Firstly, they cast doubt on the claim that adolescent cannabis users are more vulnerable to some short-term effects of cannabis than adult cannabis users. Secondly, our results add further weight to the claim that doses of vaporised CBD, which are near to naturally occurring levels, mitigate against the acute harms of THC (37,63). Harm reduction messages should avoid stating that CBD found in recreational cannabis protects against the acute psychotomimetic or memory-impairing effects of cannabis.

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Author contribution

WL - conceptualisation, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualisation, writing - original draft, and writing - review and editing; KT - data curation, formal analysis, investigation, project administration, validation, visualisation, writing - original draft, and writing - review and editing; CM - conceptualisation, data curation, investigation, funding acquisition, methodology, project administration, supervision, and writing - review and editing; AB - conceptualisation, formal analysis, investigation, methodology, project administration, supervision, and writing - review and editing; SO - investigation, project administration, writing - original draft, and writing - review and editing; KP - investigation, project administration, methodology, writing - original draft, and writing - review and editing; MB - conceptualisation, supervision, and writing - review and editing; ZRH - investigation, project administration, writing - original draft, and writing - review and editing; DH - investigation, project administration, writing - original draft, and writing - review and editing; NFV - investigation, project administration, writing - original draft, and writing - review and editing; SW - project administration, writing - original draft, and writing - review and editing; AE - conceptualisation, methodology, and writing - review and editing; EC - conceptualisation, methodology, and writing - review and editing; MW - conceptualisation, formal analysis, investigation, methodology, project administration, supervision, and writing - review and editing; TF - conceptualisation, funding acquisition, investigation, methodology, project administration, supervision, validation, visualisation, writing - original draft, and writing - review and editing; HVC - conceptualisation, funding acquisition, investigation, methodology, project administration, supervision, validation, visualisation, writing - original draft, and writing - review and editing

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Table 1. Schedule of experiment events for drug administration sessions to the nearest five minutes, relative to the start of drug administration (T-inh).

Time (min)	Timepoint	Event
-70		In-person eligibility checks: alcohol breathalyser, saliva drugs test, pregnancy test, recent drug use, TLFB, physical checks, BMI
-40		Cannulation, radiographer checks
-5	T1	Blood sample, BP/HR, VAS
0	T-inh	Drug administration
+20	T2	Blood sample, BP/HR, VAS
+25		Prose Recall (immediate)
+30	T3	Blood sample, BP/HR, VAS
+45		MRI scan
+120	T4	BP/HR, subjective effects
+125		Prose Recall (delayed)
+125		Psychotomimetic States Inventory
+140		Neurocognitive Tasks
+160	T5	Blood sample, BP/HR, VAS
+180		PANSS Interview
+210		Drug guess, subjective ratings, sobriety tests, discharge

TLFB = Timeline Follow-back, BMI= body mass index, HR=heart rate, BP=blood pressure, VAS= visual analogue scale, PSI= psychotomimetic states inventory, MRI = magnetic resonance imaging, PANSS= Positive and Negative Syndrome Scale. T-inh = The time that drug inhalation started. Note – MRI data, neurocognitive task data, and pharmacokinetic and physiological data at T3, T4 and T5 will be reported elsewhere.

Table 2. Summary of participants' baseline sociodemographic characteristics and drug use.

		Adolescents (n=24)	Adults (n=24)	Both (n=48)
Gender	Female	12 (50.0%)	12 (50.0%)	24 (50.0%)
	Male	12 (50.0%)	12 (50.0%)	24 (50.0%)
Age (years)*		17.17 (0.43) [16.50-17.92]	27.77 (1.04) [26.33-29.58]	22.47 (5.41) [16.50-29.58]
BMI (kg/m²)		21.89 (2.81) [17.36-26.67]	23.18 (2.73) [19.40-27.80]	22.53 (2.82) [17.36-27.80]
Ethnicity	White	17 (70.8%)	18 (75.0%)	35 (72.9%)
	Mixed	4 (16.7%)	1 (4.2%)	5 (10.4%)
	Asian	1 (4.2%)	3 (12.5%)	4 (8.3%)
	Black	0 (0.0%)	2 (8.3%)	2 (4.2%)
	Other	1 (4.2%)	0 (0.0%)	1 (2.1%)
	Prefer not to say	1 (4.2%)	0 (0.0%)	1 (2.1%)
SES	Mother's education below undergraduate degree	8 (33.3%)	8 (33.3%)	16 (33.3%)
	Mother's education undergraduate degree or above	16 (66.7%)	16 (66.7%)	32 (66.7%)
BDI*		10.38 (8.55) [0.00-28.00]	5.29 (6.45) [0.00-22.00]	7.83 (7.92) [0.00-28.00]
s-UPPS-P*		48.17 (7.51) [34.00-61.00]	42.75 (8.87) [30.00-64.00]	45.46 (8.58) [30.00-64.00]
CUDIT-R*		10.17 (3.14) [5.00-16.00]	7.21 (3.31) [3.00-15.00]	8.69 (3.53) [3.00-16.00]
AUDIT*		5.88 (5.39) [0.00-21.00]	7.71 (4.59) [1.00-18.00]	6.79 (5.04) [0.00-21.00]
Cannabis use frequency (days/week) measured at baseline		1.41 (0.77) [0.25-3.50]	1.45 (0.77) [0.25-2.75]	1.43 (0.76) [0.25-3.50]
Cannabis use frequency (days/week) measured at screening	0.5	4 (16.7%)	4 (16.7%)	8 (16.7%)
	1	7 (29.2%)	5 (20.8%)	12 (25.0%)
	2	8 (33.3%)	7 (29.2%)	15 (31.3%)
	3	5 (20.8%)	8 (33.3%)	13 (27.1%)
Estimated amount of cannabis used on day of use (grams)		0.81 (0.56) [0.25-2.50]	0.50 (0.52) [0.10-2.00] {n=23}	0.66 (0.55) [0.10-2.50] {n=47}
Age of first cannabis use (years)*		14.55 (1.03) [11.92-16.08]	18.17 (2.62) [14.00-24.42]	16.36 (2.69) [11.92-24.42]
Lifetime days of cannabis use*		153.67 (89.97) [11.00-418.00]	544.29 (630.94) [136.00-3120.00]	349.13 (487.63) [11.00-3127.00]
Weekly alcohol use*	No	19 (79.2%)	6 (25.0%)	25 (52.1%)
	Yes	5 (20.8%)	18 (75.0%)	23 (47.9%)
Weekly cigarette roll-up use	No	15 (62.5%)	19 (79.2%)	34 (70.8%)
	Yes	9 (37.5%)	5 (20.8%)	14 (29.2%)
Monthly use of any other illicit drug	No	22 (91.7%)	22 (91.7%)	44 (91.7%)
	Yes	2 (8.3%)	2 (8.3%)	4 (8.3%)

For continuous data, mean (SD) [minimum-maximum] is shown, for categorical data, n (%) is shown. SES=socioeconomic status, AUDIT=Alcohol use disorders identification test, BDI=Beck depression inventory, CUDIT-R=Cannabis use disorder identification test-revised, s-UPPS-P= Short Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency. * $p < 0.05$.

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Table 3. Summary of key results for primary and secondary outcome variables. Significant results ($p < .05$) are denoted 'Y' and non-significant results are denoted '-'.

Outcome	Drug*Age-group Interaction	Main effect of Drug	'THC' > 'PLA'	'THC+CBD' > 'THC'
Primary				
Feel drug effect (T2)	-	Y	Y	-
Prose recall delayed	-	Y	Y	-
PSI total	-	Y	Y	-
Secondary				
Subjective measures (VAS)				
Feel Drug Effect (T2-T5)	-	Y	Y	Y
Like Drug Effect (T2-T5)	-	Y	Y	-
Dislike Drug Effect (T2-T5)	-	-	-	-
Anxious (T1-T5)	-	Y	Y	-
Paranoid (T1-T5)	-	Y	Y	-
Want cannabis (T1-T5)	-	-	-	-
Happy (T1-T5)	Y*	-	-	-
Prose Recall				
Prose Recall immediate	-	Y	Y	-
PSI Subscales				
Delusory thinking	-	-	-	-
Perceptual distortion	-	Y	Y	-
Cognitive disorganisation	-	Y	Y	Y
Anhedonia	-	-	-	-
Mania	-	Y	-	-
Paranoia	-	Y	-	-
PANSS Subscales				
PANSS Positive	-	Y	Y	-
PANSS Negative	-	Y	Y	-
Plasma and heart rate				
THC plasma concentration (T2)	-	Y	Y	Y
CBD plasma concentration (T2)	Y ^o	Y	-	Y
Heart Rate (T2)	-	Y	Y	Y

*For 'Happy', adults had higher ratings than adolescents on 'PLA' but similar ratings on 'THC' and 'THC+CBD'. Moreover, within adolescents, ratings during 'THC' and 'THC+CBD' were higher than 'PLA', but within adults ratings during 'THC' and 'THC+CBD' were lower than during 'PLA'. ^oFor CBD plasma levels, this interaction was driven by higher CBD levels on 'THC+CBD' in adults compared to adolescents, but similar levels in adults and adolescents during 'PLA' or 'THC'. PSI=psychotomimetic states inventory; PANSS=Positive and Negative Syndrome Scale; VAS=visual analogue scale.

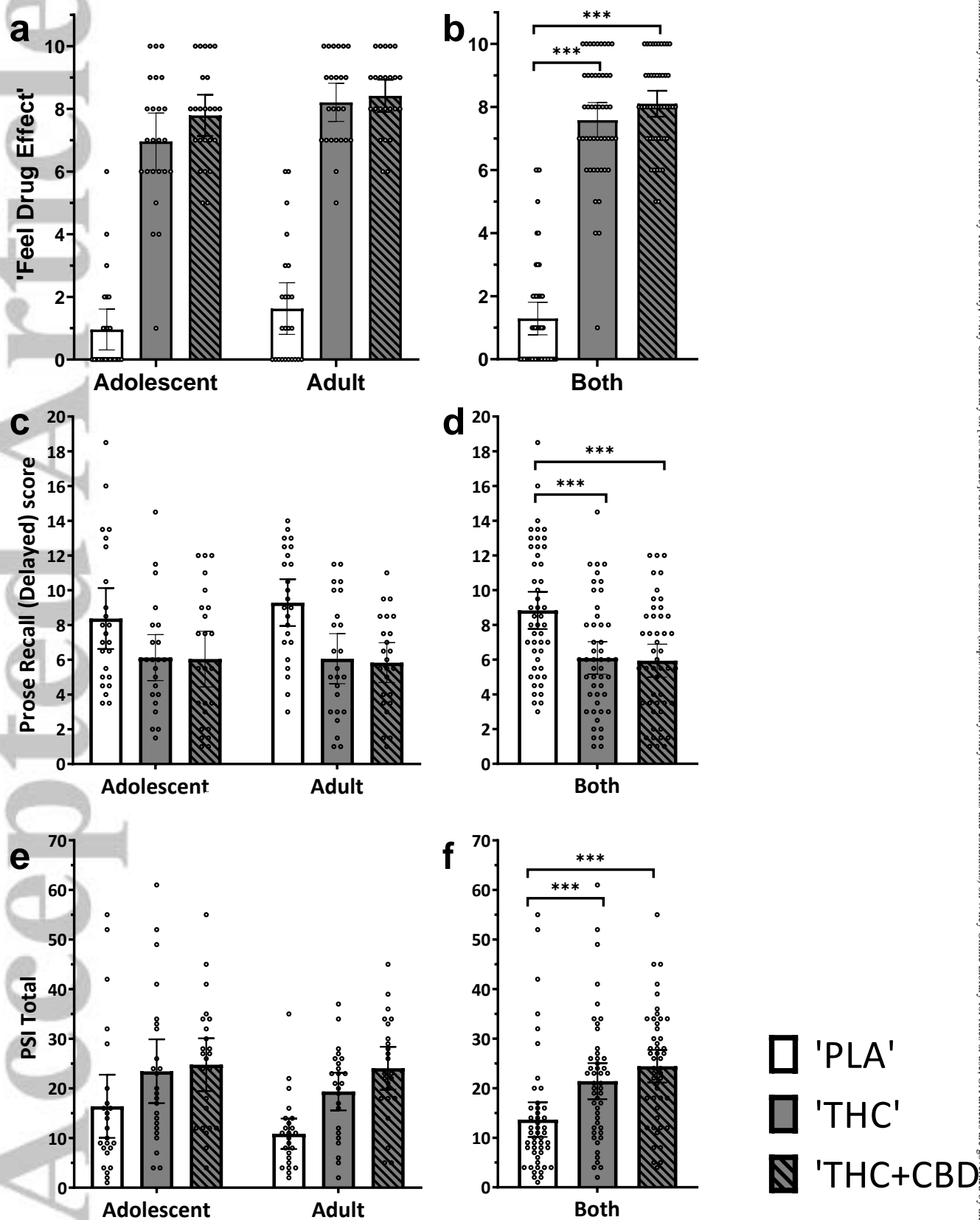


Figure 1. Mean values with data points overlaid and 95% confidence intervals displayed for primary outcomes. a) VAS 'feel drug effect' at T2, c) prose recall score (delayed) at T4 and e) PSI total at T4, for adolescents (n=24) and adults (n=24) during 'THC', 'THC+CBD' and 'PLA' conditions. Main effect of drug across age-groups displayed in b, d, and f where their data is combined (n=48). **p<0.01, ***p<0.001. VAS=visual analogue scale, PSI=psychotomimetic states inventory.