Supplementary materials

Table 1 Inclusion Criteria across the Four Studies

Inclusion Criteria across the Four Studies Stratified by Participant Group.

	Hindocha, Freeman, et al. (2015)				Hindocha et al. (2017)	Lawn et al. (2016)	Mokrysz et al. (2016)	
	SPQ low		SPQ high					
	Days per month of cannabis use						Age	
	>25	**Daily**	**>25**	**Daily**			**<18**	**Adult**
Age	16-23	16-23	16-23	16-23	18-60	18-70	16-17	24-25
Male Gender							✓	✓
Have smoked cannabis before	✓	✓	✓	✓	✓	✓	✓	✓
Have smoked cannabis with tobacco				-	✓			
More than 4 times in the last year	-	-	-	-	✓	✓	✓	✓
Currently smokes cannabis 3 times or less a week	-	-	-	-	✓	✓	✓	✓
Can smoke a whole joint by self	-	-	-	-	✓	-	-	-
Smoked cannabis in the last six months	✓	✓	✓	✓	✓	-	✓	✓
Currently smokes cannabis at least once a month	✓	✓	✓	✓	✓	-	-	-
Fluent in English	✓	✓	✓	✓	✓	✓	✓	✓
Regular user ≥ 6 months	-	-	-	-	✓	-	✓	✓
Dependant on nicotine	-	-	-	-	✓	-	-	-
Used tobacco in joints for the last six months	-	-	-	-	✓	-	-	-
Healthy BMI	-	-	-	-	-	-	✓	✓
Normal range heart rate	-	-	-	-	-	-	✓	✓
Abstain from all tobacco and drugs 12hr before testing					✓			
Abstain from all illicit drugs and alcohol 24hr before testing	✓	✓	✓	✓	-	✓	✓	✓
Normal corrected vision	✓	✓	✓	✓	✓	✓	-	-
Cannabis Severity of Dependence Scale score 3 or less	-	-	-	-	✓	-	✓	✓

Notes. ✓ = assessed at screening; - = not assessed; SPQ = Schizotypal Personality Questionnaire; BMI = Body Mass Index. Where the study recruited a specific group of participants this is illustrated: Adult, <18 = Adolescents, >25 = recreational smoker of 1–24 cannabis days per month; Daily = daily cannabis use including 25 or more days per month of cannabis use.

Table 2 Exclusion Criteria across the Four Studies

Exclusion Criteria across the Four Studies Stratified by Participant Group.

	Hindocha, Freeman, et al. (2015)				Hindocha et al. (2017)	Lawn et al. (2016)	Mokrysz et al. (2016)	
	SPQ low		SPQ high					
	Days per month of cannabis use						Age	
	>25	**Daily**	**>25**	**Daily**			**<18**	**Adult**
Regular unpleasant reaction to cannabis	-	-	-	-	✓	✓	✓	✓
Use other illicit drugs > once a week	✓	✓	✓	✓	✓	-		
Use other illicit drugs > twice per month	-	-	-	-		✓	✓	✓
Alcohol use ≥ 5 times a week	-	-	-	-	✓	✓	✓	✓
Trying to stop using cannabis	-	-	-	-	✓	-	-	-
Medical issues:	✓	✓	✓	✓	✓	✓	✓	✓
Heart Problems	✓	✓	✓	✓	✓	✓	✓	✓
High Blood Pressure	✓	✓	✓	✓	✓	✓	✓	✓
Asthma	✓	✓	✓	✓	✓	-	-	-
High Cholesterol	-	-	-	-	-	-	✓	✓
Colour blindness	✓	✓	✓	✓	-	✓	✓	✓
Current psychiatric medication/ Psychological therapy	✓	✓	✓	✓	✓	✓	✓	✓
Current mental health problem	✓	✓	✓	✓	-	-	✓	✓
Current or historical diagnosis of psychosis	✓	✓	✓	✓	✓	✓	✓	✓
Immediate Family history of psychosis	-	-	-	-	✓	✓	✓	✓
Pregnant or breastfeeding	✓	✓	✓	✓	✓	✓		
Learning impairments	✓	✓	✓	✓	✓	-	-	-
Diagnosis of substance abuse	✓	✓	✓	✓	✓	-	✓	✓
Smokes cannabis > 4 times a week	-	-	-	-	✓	✓	✓	✓
Ever regularly used cannabis ≥ 6 days per week	-	-	-	-	-	-	✓	✓
MRI contraindications	-	-	-	-	-	✓	-	-
Score ≥ 3 SDS	-	-	-	-	✓	-	✓	✓
Score ≥ 4 SDS	-	-	-	-	✓	-		
Score ≥ 4 FTND	-	-	-	-	✓	-	-	-
First cigarette within 3 hours of waking	-	-	-	-	✓	-	-	-

Notes. ✓ = assessed at screening; - = not assessed; SPQ = Schizotypal Personality Questionnaire; BMI = Body Mass Index. Where the study recruited a specific group of participants this is illustrated: Adult, <18 = Adolescents, >25 = recreational smoker of 1–24 cannabis days per month; Daily = daily cannabis use including 25 or more days per month of cannabis use. SDS = Cannabis Severity of Dependence Scale, FTND= Fagerstrom Test of Nicotine Dependence.

Table 3 The Effect and Mean Difference for Anxiety Ratings across Four Studies

The Effect and Mean Difference on Pre- and Post- Drug Administration Anxiety Ratings for Placebo and THC conditions across Four Studies

	Placebo				THC			
			95% Confidence Interval for Difference				95% Confidence Interval for Difference	
	d	MD	Lower Bound	Upper Bound	*d*	MD	Lower Bound	Upper Bound
Hindocha, Freeman, et al. (2015)	0.076	0.145	- 0.185	0.475	0.007	0.024	- 0.589	0.637
Hindocha et al. (2017)	0.063	- 0.167	- 0.623	0.290	0.042	0.208	- 0.640	1.057
Lawn et al. (2016)	0.252**	- 0.813	-1.371	-0.254	0.010	0.063	- 0.977	1.102
Mokrysz et al. (2016)	0.368***	-0.750	-1.103	-0.397	0.191*	0.725	0.068	1.382
Combined	0.244**	- 0.310	-0.530	-0.110	0.128	0.306	- 0.083	0.656

Notes. Bonferroni corrected pairwise comparisons across Hindocha, Freeman, et al. (2015) n = 46 Hindocha et al. (2017) n = 24, Lawn et al. (2016) n = 16, Mokrysz et al. (2016) n = 40, for the interaction drug x time x study and the combined sample n = 128 *d* = Cohen's d; MD = mean difference. Negative scores indicate reduced anxiety following drug administration.
*p < .050, **p < .010, ***p < .001

Table 4 The Effect and Mean Difference for Alert Ratings across Four Studies

The Effect and Mean Difference on Pre- and Post-Drug Administration Alert Ratings for Placebo and THC conditions across Four Studies

	Placebo				THC			
			95% Confidence Interval for Difference				95% Confidence Interval for Difference	
	d	MD	Lower Bound	Upper Bound	*d*	MD	Lower Bound	Upper Bound
Hindocha, Freeman, et al. (2015)	0.204*	-0.386	0.058	0.715	0.188*	0.580	-1.114	-0.045
Hindocha et al. (2017)	0.048	-0.125	-0.579	0.329	0.390***	-1.667	.926	2.407
Lawn et al. (2016)	0.292**	-0.938	-1.494	-0.381	0.501***	-2.625	-3.532	-1.718
Mokrysz et al. (2016)	0.209*	-0.425	-0.777	-0.073	0.605***	-2.000	-2.573	-1.427
Combined	0.344***	-0.664	-0.214	-0.219	0.602***	1.538	-1.984	-1.092

Notes. Bonferroni corrected pairwise comparisons across Hindocha, Freeman, et al. (2015) n = 46, Hindocha et al. (2017) n = 24, Lawn et al. (2016) n = 16, Mokrysz et al. (2016) n = 40, for the interaction drug x time x study and the combined sample n = 128. *d* = Cohen's d; MD = mean difference. Negative scores indicate reduced alertness following drug administration.
*p < .050, **p < .010, ***p < .001

Table 5 The Effect and Mean Difference for Stoned Ratings in Four Studies.

The Effect and Mean Difference on Pre- and Post- Drug Administration Stoned Ratings for Placebo and THC conditions across Four Studies

			95% Confidence Interval for Difference	
	d	MD	Lower Bound	Upper Bound
Hindocha, Freeman, et al. (2015)	0.304***	1.389	0.597	2.181
Hindocha et al. (2017)	0.593***	3.833	2.713	4.954
Lawn et al. (2016)	0.497***	3.937	2.565	5.310
Mokrysz et al. (2016)	1.013***	5.075	4.207	5.943
Combined	1.089***	3.318	2.785	3.850

Notes. Bonferroni corrected pairwise comparisons across Hindocha, Freeman, et al. (2015) n = 46, Lawn et al. (2016) n = 16, Hindocha et al. (2017) n = 24, Mokrysz et al. (2016) n = 40 for the interaction drug x study and the combined sample n = 128. *d* = Cohen's d; MD = mean difference. ***$p < .001$

Table 6 The Effect and Mean Difference for Wanting More Cannabis Ratings across Four Studies

The Effect and Mean Difference on Pre- and Post- Drug Administration Wanting More Cannabis Ratings for Placebo and THC conditions across Four Studies

	Placebo				THC			
			95% Confidence Interval for Difference				95% Confidence Interval for Difference	
	d	MD	Lower Bound	Upper Bound	*d*	MD	Lower Bound	Upper Bound
Hindocha, Freeman, et al. (2015)	0.121	-0.386	-0.937	0.164	0.108	-0.575	-1.500	0.350
Hindocha et al. (2017)	0.104	-0.458	-1.221	0.304	0.102	-0.507	-1.370	0.356
Lawn et al. (2016)	0.232*	-1.250	0.316	2.184	0.036	-0.250*	-1.444	0.944
Mokrysz et al. (2016)	0.132	-0.450	-1.041	0.141	0.192	-1.625	-3.088	-0.162
Combined	0.108	0.217	-0.136	0.571	0.094	-0.266	-0.762	0.230

*Note*s. Bonferroni corrected pairwise comparisons across Hindocha, Freeman, et al. (2015) n = 46 Hindocha et al. (2017) n = 24, Lawn et al. (2016) n = 16, Mokrysz et al. (2016) n = 40 for the interaction drug x time x study, and the combined sample n = 128. *d* = Cohen's d; MD = mean difference. Negative scores indicate reduced wanting more cannabis following drug administration. *$p < .050$

Table 7 The Effect and Mean Difference for the Prose Recall Scores

The Effect of Drug Condition (Placebo versus THC) on Immediate and Delayed Prose Recall across Four Studies.

	Immediate				Delayed			
			95% Confidence Interval for Difference				95% Confidence Interval for Difference	
	d	MD	Lower Bound	Upper Bound	*d*	MD	Lower Bound	Upper Bound
Hindocha, Freeman, et al. (2015)	0.240*	-1.396	-2.405	-0.387	0.196*	1.188	-2.239	-0.387
Hindocha et al. 2017	0.397***	-3.271	-4.698	-1.844	0.410***	3.521	-5.008	-1.844
Lawn et al. 2016	0.285**	-2.875	-4.623	-1.127	0.297**	3.125	-4.946	-1.127
Mokrysz et al. 2016	0.360***	-2.300	-3.406	-1.194	0.357***	2.375	-3.527	-1.194
Combined	0.651***	-2.215	-2.810	-1.620	0.643***	-2.219	-2.822	-1.616

Notes. Bonferroni corrected pairwise comparisons across Hindocha, Freeman, et al. (2015) n = 46, Hindocha et al. (2017) n = 24, Lawn et al. (2016) n = 16, Mokrysz et al. (2016) n = 40, for the drug x study interaction, and the combined sample n = 128. *d* = Cohen's d; MD = mean difference.
*p < .05, **p < .01, ***p < .001

Table 8 The Effect and Mean Difference for PSI Score across Four Studies

The Effect of Drug Condition (Placebo versus THC) on Psychotomimetic States Inventory Score across Four Studies.

			95% Confidence Interval or Difference	
Study	*d*	MD	Lower Bound	Upper Bound
Hindocha, Freeman, et al. (2015)	0.147	3.962	-0.697	8.621
Hindocha et al. (2017)	0.520***	19.792	13.203	26.380
Lawn et al. (2016)	0.313***	14.578	6.509	22.647
Mokrysz et al. (2016)	0.658***	19.371	14.268	24.475
Combined	0.764***	13.100	10.100	16.101

Notes. Bonferroni corrected pairwise comparisons across Hindocha, Freeman, et al. (2015) n = 46, Hindocha et al. (2017) n = 24, Lawn et al. (2016) n = 16, Mokrysz et al. (2016) n = 40, and the combined sample n = 128. PSI = Psychotomimetic States Inventory; *d* = Cohen's d; MD = mean difference.

***$p < .001$

Anxiety ratings: There was a significant interaction between drug x time x cannabis use frequency ($F_{317.854} = 5.217$, $p = .023$), and a significant drug x time interaction ($F_{317.046} = 11.298$, $p = .001$). There was also a main effect of drug ($F_{317.046} = 6.489$, $p = .011$) but no main effect of time or cannabis use frequency and no drug x cannabis use frequency interaction, or drug x cannabis use frequency interaction. This model showed significant variance in intercepts across studies and participants ($Var_{u0j} = 1.376$, $\chi^2 = 6.336$, $p < .001$). Bonferroni corrected, pairwise comparisons showed that anxiety ratings significantly reduced from pre- drug to post-drug in the placebo condition (MD: -0.310, $p = .007$). There was a non-significant increase in anxiety ratings from pre- to post-drug administration in the THC condition (MD: 0.306, $p = .148$). Post-drug anxiety ratings were significantly lower following placebo compared to the THC condition (MD: -0.689, $p < .001$), but there was no difference between the placebo and THC pre-drug ratings (MD: 0.073, $p = .654$). As there was no evidence of a drug effect in the THC condition further moderation analyses of this variable were not conducted.

Wanting more cannabis ratings: There was a significant interaction between drug x time ($F_{355.338} = 4.893$, $p = .028$, 95% CI: -0.117 to -0.004) and a main effect of cannabis use frequency ($F_{128.893} = 5.962$, $p = .016$). There was no evidence of a main effect of drug or time, there was no drug x time x cannabis use frequency or drug x cannabis use frequency interaction. This model showed variance in intercepts across studies and participants ($Var_{u0j} = 4.887$, $\chi^2 = 6.953$, $p < .001$).Bonferroni corrected, pairwise comparisons showed there was no difference between the pre-drug and post- drug wanting more cannabis ratings in the THC (MD: -0.266, $p = .291$) or placebo (MD: -0.217, $p = .225$) condition. Figure 1 shows that post-drug wanting more cannabis ratings were significantly lower following THC compared to placebo (MD: -0.561, $p = .024$).

Table 9 MLM of Drug Effect on Alert Ratings, Prose Recall and Psychotomimetic States Inventory Scores with Cannabis Use Frequency without adolescents (n = 22)

Alert Ratings

	df	*F*	*p*
Intercept	105.985	273.319***	0.001
Drug	238.653	13.781***	0.001
Time	238.648	26.789***	0.001
Drug * time	238.653	22.095***	0.001
Cannabis use frequency	106.170	1.238	0.268
Drug * cannabis use frequency	239.673	0.310	0.578
Time * cannabis use frequency	239.628	0.857	0.356
Drug * time * cannabis use frequency	239.673	7.473*	0.007

Prose Recall

	df	*F*	*p*
Intercept	124.288	177.478***	0.001
Drug	211.338	66.738***	0.001
Time	211.338	4.072*	0.045
Drug * time	211.338	.094	0.760
Cannabis use frequency	123.901	.182	0.671
Drug * cannabis use frequency	210.942	7.700**	0.006
Time * cannabis use frequency	210.942	0.107	0.744
Drug * time * cannabis use frequency	210.942	0.038	0.845

Psychotomimetic States Inventory

	df	*F*	*p*
Intercept	106	138.6878***	0.001
Drug	106	49.5788***	0.001
Cannabis use frequency	106	0.016	0.898
Drug * cannabis use frequency	106	8.0788**	0.005

Notes. Degrees of freedom numerator = 1; *df* = degrees of freedom; *F* = F-statistic; *p* = p-value

***p* <.010, ****p* <.001

Stoned ratings without adolescents (n = 22)

There was a significant interaction between drug and cannabis use frequency (F_{106}=8.351, p=.005) and main effects of drug (F_{106} =76.399, p<.001) and cannabis use frequency

(F_{106}=9.707, p=.002). This model showed variance in intercepts across studies and participants (Var_{u0j}=0.909, χ^2= 2.164, p=.030).

Schizotypal Personality Questionnaire and the Psychotomimetic States Inventory without adolescents (n = 22)

There was no evidence for a drug x SPQ interaction. There was a positive association between SPQ scores and PSI scores in both the placebo and THC condition (F_{106}=33.737, p=.001). In a final model which included both possible moderators of SPQ score and cannabis use frequency, there was no evidence to support an interaction between these factors. This pattern of results did not differ from the analyse including the full sample.