



Citation for published version:

Freeman, AM, Mokrysz, C, Hindocha, C, Lawn, W, Morgan, CJ, Freeman, TP, Saunders, R & Curran, HV 2021, 'Does variation in trait schizotypy and frequency of cannabis use influence the acute subjective, cognitive and psychotomimetic effects of delta-9-tetrahydrocannabinol? A mega-analysis', *Journal of Psychopharmacology*, vol. 35, no. 7, pp. 804-813. <https://doi.org/10.1177/0269881120959601>

DOI:

[10.1177/0269881120959601](https://doi.org/10.1177/0269881120959601)

Publication date:

2021

Document Version

Peer reviewed version

[Link to publication](#)

Publisher Rights

CC BY-NC-ND

Freeman, Abigail M ; Mokrysz, Claire ; Hindocha, Chandni ; Lawn, Will ; Morgan, Celia Ja ; Freeman, Tom P ; Saunders, Rob ; Curran, H Valerie. / Does variation in trait schizotypy and frequency of cannabis use influence the acute subjective, cognitive and psychotomimetic effects of delta-9-tetrahydrocannabinol? A mega-analysis. In: *Journal of Psychopharmacology*. 2021. (C) Sage Publications, 2021. Reproduced by permission of SAGE Publications.

University of Bath

Alternative formats

If you require this document in an alternative format, please contact:
openaccess@bath.ac.uk

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Does variation in trait schizotypy and frequency of cannabis use influence the acute subjective, cognitive and psychotomimetic effects of delta-9-tetrahydrocannabinol? A Mega-analysis

Abstract

Background

While the acute effects of cannabis are relatively benign for most users, some individuals experience significant adverse effects. This study aimed to identify if variation in schizotypal personality traits and frequency of cannabis use influence the acute effects of delta-9-tetrahydrocannabinol (THC).

Methods

Individual participant data from four double-blind, randomised, placebo-controlled, acute crossover studies involving 128 cannabis users were combined for a mega-analysis. Using multilevel linear models and moderation analyses, frequency of cannabis use and schizotypal personality traits were investigated as potential moderators of the subjective, cognitive and psychotomimetic effects of acute THC.

Results

There was evidence of a moderating effect where increased frequency of cannabis use was associated with reduced intensity of subjective (changes in alertness and feeling stoned) and psychosis-like effects following THC when compared to placebo. Moderating effects of cannabis use frequency on acute memory impairment were weak. Trait schizotypy did not moderate the acute psychosis-like effects of THC compared to placebo.

Conclusions

Our results suggest that a pattern of domain-specific tolerance develops to the acute effects of THC. Tolerance to the alertness reducing effects occurred more readily than tolerance to psychotomimetic effects. Only partial tolerance to feeling stoned was found, and there was weak evidence for tolerance to memory impairment. Trait schizotypy did not moderate THC's effects on psychotomimetic symptoms.

Introduction

Although for most users, cannabis is a relatively benign drug with few negative consequences, some users experience adverse subjective effects of the drug (Curran et al., 2016; Green et al., 2003; Hammersley and Leon, 2006). Understanding which factors influence an individual's vulnerability or resilience to the effects of cannabis is an increasingly important research priority, especially given the current relaxation of cannabis legislative controls in many parts of the world. In some healthy volunteers, cannabis induces transient subjective feelings of intoxication, psychotic-like symptoms, and impairments in memory, attention and learning (Murray et al., 2016). Therefore, a key research question is why are some people more vulnerable to the acute adverse effects of cannabis than others?

The main active ingredient in cannabis is delta-9-tetrahydrocannabinol (THC) which can induce a range of transient, dose-dependent, subjective intoxicating effects (D'Souza et al., 2012; D'Souza et al., 2004). Individual responses to THC vary widely not only between individuals but also within individuals on different occasions (for a review see Green et al., 2003). Some individuals, including those without a history of psychosis, show a dose-dependent increase in both self-and clinician rated psychosis-like symptoms following the acute administration of a single dose of THC (D'Souza et al., 2004; Morrison et al., 2009; Bhattacharyya et al., 2015; D'Souza et al., 2012; D'Souza et al.,

2008; Morrison and Stone, 2011). In terms of the cognitive effects of the drug, THC consistently impairs verbal memory (Broyd et al., 2016).

A potential key factor in predicting an individual's response to THC may be the frequency of their recent cannabis use. However, many human experimental studies of cannabis report limited information regarding cannabis use history, making it difficult to draw inferences. A recent systematic review investigating participants' cannabis use frequency suggested that tolerance effects may explain conflicting results from experimental studies (Colizzi and Bhattacharyya, 2018). However, there was much variability in findings across different studies. Some studies have found that THC acutely impairs performance on various outcomes in occasional cannabis users, yet frequent cannabis users are unaffected (Hart et al., 2001; Ramaekers et al., 2011). Other studies have found that frequent users are still sensitive to many effects of THC (Metrik et al., 2012; Ramaekers et al., 2016; Van Wel et al., 2013). A recent mega-analysis also found evidence of a tolerance effect specifically to the psychomimetic effects of THC in those with a history of frequent and recent cannabis use (Ganesh et al., 2020). Few studies have directly investigated tolerance effects. Moreover, small samples and discrepant findings are common in the limited number of studies that have examined this.

Another factor which potentially predicts an individual's response to acute THC, particularly the psychosis-like effects, is their level of schizotypal personality traits. Past

and current cannabis users are more likely to report elevated schizotypal traits than non-users (Williams et al., 1996; Schiffman et al., 2005; Mass et al., 2001; Nunn et al., 2001) but the nature of the relationship between cannabis use and schizotypy remains unclear. Naturalistic (for example, Mason et al., 2009) and retrospective (Barkus et al., 2006; Barkus and Lewis, 2008; Stirling et al., 2008; Spriggs and Hides, 2015; Verdoux et al., 2003) studies have linked higher trait schizotypy with an increased vulnerability to the psychotomimetic effects of cannabis. However, two recent studies (Morgan et al., 2018b; Barkus et al., 2016) did not find any such link.

The current study aims to build on these initial findings by combining data from four crossover laboratory studies, administering acute THC or medicinal grade cannabis. We hypothesised that increased cannabis use frequency would be associated with heightened tolerance (i.e. reduced response) to subjective, cognitive and the psychotomimetic effects of THC (Colizzi et al., 2018; Lichtman and Martin, 2005). The second hypothesis was that higher trait schizotypy would be associated with heightened psychotomimetic effects of THC (Barkus and Lewis, 2008; Hori et al., 2013; Mason et al., 2009). Finally, we explored whether tolerance effects (reflecting down-regulation of CB1 receptors) would be influenced by level of schizotypal traits.

Methods

The study protocol and statistical analysis plan were preregistered on the Open Science Framework (OSF; Freeman et al., 2018). The trials included in the current study were chosen for mega-analysis because of the strong homogeneity of methodology. Table 1 shows the study characteristics of the four trials for which the protocols were retrieved (Hindocha et al., 2015; Hindocha et al., 2017; Lawn et al., 2016; Mokrysz et al., 2016).

Eligibility criteria

Inclusion criteria

- i. The study recruited volunteers who reported cannabis use but were otherwise healthy.
- ii. Study drugs were administered under experimental conditions.
- iii. The study included an equivalent dose of THC or cannabis containing THC with no cannabidiol content (CBD < 0.1%). Hereafter these are referred to as THC.
- iv. The study directly compared THC to a matched placebo condition under double-blind conditions.
- v. The study drugs were administered via a standardised comparable a route of administration to allow for similar pharmacokinetic profile effect (e.g. inhaled) across studies and participants.

Exclusion criteria

- i. Studies which did not include have a placebo condition.

Design and Participants

All studies used a double-blind, placebo-controlled, repeated-measures, crossover design, including one factor (drug condition) with two levels (placebo and THC). Participants were randomised to treatment order using a Latin squares design whereby the order of drug treatment was counterbalanced. A summary of the inclusion and exclusion criteria for each study is provided in the supplementary materials (Supplementary Tables S1 and S2). The pooled sample comprised of 94 men and 35 women (n=129). All participants had previously used cannabis.

Drug administration

Each study manipulated the drug condition by administering either placebo (vaporized or smoked in a joint) or THC (8-10mg vaporized or smoked in a joint) to all participants on two separate testing days at least seven days apart. These doses of THC reflect, as recently defined, approximately two standard THC units (one standard unit = 5mg THC) and which has been shown to produce acute subjective, cognitive and psychomimetic effects in experimental studies (Freeman and Lorenzetti, 2019). Some studies included a

condition where CBD was co-administered, however, as not all studies included a CBD condition and there was variation in THC:CBD ration across studies, these data was not analysed in the current study. Further information about the drug administration is provided in Table 1.

Table 1 Study Characteristics Across the Four Studies

Study Characteristics Across the Four Studies: Hindocha et al. (2015), Hindocha et al. (2017), Lawn et al. (2016) and Mokrysz et al. (2016)

Study	Design	Participants and cannabis use history	Interventions	Outcome measures
Hindocha et al. (2015)	A randomised, placebo-controlled, double-blind, crossover study with four treatment conditions.	48 healthy participants, 24 reported current daily use of cannabis; 24 reported current recreational use of cannabis	Placebo; THC 8 mg	Baseline: Drug History; SPQ Testing days: PSI, Prose recall VAS: alert, anxious, stoned, I want to have cannabis
Hindocha et al. (2017)	A randomised, placebo-controlled, double-blind, crossover study with four treatment conditions.	24 healthy participants, with minimal dependence on cannabis and tobacco	Placebo; THC 10 mg	Baseline: Drug History; SPQ Testing days: PSI, Prose recall VAS: alert, anxious, stoned, I am craving cannabis
Lawn et al. (2016)	A randomised, placebo-controlled, double-blind, crossover study with three treatment conditions.	17 ^a healthy participants reported current cannabis use (≥ 4 times in the last year, ≤ 3 times/week)	Placebo; THC 8mg	Baseline: Drug History; SPQ Testing days: PSI, Prose recall VAS: alert, anxious, stoned, I want to smoke cannabis
Mokrysz et al. (2016)	A randomised, placebo-controlled, double-blind, crossover study with two treatment conditions.	40 health participants; 20 adolescents and 20 adults; cannabis use 1-3 days per week	Placebo; THC 8mg	Baseline: Drug History; SPQ Testing days: PSI, Prose recall VAS: alert, anxious, stoned, I want to have cannabis

Notes. Hindocha et al. (2015): THC (8mg THC) and placebo (0mg THC) delivered in ethanol vehicle by vaporizer, Hindocha et al. (2017): cannabis (10mg THC) and placebo cannabis (0.05mg THC) delivered with denicotinized tobacco by joint, Lawn et al. (2016): cannabis (8mg THC) and placebo cannabis (0.05mg THC) delivered by vaporizer, Mokrysz et al. (2016): cannabis (8mg THC) and placebo cannabis (0.05mg THC) delivered by vaporizer. SPQ = Schizotypy Personality Questionnaire; Prose recall = immediate and delayed prose recall; VAS = visual analogue scale; PSI = Psychotomimetic States Inventory. a) An additional participant was recruited in Lawn et al. (2016) because of excessive head movement; therefore, not all data were available for this participant and data from the original participant was excluded from the analysis.

Assessments

Outcome Variables

Subjective intoxication: Participants completed visual analogue scales (VAS) of subjective intoxicating effects (including 'anxiety, ' 'alertness, ' 'stoned, ' and 'wanting more cannabis') before drug administration, and again at estimated peak drug effect following administration (~20 minutes). Each study used slightly different wording to assess wanting more cannabis based on the specific aims of the study (see Table 1), and these were combined as one item "wanting more cannabis". In Hindocha et al. (2015) the study used an 11-point VAS scale, and therefore data were rescaled to reflect the change from a 1-10 scale to a 0-10 scale using the per cent of maximum possible score (POMP) method (Cohen et al., 1999).

Prose Recall Task: Episodic memory was assessed using the prose recall subtest of the Rivermead Behavioural Memory Test (Wilson, 1993). At all testing sessions, participants listened to a 30-second 'news bulletin' and then wrote down what they remembered immediately and again after a delay which was filled with other assessments. In Mokrysz et al. (2016), the time given to recall items was limited to one minute. Each story contained 21 'idea units' and responses were scored systematically.

Psychotomimetic States Inventory (PSI): The PSI was administered following drug administration on both test days. The PSI is a 48-item scale designed to measure drug-induced changes in psychosis-like experiences (Mason et al., 2008). The measure has previously been shown to be sensitive to cannabis-induced psychotomimetic effects. The measure has six subscales including; Delusory Thinking, Perceptual Distortions, Cognitive Disorganization, Anhedonia, Mania and Paranoia

Moderating variables

Cannabis use history: A detailed structured interview of lifetime cannabis use was carried out at baseline. The interview recorded lifetime use ever (yes/no), time since last use (days), duration of use (years), use frequency (the number of days per month of cannabis use) and time to smoke 3.5g (1/8th ounce) of cannabis. In a large scale study, which tested 15 self-report and biological measures of cannabis use, cannabis use frequency (the number of days per month of cannabis use) was the single most predictive self-report measure of tolerance to the acute effects of THC. It was also the strongest self-report measure at predicting cannabis dependency (Curran et al., 2018). Therefore, cannabis use frequency (the number of days per month of cannabis use) was taken as the primary measure of cannabis use in the current study.

Schizotypal Personality Questionnaire (SPQ): All participants completed the SPQ at baseline. The SPQ is a 74-item questionnaire designed to assess trait schizotypy (Raine, 1991). The questionnaire is closely modelled on the Diagnostic Statistical Manual-III-Revised (APA, 1987) schizotypal personality disorder criteria and provides a self-report measure of schizotypal personality. The SPQ measures three factors cognitive and perceptual, interpersonal, disorganized.

Risk of bias assessment

Risk of bias was assessed using the Cochrane Collaboration's tool for assessing the risk of bias in crossover trials (Higgins et al., 2011).

Data collection and integrity

Following pre-registration of the protocol and analysis plan, the individual participant data (IPD) was requested via email from a lead researcher for each study. The data were combined to create a new aggregated dataset. The data were checked for consistency and integrity, by cross-checking the new dataset against the original data sets and by recreating findings reported in tables for each study. Queries and confirmation of missing data were followed up via email and telephone.

Data synthesis and statistical analysis

The IPD from the four studies were pooled to conduct a meta-analysis (Olkin, 1995) with participant-level data, also known as a mega-analysis (DeRubeis et al., 1999). A mega-analysis was considered appropriate in terms of the interventions and study protocols (Elbourne et al., 2002; Higgins and Green, 2008). The statistical plan (Freeman *et al.*, 2018) was updated to a one-step IPD approach using Multi-Level Models (MLM) to account for data structure and heterogeneity between studies.

Three levels were specified; the repeated-measurements within-participant (level one), the participant (level two) and the study (level three). The effect of the drug (placebo and THC) and the moderators; cannabis use frequency (the number of days per month of cannabis use) and SPQ scores were evaluated in mixed-effects MLM with maximum likelihood estimation to quantify changes in subjective intoxicating effect ratings (continuous: anxiety, alert, stoned, and want more cannabis), prose recall (continuous: immediate and delayed) and PSI scores (continuous). For the PSI there was no pre-drug measurement, and for the VAS stoned pre-drug measurements were not analysed due to floor effects. Therefore, for both PSI scores and stoned ratings only post-drug scores were analysed using a single fixed factor of drug. For the remaining variables of interest an additional factor of time was also included to account for the pre- and post-drug ratings of anxiety, alert and want more cannabis and for the delay in the prose recall task. The

interaction between drug x time was also entered as a fixed effect. The interaction between the participant and study factors were included next as a random intercept using a variance components structure. The random intercept accounts for heterogeneity between the studies and baseline differences between participants by allowing the intercepts to differ. The clustering of participants within studies is accounted for by estimating the intercept for each study and assuming the study intercepts (baseline) are randomly drawn from a distribution. All models were improved by the inclusion of the participant x study interaction, evidenced by χ^2 likelihood ratio tests ($p < .05$) and reductions in Bayesian Information Criterion (reduction > 2) as recommended by Raftery (1995). Sensitivity analyses were run to investigate whether the results persisted after excluding adolescents ($n = 22$; aged 16-18) from the analyses.

Interpretation of interactions

The moderation model used in this study is analogous to an interaction effect in regression analysis. The moderation of drug effects were illustrated in a fixed effects model using MEMORE for SPSS (Montoya, 2019). Where possible, the Johnson-Neyman (JN) approach was used to quantify the moderation effect. The JN-point is where the confidence interval around the conditional effect of the drug (e.g. the moderating effect of cannabis use frequency) intersects zero on the y-axis, representing the outcome variable of interest (e.g. ratings of stoned). Therefore, the JN-approach identifies the value of the moderator at which the drug is no longer effective (e.g. the critical level of cannabis

use frequency, at which THC no longer increases ratings of stoned compared to placebo). If this was not possible, due to the drug having a significant effect at all values of the moderator, a pick-a-point approach was used (Hayes, 2017). All statistical tests were two-tailed with an alpha level of .05 with a local Bonferroni correction for multiple tests.

Results

Table 1 provides a summary of the study characteristics. The total number of participants included in the analysis was 128. There were no concerns with data integrity identified when checking the IPD. Two participants had missing data on the VAS for one testing session in Hindocha et al. (2015). The four studies included in this mega-analysis were rated as having a low risk of bias across all domains (Higgins et al., 2011). The effect and mean difference for each outcome variable for each study and for the mega-analysis is shown in the supplementary materials (Supplementary Tables S3 and S8). There was no drug effect for anxiety ratings or wanting more cannabis ratings; these results are reported in the supplementary materials only (Supplementary pages 10-11).

Demographics and participant characteristics (Table 2)

As shown in Table 2, there were differences across studies in participants' age ($F_{3,124}=8.03, p<.001$), gender ($\chi^2_{(3)}=25, p<.001$), number of years of cannabis use ($F_{3,124}=3.880, p=.011$) and days/month ($F_{3,124}=17.85, p<.001$). The study participants did

not differ in the number of days since last cannabis use ($F_{3,124}=2.461, p=.066$) or SPQ scores ($F_{3,124}=0.307, p=.821$). In pairwise comparisons, participants in Hindocha et al. (2015) used cannabis more frequently than each of the other studies (against Lawn et al. (2016), $t_{62}=-3.826, p<.001$, Hindocha et al. (2017), $t_{70}=-4.834, p<.012$, Mokrysz et al. (2016), $t_{86}=-5.151, p<.001$). To illustrate the similarities and differences across study groups, the mean alert and stoned VAS ratings, prose recall and PSI scores are shown in Figure 1.

Table 2 Demographic Information across Four Studies

Means (SD) for Demographic Information across Four Studies and in the Combined Sample.

	Hindocha et al. (2015)	Hindocha et al. (2017)	Lawn et al. (2016)	Mokrysz et al. (2016)	Combined
n	48	24	16	40	128
Gender (% female)	29%	50%	50%	0%	27.13%
Age (years)	21.71 (1.90)	24.46 (3.95)	26.85 (7.35)	21.29 (4.33)	22.66 (4.41)
SPQ score	16.37 (13.89)	17.83 (10.83)	15.25 (6.40)	18.05 (11.30)	17.03 (11.73)
Cannabis use					
Days since last use	5.72 (17.44)	7.91 (9.63)	19.25 (45.27)	4.05 (3.24)	7.30 (19.93)
Range for last use	119 (1-120)	41 (1-42)	179 (1-180)	13 (1-14)	179 (1-180)
Days per month	18.50 (10.40)	7.75 (4.42)	8.06 (5.47)	9.25 (4.94)	12.29 (8.84)
Range for days per month	30 (1-31)	17 (1-18)	19 (1-20)	20 (2-22)	30 (1-31)
Years used	6.01 (2.77)	6.79 (3.94)	8.93 (7.01)	5.06 (3.49)	6.22 (4.08)

Notes. SD = Standard Deviation; n = number of participants; SPQ = Schizotypal Personality Questionnaire; Cannabis use frequency = days per month of cannabis use. Range includes the minimum and maximum values in parentheses.

Subjective intoxication ratings of drug effects (Table 3)

Alert ratings: As shown in Table 3 there was a significant interaction between drug, time and cannabis use frequency ($F_{283.100}=7.253, p=.008$), a significant drug x time interaction ($F_{281.911}=22.356, p<.001$), and main effects of drug ($F_{281.911}=8.242, p=.004$) and time ($F_{281.904}=26.639, p<.001$). This model showed significant variance in intercepts across studies and participants ($\text{Var}_{u0j}=4.700, \chi^2=7.269, p<.001$). Bonferroni corrected, pairwise comparisons showed that alert ratings significantly reduced from pre- to post-drug in both the placebo (MD:-0.439, $p<.001$) and THC (MD:-1.538, $p<.001$) conditions. Post-drug alert ratings were significantly lower following THC than placebo (MD-1.133, $p<.001$; Figure 1).

To quantify the interaction, the JN-point was calculated using MEMORE (Figure 2). When the number of days per month of cannabis use reported is ~12 days (M:12.081) the expected change in alert ratings from pre- to post-drug in the THC condition compared to placebo is -1.078 ($t_{124}=-6.223, p<.001, 95\% \text{ CI } -0.735 \text{ to } -1.421$). For each additional day of cannabis use per month, there is a -0.086-point reduction in the difference in the change from pre-to post drug scores in the THC condition compared to placebo ($t_{124}=-4.315, p<.001, 95\% \text{ CI } -0.125 \text{ to } -0.046$). The JN technique showed that THC does not

reduce alert ratings compared to placebo when participants report using cannabis above 19 days per month ($t_{124} = 1.979, p = .050, 95\% \text{ CI } 0 - 0.897$).

Table 3 MLM of Drug Effect on Alert Ratings, Prose Recall and Psychotomimetic States Inventory Scores with Cannabis Use Frequency

<i>Alert Ratings</i>			
	<i>df</i>	<i>F</i>	<i>p</i>
Intercept	127.815	281.520***	0.001
Drug	281.911	8.242**	0.004
Time	281.904	26.639***	0.001
Drug * time	281.911	22.356***	0.001
Cannabis use frequency	128.008	0.413	0.522
Drug * cannabis use frequency	283.1	0.044	0.833
Time * cannabis use frequency	283.048	0.531	0.467
Drug * time * cannabis use frequency	283.1	7.253*	0.008
<i>Prose Recall</i>			
	<i>df</i>	<i>F</i>	<i>p</i>
Intercept	143.81	186.999***	0.001
Drug	254.294	67.642***	0.001
Time	254.294	4.241*	0.04
Drug * time	254.294	0.02	0.889
Cannabis use frequency	143.523	0.333	0.565
Drug * cannabis use frequency	253.996	7.229**	0.008
Time * cannabis use frequency	253.996	0.099	0.754
Drug * time * cannabis use frequency	253.996	0.027	0.869
<i>Psychotomimetic States Inventory</i>			
	<i>df</i>	<i>F</i>	<i>p</i>
Intercept	128	148.094***	0.001
Drug	128	53.484***	0.001

Cannabis use frequency	128	0.054	0.816
Drug * cannabis use frequency	128	7.806**	0.006

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

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

Stoned ratings: There was a significant interaction between drug and cannabis use frequency ($F_{128}=8.673$, $p=.004$) and main effects of drug ($F_{128}=91.625$, $p<.001$) and cannabis use frequency ($F_{128}=9.780$, $p=.002$). This model showed variance in intercepts across studies and participants ($\text{Var}_{u0j}=0.992$, $\chi^2=2.509$, $p=.012$). Bonferroni corrected, pairwise comparisons showed that stoned post-drug ratings were significantly higher in the THC than placebo (MD:3.318, $p<.001$). When the number of days per month of cannabis use reported is ~12 days (M: 12.081) the expected change in stoned ratings from placebo to the THC condition is 3.317 ($t_{124}=2.714$, $p<.001$, 95% CI 2.781 to 3.854). For each additional day of cannabis use per month, there is a -0.090 decrease in the difference between post-drug placebo and THC stoned ratings ($t_{126}=-2.921$, $p<.004$, 95% CI -0.151 to -0.29). The JN-point could not be calculated using MEMORE as THC significantly increased stoned ratings regardless of the number of days per month of cannabis use reported. Therefore, a pick-a-point approach was used to display the interaction (Figure 2).

Prose recall: There was an interaction between drug and cannabis use frequency ($F_{253.996}=7.229, p=.008$) and main effects of drug ($F_{254.294}=67.642, p<.001$) and time ($F_{254.294}=4.241, p=.040$). No main effect of cannabis use frequency, drug x time, time x cannabis use frequency interaction, or drug x time x cannabis use frequency interaction emerged (Table 3). This model showed significant variance in intercepts across studies and participants ($\text{Var}_{u0j}=11.166, \chi^2=7.563, p<.001$). Bonferroni corrected, pairwise comparisons found that significantly fewer units were recalled following THC at both the immediate (MD:-2.215, $p<.001$) and delayed time points (MD:-2.219, $p<.001$). There was a further reduction in the number of units recalled following a delay which was significant in the THC condition (MD:-0.664, $p<.001$) but not in the placebo condition (MD:-0.660, $p=.108$). Exploratory analyses of the possible moderation of the effect of THC on each condition, immediate and delayed prose recall, by cannabis use frequency were investigated independently using MEMORE. The effect did not reach significance at either time point.

Psychotomimetic States Inventory: As shown in Table 3 there was a drug x cannabis use frequency interaction ($F_{128}=7.806, p=.006$) and a main effect of drug ($F_{128}=53.484, p<.001$). This model showed significant variance in intercepts across studies and participants ($\text{Var}_{u0j}=70.699, \chi^2=3.986, p<.001$).

To quantify the interaction between drug and cannabis use frequency, the JN-point was calculated using MEMORE (Figure 2). When the number of days per month of cannabis use is at ~12 days (M:12.081) the expected change in PSI scores post-drug ratings from placebo to THC is 13.072 ($t_{124}=8.586$, $p<.001$, 95% CI 10.059 to 16.085). For each additional day of cannabis use per month, there is a -0.478-point reduction in the difference between the post-drug placebo and THC PSI scores ($t_{126}=-2.772$, $p=.006$, 95% CI -0.821 to -0.137). There was also a 0.211-point increase in post-drug PSI score in the placebo condition for every additional day of cannabis use reported ($t_{126}=-2.007$, $p=.047$, 95% CI 0.003 to 0.420). The JN-point shows that THC does not increase PSI scores when compared to placebo when participants report using cannabis above 27 days per month ($t_{126}=1.979$, $p=.050$, 95% CI 0.000 – 11.851). This indicates that THC produces a smaller increase in PSI scores in those who report more frequent cannabis use.

Schizotypal Personality Questionnaire and the Psychotomimetic States Inventory: 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 ($F_{128}=44.390$, $p=.001$). 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.

Sensitivity analyses

The exclusion of adolescents (n = 22; aged 16-18) from the analyses did not alter the pattern of effects found. The findings from these analyses are reported in the supplementary materials (Supplementary materials Table S9 and pages 12 and 13).

Discussion

This mega-analysis included 128 participants from four placebo-controlled, double-blind, laboratory studies with homogenous methodology. The study aimed to determine how frequency of cannabis use and schizotypal personality traits influence the subjective, cognitive and psychotomimetic effects of THC. The results suggest that domain-specific tolerance develops to the acute effects of THC. There was evidence of a moderating effect where increased frequency of cannabis use was associated with reduced intensity of subjective (alertness and stoned ratings) and psychosis-like effects following THC when compared to placebo. More frequent cannabis use was associated with higher levels of psychosis-like effects when participants were not acutely intoxicated, measured by PSI scores following administration of a placebo. However, level of trait schizotypy did not moderate the psychosis-like effects of THC.

Frequency of cannabis use

More frequent recent use of cannabis was associated with blunted responses to the subjective intoxicating effects (Ramaekers et al., 2016) and psychosis-like effects of THC

(D'Souza et al., 2008; Mason et al., 2009; Desrosiers et al., 2015). However, tolerance to specific subjective effects of THC may develop differentially. For example, the reported increases in stoned ratings following THC versus placebo occurred even in daily cannabis users. However, tolerance to the alertness-reducing effects of THC appear to develop more readily as those who used the drug over 19 days per month reported no distinguishable change in alertness levels following THC when compared to placebo. Further, increased frequency of cannabis use seemed to have a weak, if any, moderating effect on THC-induced verbal memory impairment. Thus, tolerance to acute sedative effects occurs before that to euphoric intoxicating effects and, in turn, before memory impairing effects.

Our findings suggest that tolerance to the psychosis-like effects develops, however, later and only when individuals are using cannabis daily. For participants who reported almost daily cannabis use, THC-induced psychosis-like effects were no longer distinguishable from placebo-induced effects. Additionally, more frequent cannabis use predicted higher levels of psychosis-like experiences in the placebo condition. This suggests that when not acutely intoxicated (i.e. in the placebo condition), these participants were experiencing greater sub-clinical psychotic-like symptoms. This suggests that although they become tolerant to the acute effects of cannabis, overall they are experiencing more psychosis-like effects when not intoxicated. This is important as the adverse effects associated with continued cannabis use may be reduced if individuals

at risk of developing a psychotic disorder reduce their cannabis use frequency (Schoeler et al., 2016).

The development of differential tolerance is seen with other psychoactive drugs. For example, tolerance develops to the different desired effects and adverse effects of benzodiazepines and opioids at different speeds and different degrees (Dumas and Pollack, 2008; Curran, 1991). Preclinical evidence shows that repeated THC administration may lead to the development of domain-specific tolerance due to differences in the density and location of cannabinoid receptors in the brain (Pertwee, 2008; De Vry et al., 2004). Although the mechanism of tolerance to the effects of THC in humans is not well understood, it is possible that with repeated exposure, tolerance develops as a result of the downregulation and desensitisation of CB₁ receptors (Ameri, 1999; D'Souza et al., 2008). The extent to which THC activates or blocks CB₁ receptors may depend on the density of these receptors in a specific region or network. The highest density of CB₁ receptors are found in the frontal and limbic brain regions, and the hippocampus, amygdala, cerebellum, thalamus and basal ganglia which are associated with reward, emotional and cognitive processing (Bloomfield et al., 2018).

Schizotypy

Contrary to our second hypothesis, we did not find a significant interaction between schizotypal trait scores and THC-induced psychosis-like effects on the PSI. There was a significant positive correlation between psychotomimetic states and schizotypal traits, as expected given that these were state and trait measures of the same construct. However, frequency of cannabis use was associated with state psychotic-like symptoms but not trait schizotypy in our sample.

Other factors such as genetics or perceived stress may predispose an individual to cannabis use, schizotypal traits and acute psychosis-like effects of cannabis. Morgan et al. (2018a) report that both childhood adversity and cannabis use predict higher rates of psychosis-like experiences, and that experiences of childhood adversity predict the use of cannabis in later life. Further studies should take these variables into account to build a clearer understanding of these complex inter-relationships. For ethical and clinical reasons, all four studies included in the current analysis excluded participants who had regular or severe adverse responses to cannabis. It is possible that the link between high trait schizotypy and psychosis-like experiences is only present in those who experience severe and repeated negative responses to cannabis. For example, there is some evidence to suggest that acute administration of THC might differentially affect those with a

clinical presentation of psychosis compared to controls (D'Souza et al., 2005; Henquet et al., 2006; Vadhan et al., 2017).

Strengths and limitations

Strengths of this study include preregistration of its protocol and hypotheses before data was accessed. By combining the data of four studies conducted within the same research group, it was possible to create a sample of almost 130 cannabis users who had undergone double-blind placebo-controlled acute THC administration tested using a comparable methodology. Another strength is that the analysis also retained the within-subject effects by including IPD and using novel sophisticated methods for moderation analyses.

There are limitations to combining data sets, and it is possible that methodological differences contribute to the findings of this study. For example, it is possible that differences in participant characteristics in each study could have contributed to these findings. However, appropriate methods were used to account for the heterogeneity between studies (Higgins & Green, 2008). In our analysis study was fitted as a random effect, which can account for variation across studies and increases the likelihood that our findings are generalisable across experimental studies of this kind. Our mega-analysis permitted investigation of a large sample including a range of scores for cannabis use frequency and schizotypal personality trait scores. However, as each the studies varied in

their inclusion criteria, certain scores (e.g. daily users) were not equally distributed across studies.

The studies included in this analysis excluded participants with regular severe adverse reactions to cannabis, and therefore, these findings may not be generalizable to those who report severe responses to cannabis. For PSI scores there was no pre-drug measurement. Future studies would be strengthened by including both a pre and post-drug administration measure of PSI. As schizotypy is a multidimensional trait, future studies could extend these findings by investigating how specific subscales moderate the acute effects of cannabis. It is possible that participant's SPQ scores were influenced by intoxication experiences as the questionnaire addressed participants experiences in general but did not distinguish between intoxicated and non-intoxicated experiences. This study did not collect biological samples and therefore it was not possible to compare THC blood levels across the studies. Studies also used self-report measures rather than biological measures to estimate cannabis use history. Additionally, the studies included in this analysis did not verify last use of cannabis using urinary measures. Frequency of cannabis use has previously been found to be the strongest predictor of cannabis dependence and tolerance to psychosis-like symptoms (Curran et al., 2018). However, the number of days per month of cannabis use is a general measure of use, and the potency and dose of cannabis used at each use may also influence the development of tolerance effects.

Conclusion

This study has shown that domain-specific tolerance develops to the acute effects of THC and these results support the idea that differences in participant's cannabis use history may be partially account for disparate findings across experimental studies investigating the acute effects of THC. It provides important new insights about the nature of previously reported associations between schizotypal traits and cannabis-related psychosis-like experience. Findings of this study offer new insight into how increased use may raise psychosis-like experiences beyond the acute effects of the drug. This study suggests that safer use guidelines for consumers may focus upon reducing the frequency of cannabis use, and helping individuals recognise the signs and symptoms of acute psychosis-like experiences.

References

- Ameri A (1999) The effects of cannabinoids on the brain. *Progress in Neurobiology* 58(4): 315-348.
- APA APA (1987) *Diagnostic and Statistical Manual of Mental Disorders*. Washington, D.C.: APA.
- Barkus E and Lewis S (2008) Schizotypy and psychosis-like experiences from recreational cannabis in a non-clinical sample. *Psychological Medicine* 38(9): 1267-1276.
- Barkus E, Morrison PD, Di Forti M, et al. (2016) Are deficits in cognition associated with psychotic-like experiences after cannabis? *Human Psychopharmacology: Clinical and Experimental* 31(6): 402-411.
- Barkus E, Stirling J, Hopkins R, et al. (2006) Cannabis-Induced Psychosis-Like Experiences Are Associated with High Schizotypy. *Psychopathology* 39(4): 175-178.
- Bhattacharyya S, Atakan Z, Martin-Santos R, et al. (2015) Impairment of inhibitory control processing related to acute psychotomimetic effects of cannabis. *European Neuropsychopharmacology* 25(1): 26-37.
- Bloomfield MA, Hindocha C, Green SF, et al. (2018) The neuropsychopharmacology of cannabis: a review of human imaging studies. *Pharmacology Therapeutics*. DOI: 10.1016/j.pharmthera.2018.10.006.(195): 132-161.

- Broyd SJ, van Hell HH, Beale C, et al. (2016) Acute and Chronic Effects of Cannabinoids on Human Cognition-A Systematic Review. *Biological Psychiatry* 79(7): 557-567.
- Cohen P, Cohen J, Aiken LS, et al. (1999) The problem of units and the circumstance for POMP. *Multivariate Behavioral Research* 34(3): 315-346.
- Colizzi M and Bhattacharyya S (2018) Cannabis use and the development of tolerance: a systematic review of human evidence. *Neuroscience & Biobehavioral Reviews*. DOI: 10.1016/j.neubiorev.2018.07.014.(93): 1-25.
- Colizzi M, McGuire P, Giampietro V, et al. (2018) Modulation of acute effects of delta-9-tetrahydrocannabinol on psychotomimetic effects, cognition and brain function by previous cannabis exposure. *European Neuropsychopharmacology* 28(7): 850-862.
- Curran HV (1991) Benzodiazepines, memory and mood: a review. *Psychopharmacology* 105(1): 1-8.
- Curran HV, Freeman TP, Mokrysz C, et al. (2016) Keep off the grass? Cannabis, cognition and addiction. *Nature Reviews Neuroscience* 17(5): 293-306.
- Curran HV, Hindocha C, Morgan CJ, et al. (2018) Which biological and self-report measures of cannabis use predict cannabis dependency and acute psychotic-like effects? *Psychological Medicine*. DOI: 10.1017/S003329171800226X. 1-7.

- D'Souza DC, Fridberg DJ, Skosnik PD, et al. (2012) Dose-related modulation of event-related potentials to novel and target stimuli by intravenous Δ 9-THC in humans. *Neuropsychopharmacology* 37(7): 1632-1646.
- D'Souza DC, Perry E, MacDougall L, et al. (2004) The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 29(8): 1558-1572.
- D'Souza DC, Ranganathan M, Braley G, et al. (2008) Blunted psychotomimetic and amnestic effects of Δ -9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology* 33(10): 2505-2016.
- D'Souza DC, Abi-Saab WM, Madonick S, et al. (2005) Delta-9-tetrahydrocannabinol effects in schizophrenia: Implications for cognition, psychosis, and addiction. *Biological Psychiatry* 57(6): 594-608.
- De Vry J, Jentzsch K, Kuhl E, et al. (2004) Behavioral effects of cannabinoids show differential sensitivity to cannabinoid receptor blockade and tolerance development. *Behavioural Pharmacology* 15(1): 1-12.
- DeRubeis RJ, Gelfand LA, Tang TZ, et al. (1999) Medications versus cognitive behavior therapy for severely depressed outpatients: mega-analysis of four randomized comparisons. *The American Journal of Psychiatry* 156(7): 1007-1013.

- Desrosiers NA, Ramaekers JG, Chauchard E, et al. (2015) Smoked cannabis' psychomotor and neurocognitive effects in occasional and frequent smokers. *Journal of Analytical Toxicology* 39(4): 251-261.
- Dumas EO and Pollack GM (2008) Opioid tolerance development: a pharmacokinetic/pharmacodynamic perspective. *The AAPS Journal* 10(4): 537-551.
- Elbourne DR, Altman DG, Higgins JPT, et al. (2002) Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 31(1): 140-149.
- Freeman AM, Mokrysz C, Saunders R, et al. (2018) Do Trait Schizotypy and Drug Use Factors Predict Vulnerability and/or Resilience to the Acute Effects of Cannabis? Reportno. Report Number|, Date. Place Published|: Institution|.
- Freeman TP and Lorenzetti V (2019) 'Standard THC units': a proposal to standardize dose across all cannabis products and methods of administration. *Addiction*.
- Ganesh S, Cortes-Briones J, Ranganathan M, et al. (2020) Psychosis-relevant effects of intravenous delta-9-tetrahydrocannabinol-A mega analysis of individual participant-data from human laboratory studies. *International Journal of Neuropsychopharmacology*.
- Green B, Kavanagh D and Young R (2003) Being stoned: a review of self-reported cannabis effects. *Drug and Alcohol Review* 22(4): 453-460.

- Hammersley R and Leon V (2006) Patterns of cannabis use and positive and negative experiences of use amongst university students. *Addiction Research & Theory* 14(2): 189-205.
- Hart CL, Van Gorp W, Haney M, et al. (2001) Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology* 25(5): 757-765.
- Hayes AF (2017) *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. Guilford Publications.
- Henquet C, Rosa A, Krabbendam L, et al. (2006) An Experimental Study of Catechol-O-Methyltransferase Val158Met Moderation of Δ -9-Tetrahydrocannabinol-Induced Effects on Psychosis and Cognition. *Neuropsychopharmacology* 31(12): 2748-2757.
- Higgins JPT, Altman DG, Gøtzsche PC, et al. (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal* 343: d5928.
- Higgins JPT and Green S (2008) *Cochrane handbook for systematic reviews of interventions*. England: The Cochrane Collaboration and John Wiley & Sons Ltd.
- Hindocha C, Freeman TP, Schafer G, et al. (2015) Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users. *European Neuropsychopharmacology* 25(3): 325-334.

- Hindocha C, Freeman TP, Xia JX, et al. (2017) Acute memory and psychotomimetic effects of cannabis and tobacco both 'joint' and individually: A placebo-controlled trial. *Psychological Medicine* 47(15): 2708-2719.
- Hori H, Matsuo J, Teraishi T, et al. (2013) Moderating effect of schizotypy on the relationship between smoking and neurocognition. *European Psychiatry* 28(8): 457-462.
- Lawn W, Freeman TP, Pope RA, et al. (2016) Acute and chronic effects of cannabinoids on effort-related decision-making and reward learning: an evaluation of the cannabis 'amotivational' hypotheses. *Psychopharmacology* 233(19-20): 3537-3552.
- Lichtman A and Martin B (2005) Cannabinoid tolerance and dependence. *Handbok of Experimental Pharmacology*. Springer, pp.691-717.
- Mason OJ, Morgan CJA, Dhiman S, et al. (2009) Acute cannabis use causes increased psychotomimetic experiences in individuals prone to psychosis. *Psychological Medicine* 39(6): 951-956.
- Mason OJ, Morgan CJA, Stefanovic A, et al. (2008) The psychotomimetic states inventory (PSI): measuring psychotic-type experiences from ketamine and cannabis. *Schizophrenia Research* 103(1-3): 138-142.

- Mass R, Bardong C, Kindl K, et al. (2001) Relationship between cannabis use, schizotypal traits, and cognitive function in healthy subjects. *Psychopathology* 34(4): 209-214.
- Metrik J, Kahler CW, Reynolds B, et al. (2012) Balanced placebo design with marijuana: pharmacological and expectancy effects on impulsivity and risk taking. *Psychopharmacology* 223(4): 489-499.
- Mokrysz C, Freeman TP, Korkki S, et al. (2016) Are adolescents more vulnerable to the harmful effects of cannabis than adults? A placebo-controlled study in human males. *Translational Psychiatry* 6(11): e961.
- Montoya AKJBrm (2019) Moderation analysis in two-instance repeated measures designs: Probing methods and multiple moderator models. *Behavior research methods* 51(1): 61-82.
- Morgan C, Reininghaus U, Reichenberg A, et al. (2018a) Adversity, cannabis use and psychotic experiences: evidence of cumulative and synergistic effects. *British Journal of Psychiatry* 204(5): 346-353.
- Morgan CJA, Freeman TP, Hindocha C, et al. (2018b) Individual and combined effects of acute delta-9-tetrahydrocannabinol and cannabidiol on psychotomimetic symptoms and memory function. *Translational Psychiatry* 8 (181).

- Morrison P and Stone J (2011) Synthetic delta-9-tetrahydrocannabinol elicits schizophrenia-like negative symptoms which are distinct from sedation. *Human Psychopharmacology: Clinical and Experimental* 26(1): 77-80.
- Morrison PD, Zois V, McKeown D, et al. (2009) The acute effects of synthetic intravenous Δ 9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychological Medicine* 39(10): 1607-1616.
- Murray RM, Quigley H, Quattrone D, et al. (2016) Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry* 15(3): 195-204.
- Nunn JA, Rizza F and Peters ER (2001) The incidence of schizotypy among cannabis and alcohol users. *Journal of Nervous and Mental Disease* 189(11): 741-748.
- Olkin I (1995) Keynote addresses. Meta-analysis: Reconciling the results of independent studies. *Statistics in Medicine* 14(5-7): 457-472.
- Pertwee R (2008) The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ 9-tetrahydrocannabinol, cannabidiol and Δ 9-tetrahydrocannabivarin. *British Journal of Pharmacology* 153(2): 199-215.
- Raftery AE (1995) Bayesian model selection in social research. *Sociological Methodology* 25: 111-164.
- Raine A (1991) The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin* 17(4): 555-564.

- Ramaekers J, Theunissen EL, De Brouwer M, et al. (2011) Tolerance and cross-tolerance to neurocognitive effects of THC and alcohol in heavy cannabis users. *Psychopharmacology* 214(2): 391-401.
- Ramaekers J, Van Wel J, Spronk D, et al. (2016) Cannabis and tolerance: acute drug impairment as a function of cannabis use history. *Scientific Reports* 6: 26843.
- Schiffman J, Nakamura B, Earleywine M, et al. (2005) Symptoms of schizotypy precede cannabis use. *Psychiatry Research* 134(1): 37-42.
- Schoeler T, Petros N, Di Forti M, et al. (2016) Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. *The Lancet Psychiatry* 3(10): 947-953.
- Spriggs L and Hides L (2015) Patterns of cannabis use, psychotic-like experiences and personality styles in young cannabis users. *Schizophrenia Research* 165(1): 3-8.
- Stirling J, Barkus E, Nabosi L, et al. (2008) Cannabis-induced psychotic-like experiences are predicted by high schizotypy: Confirmation of preliminary results in a large cohort. *Psychopathology* 41(6): 371-378.
- Vadhan NP, Corcoran CM, Bedi G, et al. (2017) Acute effects of smoked marijuana in marijuana smokers at clinical high-risk for psychosis: A preliminary study. *Psychiatry Research* 257: 372-374.

- Van Wel J, Kuypers K, Theunissen E, et al. (2013) Single doses of THC and cocaine decrease proficiency of impulse control in heavy cannabis users. *British Journal of Pharmacology* 170(7): 1410-1420.
- Verdoux H, Gindre C, Sorbara F, et al. (2003) Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. *Psychological Medicine* 33(1): 23-32.
- Williams JH, Wellman NA and Rawlins JNP (1996) Cannabis use correlates with schizotypy in healthy people. *Addiction* 91(6): 869-877.
- Wilson BA (1993) Ecological validity of neuropsychological assessment: Do neuropsychological indexes predict performance in everyday activities? *Applied Preventive Psychology* 2(4): 209-215.

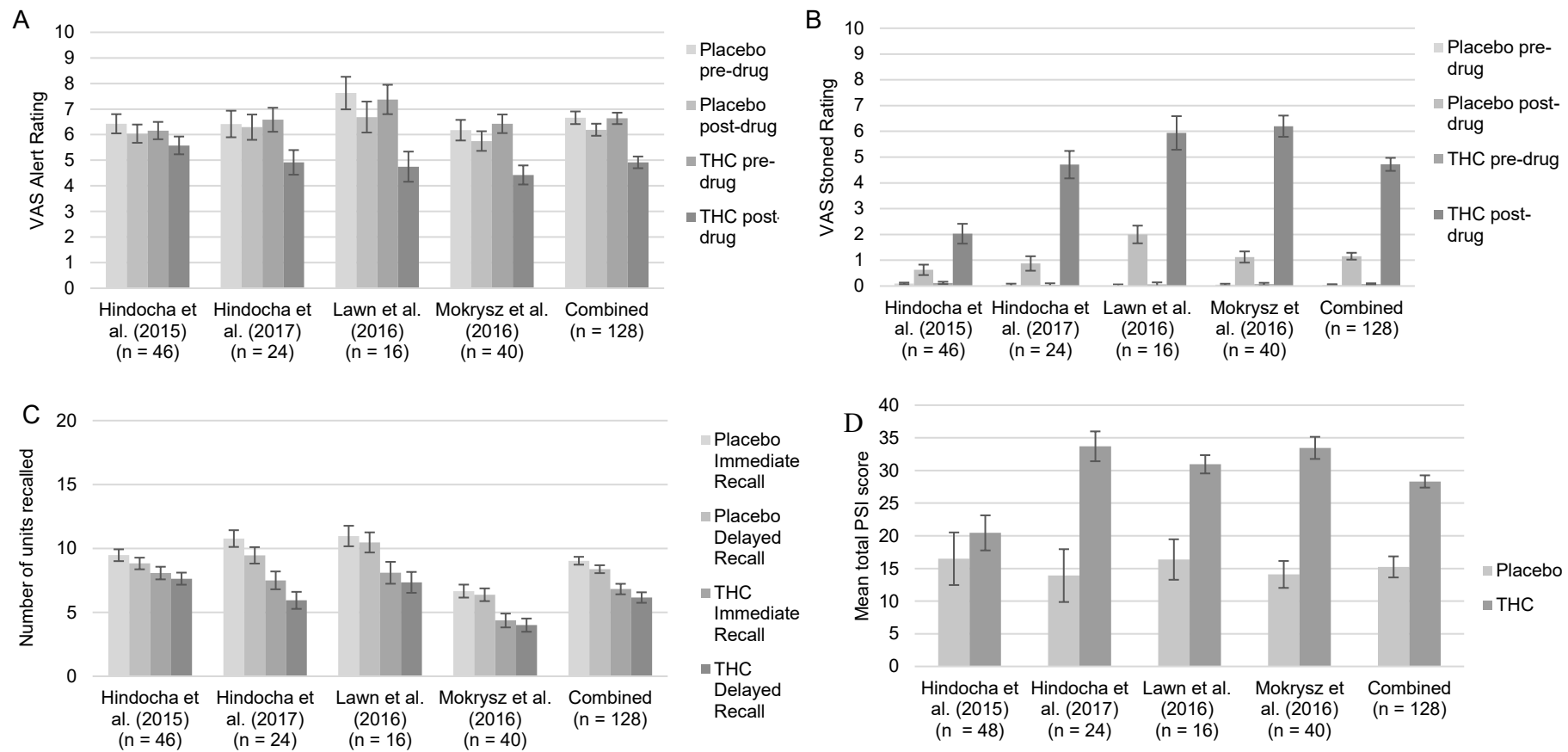


Figure 1. Means and standard errors for (A) anxiety VAS ratings, (B) stoned VAS ratings, (C) Prose recall task, (D) Psychotomimetic States Inventory score for Hindocha et al. (2015), Hindocha et al. (2017), Lawn et al. (2016), Mokrysz et al. 2016, and the combined sample.

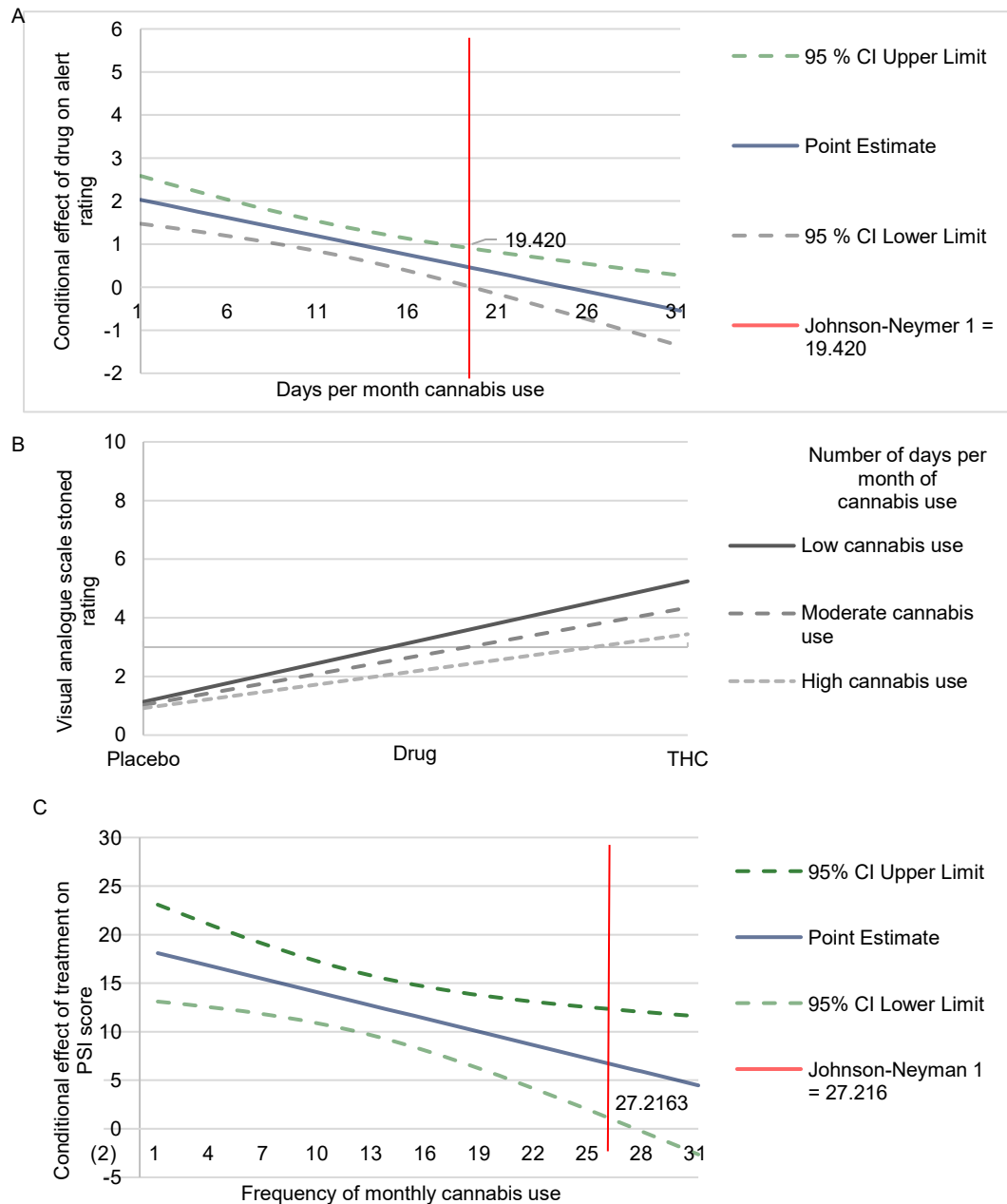


Figure 2 The conditional effects of THC on alert and stoned ratings and psychotomimetic state inventory (PSI) scores. A) illustrates the conditional effect of the drug effect on visual analogue scale ratings (VAS) for alert as a linear function of the number of days per month of cannabis use including the Johnson-Neyman (JN) transition point on alert ratings, which is displayed with the upper and lower confidence intervals at 95%. The JN-1 is where the confidence interval around the condition effect intersects zero on the y-axis. B) represents the conditional effect of the drug (placebo or THC) on stoned ratings amongst those who report the mean (moderate use $M = 12$ days) and one standard deviation above (high use $+SD = 21$ days) and below (low use $-SD = 3$ days), and high number of days per month of cannabis use. C) illustrates the conditional effect of drug on PSI score as a linear function of frequency of the number of days per month of cannabis use including the JN transition point.