Running Head: THC IMPAIRS VISUAL WORKING MEMORY

Δ^9-Tetrahydrocannabinol (THC) impairs visual working memory performance

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Abstract

With the sharply increasing prevalence of cannabis use and availability, there is an urgent need to identify cognitive impairments related to its use. It is widely believed that cannabis, or its main psychoactive component Δ^9-tetrahydrocannabinol (THC), impairs working memory, i.e., the ability to temporarily hold information in mind. However, our review of the literature yielded surprisingly little empirical support for an effect of THC or cannabis on working memory. We thus conducted a study with 3 main goals: (1) quantify the effect of THC on visual working memory in a well-powered sample (2) test the potential role of cognitive effects (mind wandering and metacognition) in disrupting working memory, and (3) demonstrate how insufficient sample size and task duration reduce the likelihood of detecting a drug effect. We conducted two double-blind, counterbalanced experiments in which healthy adults (*N=23, 23*) performed a sensitive and validated visual working memory task (the "Discrete Whole-Report task", 90 trials) after administration of THC (7.5 and/or 15 mg oral) or placebo. We also assessed self-reported 'mind wandering' (Exp 1) and metacognitive accuracy about ongoing task performance (Exp 2). THC impaired working memory performance (d = .65), increased mind wandering (Exp 1), and decreased metacognitive accuracy about task performance (Exp 2). Thus, our findings indicate that THC does impair visual working memory, and that this impairment may be related to both increased mind-\ wandering and decreased monitoring of task performance. Finally, we used a downsampling procedure to illustrate the effects of task length and sample size on power to detect the acute effect of THC on working memory.

Introduction

Cannabis and its main psychoactive constituent, Δ^9-tetrahydrocannabinol (THC), are widely believed to impair executive functioning needed to plan and achieve goals (for review, see 1). In particular, THC is believed to impair working memory, the mental workspace used to hold information "in mind" that is needed for everyday behaviors such as driving and problem solving[2,3]. Disruptions to working memory can thus disrupt ongoing behavior and lead to potentially negative outcomes, from the innocuous (e.g., forgetting that your turn-signal is on) to the dire (e.g., hitting the cyclist you forgot was in your blind-spot). Thus, understanding the acute effects of THC on working memory and cognition is of critical importance for public health and safety.

Despite the popular belief that THC impairs working memory, here we reviewed papers published on this topic from 1970 to 2019, and found that more than 70% of studies using the most commonly used working memory tasks failed to detect an effect of the drug ($p \geq .05$). Thus, it has been surprisingly difficult to demonstrate the effects of THC on working memory in controlled studies [4–9]. This finding is especially notable given the bias toward publishing 'positive' results [10–12], which should inflate the relative proportion of positive effects in the literature. This lack of empirical support for impairment of working memory after THC could indicate either that the drug truly has little effect, or that previous studies were limited, either because of insufficient sample sizes or insensitivity of the tasks. As cannabis and THC become more widely used for both medical and nonmedical purposes, it is critical to understand how the drug affects working memory and cognition.

The current study had three key goals which together test whether visual working memory is disrupted by THC, and if so, why and to what degree it is disrupted. First, we sought to characterize the effects of THC on working memory using a higher than typical number of trials and larger sample size (90 trials, combined $n = 46$). We measured working memory performance using a sensitive visual working memory task ("Discrete Whole Report"). In this task participants view 6 colored squares, attempt to remember them across a blank delay, and then freely recall the color-location pairing of all 6 squares [13,14]. Second, we tested visual working memory performance in relation to other ongoing cognitive processes, specifically increased mind wandering (Exp 1) and decreased metacognitive accuracy of task performance (Exp 2). Whereas mind wandering and decreased awareness of mind wandering are known to occur during nicotine withdrawal [15] and alcohol intoxication [16], little is known about the effect of THC on mind wandering during ongoing task performance. Finally, we examined previous studies on the effect of THC on working memory to determine whether previous failures to detect effects could be related to insufficient power. To this end, we combined our literature review with a down-sampling procedure on our own, well-powered sample (achieved power > .99) and found that with comparable sample sizes and task length to those used in the literature (e.g., 5 minute task, $n = 10$-15), we would have had insufficient power to reliably detect the impairment ($d = .65$) of working memory that we observed. Thus, we conclude that visual working memory performance is impaired under the influence of THC, and that this impairment may be related to mind wandering and poorer monitoring of ongoing task performance. We further conclude

that the majority of prior work has been underpowered to detect the effects of THC on working memory performance. Such power issues are likely typical of the literature, and more work is urgently needed to accurately quantify the effects of THC on other aspects of cognition.

Results

Subjective and physiological measures

THC produced its expected effects on physiological and subjective measures. THC (15 mg) increased heart rate, including at the time of the working memory test in both Exp 1, $t(21) = 3.55$, $p = .002$, $d = .76$, and Exp 2, $F(2,44) = 12.16$, $p = 6.3\text{x}10^{-5}$. Only 1 dose (15 mg) was used in Exp 1. In Exp 2 (15 mg , 7.5 mg), there was a linear effect of dose ($p = 2.3\text{x}10^{-5}$), but only the high dose was significantly different from placebo (high vs. placebo $p = 1.6\text{x}10^{-4}$, low vs. placebo $p = .25$). The drug did not affect systolic or diastolic blood pressure ($p > .3$). See SI Results for tables of all values. THC also increased scores on the "marijuana scale" of the ARCI ($p < .001$), and the "Feel" ($p < .001$), "Like" ($p \leq .005$), "Dislike" ($p \leq .03$), and "High" ($p < .001$) questions of the DEQ (Bonferroni-corrected for the 5 DEQ measures). The drug increased "Want more" ratings of the DEQ ($p = .002$; $p = .197$), and VAS measures "Sociable" and "Friendly" ($p < .05$, Bonferroni-corrected for 13 VAS measures) in Exp 1, but not Exp 2. See SI Results for tables of all values.

Mean working memory performance

We assessed visual working memory performance using the Discrete Whole-Report task [13,14]. In this task, participants briefly view (200 ms) an array of six brightly colored squares and remember the colors and locations of these squares across a blank delay (1,000 ms). At test, they report the color of all six squares. Working memory performance is measured as the average number of correctly recalled color-location pairings (out of 6) on each trial. THC impaired working memory performance relative to placebo in both Exp 1 (Fig 1A) and Exp 2 (Fig 1B). In Exp 1, participants correctly reported an average of 3.11 (SD = .49) items in the placebo condition and 2.77 (SD = .50) items in the 15 mg THC condition, $t(22) = 3.72$, $p = .001$, $d = .78$. In Exp 2, participants correctly reported an average of 3.02 (SD = .53) items in the placebo condition, 2.84 (SD = .44) items in the 7.5 mg THC condition, and 2.78 (SD = .54) items in the 15 mg THC condition, $F(1.52,33.42) = 4.58$, $p = .026$, $\eta_p^2 = .17$*. Although polynomial contrasts revealed a linear effect of dose in Exp 2 ($p = .005$), only the high dose was significantly different from placebo (placebo vs. high, $p = .018$; placebo vs. low, $p = .07$).

In a separate analysis, we combined the working memory performance data for Placebo vs. 15 mg THC in Exp 1 and Exp 2 , and observed the same main effect of THC on working memory performance (Fig 1C). A mixed ANOVA with within-subjects

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* Greenhouse-Geisser corrected values are reported whenever the assumption of sphericity is violated.

factor Drug and between-subjects factor Experiment revealed no main effect of Experiment, $F(1,44) = .52$, $p = .48$, $\eta_p^2 = .01$, and no interaction between Drug and Experiment, $F(1,44) = .52$, $p = .48$, $\eta_p^2 = .01$, so this combination of experiments is justified. This combination of experiments yields a total sample size of 46 subjects and a robust effect of Drug on working memory performance, Fig 1C, $t(45) = 4.43$, $p = 5.94 \times 10^{-5}$, $d = .65$. With this larger sample size, we quantified reliability, the effect of experimental block, and the effects of response number on both accuracy and response time. Task reliability (even-odd correlation) was excellent during both the placebo ($r = .91$) and the THC ($r = .90$) conditions, and individual differences in performance were preserved across the THC and Placebo conditions, as shown by a positive correlation (Fig 2A; $r = .63$, $p = 3.20 \times 10^{-6}$, 95% CI [.41, .78]).

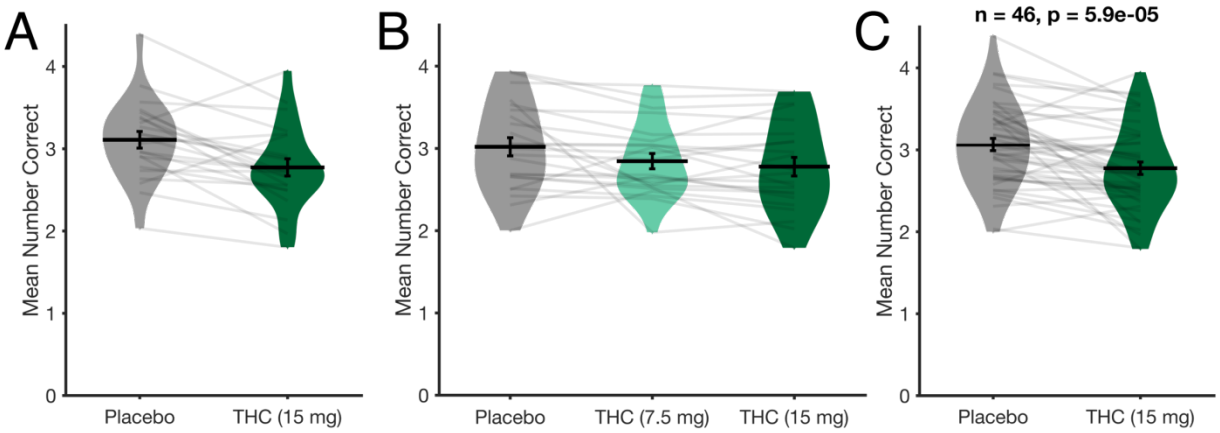

Fig 1. Mean working memory performance. Mean values for the number of items correctly identified in Exp 1 (A; N=23), Exp 2 (B; N=23) and the two experiments combined (C; N=46). Here and elsewhere, violin plots show the distribution of participants, black error bars represent 1 SEM, and transparent gray lines show individual participants. THC significantly reduced the number of remembered items in the 15 mg conditions.

Changes in working memory performance across experimental blocks and individual responses

To determine whether the effect of THC on working memory performance was related to a decline in effort or task engagement over the course of the experiment, we compared performance across the three blocks of the experiment (30 trials per block). The difference between THC and placebo scores was constant over time (Fig 2B). A repeated measures ANOVA with factors Drug and Block revealed no main effect of Block, $F(2,90) = 2.69$, $p = .074$, $\eta_p^2 = .06$, and no interaction between Drug and Block, $F(1.73,77.98) = 1.60$, $p = .210$, $\eta_p^2 = .03$.

To determine whether the effect of THC on working memory was related to careless responding and a speed-accuracy trade-off, we examined response time and accuracy for each response in the trial. Recall, participants were shown 6 items on each trial, and made 6 responses to report the remembered color of all items. If participants

were simply more careless at responding in the THC condition, then they may have responded quickly and with poor accuracy. Thus, if the THC-related working memory decrement is driven by a speed-accuracy tradeoff, we should observe faster response times for trials where participants showed lower accuracy. The empirical data did not support a speed-accuracy tradeoff account. Accuracy was overall lower in the Drug condition, particularly for the first three responses. There was a main effect of Drug, $F(1,45) = 19.64$, $p = 5.94\text{x}10^{-5}$, $\eta_p^2 = .30$, a main effect of Response Number, $F(2.44,109.58) = 909.07$, $p = 5.50\text{x}10^{-73}$, $\eta_p^2 = .95$, and an interaction between Drug and Response Number, $F(3.68,165.62) = 4.38$, $p = .003$, $\eta_p^2 = .09$. However, poorer accuracy was not associated with faster response times. Instead, response times were actually slower overall. A repeated measures ANVOA examining response times showed a main effect of Drug, $F(1,45) = 21.68$, $p = .014$, $\eta_p^2 = .13$, a main effect of Response Number, $F(1.13,50.99) = 1026.79$, $p = 1.08\text{x}10^{-36}$, $\eta_p^2 = .96$, and a significant interaction between Response Number and Drug, $F(1.13,50.64) = 11.61$, $p = 8.68\text{x}10^{-4}$, $\eta_p^2 = .21$.

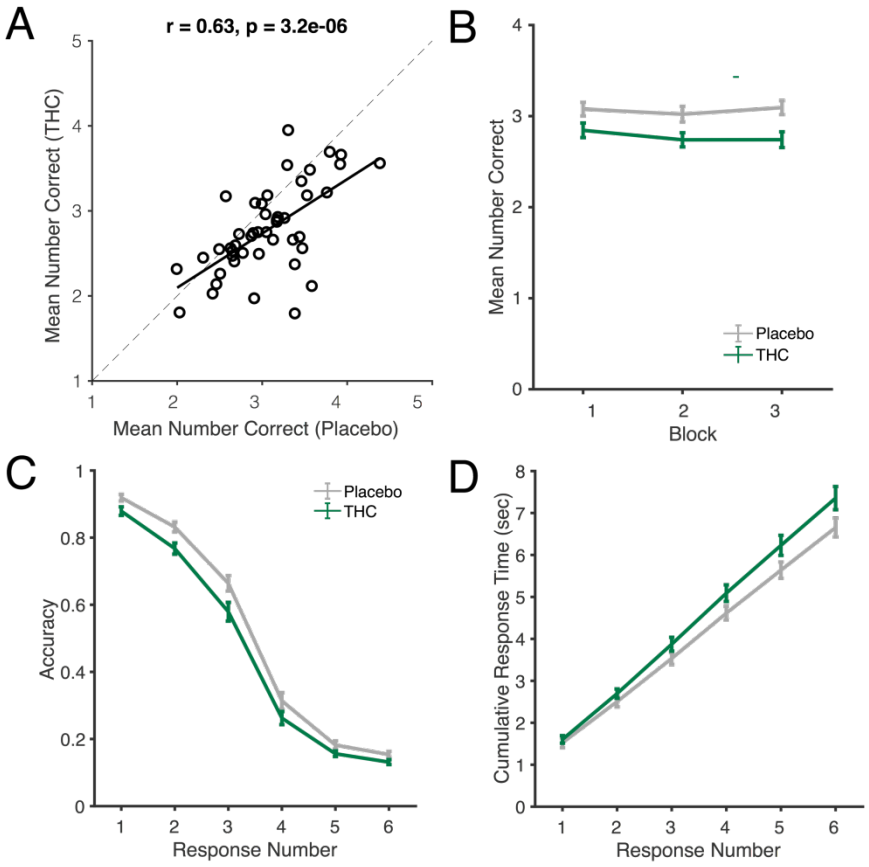

Fig 2. Illustrations of the effects of THC (15 mg) vs placebo on working memory performance (N=46, Exp 1 and Exp 2 combined). (A) Correlation between mean number correct on the working memory task after placebo and THC (15 mg) conditions. This shows that individual differences are reliable across the drug and placebo conditions, but that most individuals are impaired by the drug. (B) Mean number of items correctly identified during the three blocks of the task after placebo and THC (15

mg). Performance was consistently poorer after THC across all three blocks. (C) Working memory performance as a function of response number and drug. Responses were overall less accurate for THC versus placebo, particularly early in the trial. (D) Cumulative response time as a function of response number and drug indicates that impaired performance was not due to a speed-accuracy tradeoff; participants were overall slower for THC versus placebo.

Effects of THC on mind wandering during the task (Exp 1).

In Exp 1 only, we used "thought probes" to assay the contents of participants' thoughts while performing the working memory task. Participants were asked after a random 20% of trials about the contents of their current thoughts, which were categorized as, 'On-Task', 'Mind Wandering' or 'Zoning Out' (Fig 3A). THC significantly reduced reports of being On Task $t(22) = 5.08$, $p = 4.38\text{x}10^{-5}$, $d = 1.06$. and increased frequency of both Mind Wandering $t(22) = 4.42$, $p = 2.15\text{x}10^{-4}$, d = .92, and Zoning Out, $t(22) = 2.13$, $p = .044$, $d = .45$. In a separate ANOVA looking at the drug's effects on type of mind wandering (Past, Future, Other, or "I Don't Know"), there was no interaction between Drug and Mind Wandering Type, $F(3,48) = 2.49$, $p = .07$, $\eta_p^2 = .135$.

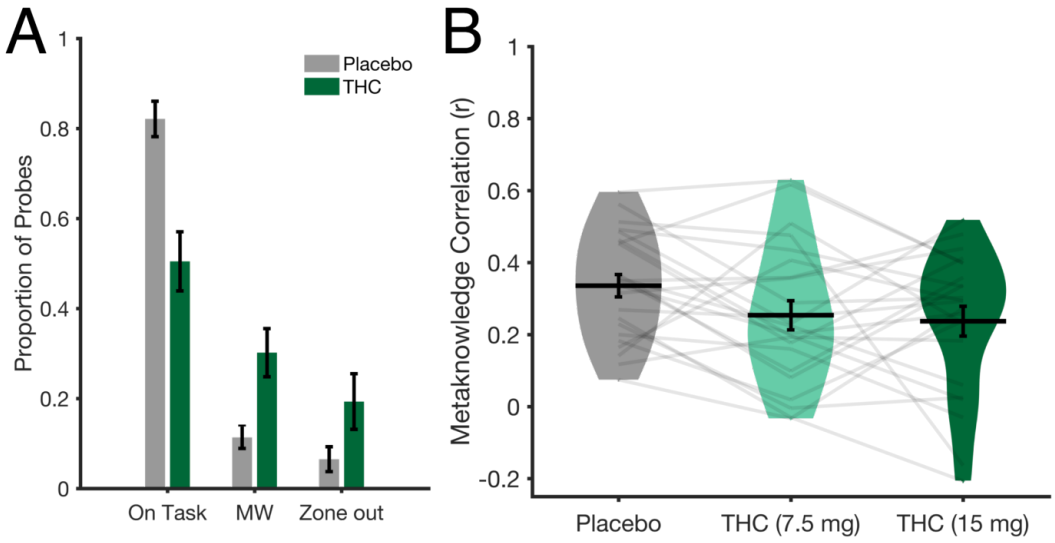

Fig 3. Changes to mind wandering and metacognitive accuracy after THC or placebo. (A) Mean changes to the distribution of thought probes in Exp 1 (placebo or 15 mg; n = 23). MW = Mind Wandering. Error bars represent 1 SEM. (B) Mean changes to metacognitive accuracy in Exp 2 (placebo, 7.5 and 15 mg; n = 23).

Effect of THC on metacognitive accuracy (Exp 2).

In Exp 2 only, we examined subjects' ability to accurately monitor ongoing task performance (i.e. metacognitive accuracy), by providing confidence ratings for each response. On each trial, participants made binary confidence judgments (i.e. "confident" or "guess") about each of their 6 responses. To measure metacognitive accuracy, we calculated the correlation between the number of *correct items* on each trial and the number of *confident responses* on each trial (separately for each individual using Spearman's *r*). Higher, positive correlation values correspond with more accurate

monitoring of task performance (e.g., the participant got N correct and reported N confident responses). We tested whether metacognitive accuracy declined as a function of Drug. A repeated measures ANOVA with factors Drug and Dose revealed a main effect of Drug, $F(2,44) = 3.43$, $p = .04$, $\eta_p^2 = .14$. Consistent with the impairment to overall performance, post-hoc *t*-tests for each dose revealed that this measure of metaknowledge was impaired for the high dose ($p = .03$) but not the low dose ($p = .07$).

Literature review and power analysis

We conducted a review of acute effects on working memory performance (SI Results). Here, we focus on studies using a single task that is routinely administered, the Digit Span (Forward and/or Backward). We found 15 publications [17–31] with a total of 57 experimental conditions which examine the acute effect of THC on Digit Span. Although the Digit Span task has been widely used, we found that the drug had no effect on this task in more than 70% (73.68%) of the conditions tested (Fig 4A). A lack of sensitivity was evident for both Forward and Backward span, as well as other working memory tasks, such as Spatial N-Back (SI Results). The lack of effect was observed in studies using a range of doses including higher doses than what was used here, and multiple modes of administration (Table S1). The apparently weak effect of THC on working memory could indicate that the drug does not affect performance but, alternatively, it could reflect a lack of power in most prior studies. Although it was not possible to calculate effect sizes for the reviewed studies, we were able to demonstrate the effects of task time and sample size on power new empirical data.

To test whether the distribution of *p*-values in the literature review was related to insufficient statistical power or a lack of an effect of THC on working memory performance, we performed a down-sampling procedure [32] on the data from Exp 2 (15 mg THC; n = 46, trials = 90). When we reduced the sample size and task length of our dataset to match those in the literature, we could nearly perfectly predict the distribution of p-values that was observed in the literature.

With 46 subjects and 90 trials per subject, the achieved power ($1 - \beta$) for our main effect of THC on working memory performance was in excess of 0.99. Fig 1B reveals the results of iterative down-sampling of this data (e.g. randomly choosing N subjects and T trials, calculating power). Each cell in this figure contains the average power for 250 random iterations. When down-sampling to a typical sample size and task duration for the literature (e.g. 15 subjects, 5 min task time), power plummets to only 0.47. In Figs 4C and 4D, we have plotted the distribution of *p*-values for Digit Span studies above and below the median sample size found in the literature. To compare predictions from our down-sampling procedure, we chose the cell from Fig 4B that most closely matched the number of subjects (5 subjects, 15 subjects), and then discretized the p-value outcomes for each of the 250 iterations (<.001, <.01, <.05, or n.s.). The digit span task takes approximately 4 – 5 minutes, corresponding to approximately 15 trials of the whole-report task. As shown in Fig 4, with 5 minutes of task time and fewer subjects per “experiment”, we obtain distributions of *p*-values that are nearly identical to those in the empirical literature (Fig 4C, 4D).

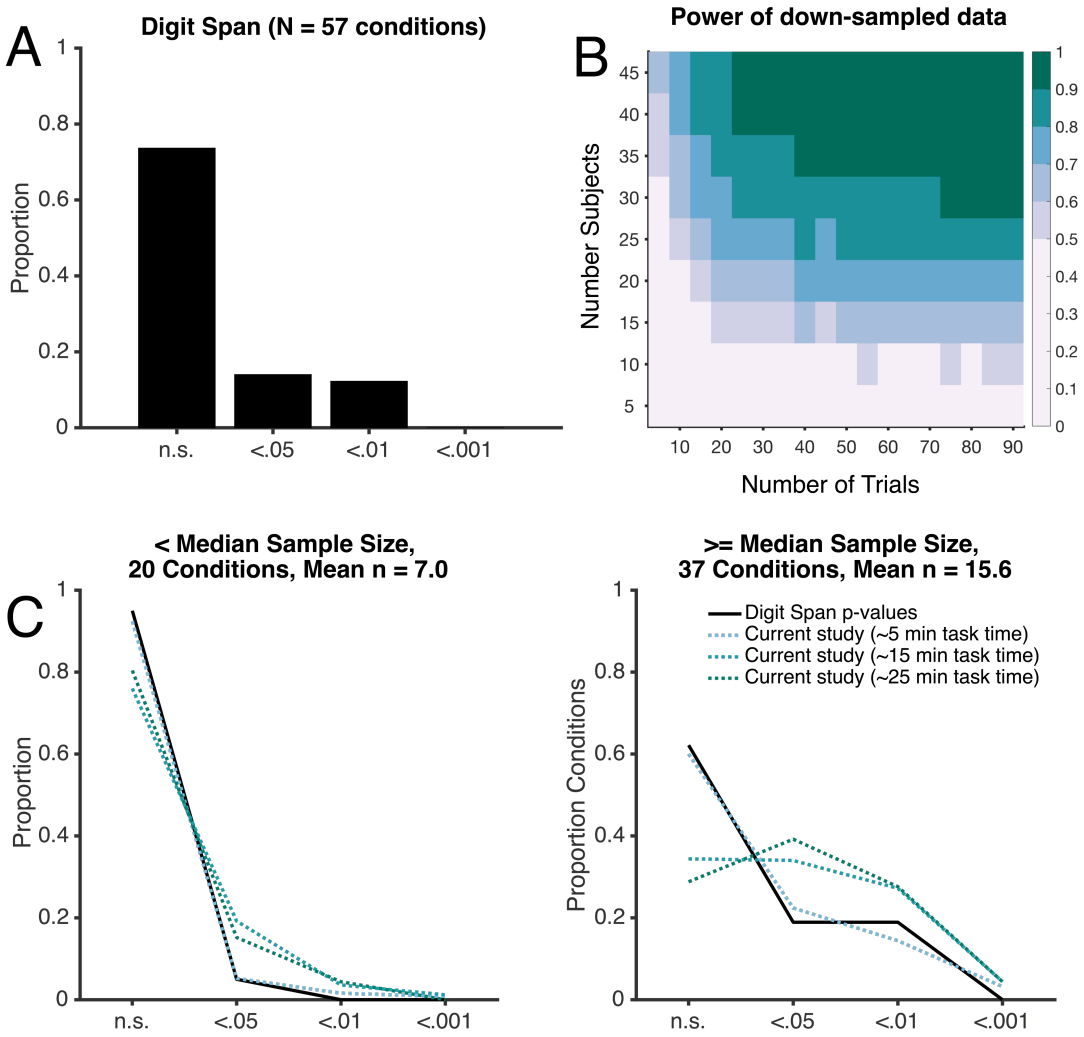

Fig 4. Power analysis predicts the distribution of *p*-values for published studies. (a) Histogram of reported *p*-values for 57 conditions of forward- and backward-digit span. (b) Down-sampling analysis of the current data. Each factorial combination of trial number (x-axis) and sample size (y-axis) contains the average power of 250 iterations sampled from the full data-set (collapsed across Exp 1 and the 15 mg of THC condition in Exp 2) (c-d) The black line shows the distribution of digit span *p*-values from the literature for conditions with fewer (c) or more (d) than the median number of subjects. Dotted lines show that this distribution of *p*-values from sampling the current visual working memory dataset with equivalent, insufficient power (e.g. 7 subjects and 5 min task time)

Discussion

The present study demonstrated that single, moderate doses of THC impair working memory, when tested under rigorous, placebo-controlled, double-blind conditions. THC, the main psychoactive constituent in cannabis, is commonly thought to impair working memory, but this effect has been difficult to demonstrate in controlled studies. We review previous studies assessing the effects of THC, and conclude that

the failures to detect effects were most likely due to inadequate statistical power. Using a well-powered sample (combined $n = 46$, $[1-\beta] > .99$), we found that single doses of THC reliably impair visual working memory, and further that the drug increases self-reports of mind wandering and decreases meta-awareness of task performance.

Here, we demonstrated that single moderate doses of THC impair visual working memory in human observers. Future work is needed to understand the mechanisms underlying this effect of THC on working memory deficits, the effects of repeated exposure to the drug, exposure at a young age, and effects in people with clinical disorders. For example, disruption to working memory is a key cognitive deficit in people with schizophrenia [33], and this deficit is hypothesized to be related to disruptions of the endocannabinoid system [34], more specifically to the dorsolateral prefrontal cortex (DLPFC)[35–37], but see [38]. The DLPFC is laden with CB1 receptors, the primary target of THC, and is a critical component of WM maintenance [39–41]. Studies of the neural mechanisms underlying WM disruption under the effects of THC may thus provide a reversible demonstration of WM deficits related to disruptions of the endocannabinoid system.

Subjective thought probes revealed that THC increased rates of mind wandering (Exp 1) and decreased accuracy of performance monitoring (Exp 2). To our knowledge, our work provides the first demonstration of THC's effects on mind wandering during a concurrent cognitive task. These finding are consistent with prior work on THC, including task-independent reports of mind wandering in structured interviews [42,43], failure to de-activate the default mode network during task performance [44], and decreased error monitoring [45]. Similar to the effects of nicotine cravings [15] and alcohol [16], THC appears to increase mind wandering and decrease awareness of task performance. These broad effects on conscious experience are likely to drive performance decrements in a broad range of cognitive tasks.

Choice of working memory task

One major difference between our study and prior studies assessing effects of THC on working memory performance is the specific task used. The tasks most commonly used in previous studies are the digit span task or a spatial *n*-back task. Our down-sampling analysis suggests that the effect size of working memory disruption in these tasks is similar to that observed in the present study (as we could accurately predict the digit span task's p-value distribution when matching sample size and task length), but those tasks may not be best suited to detect drug-induced impairments. We will briefly comment on our choice of task.

Although simple span and n-back tasks are quick and widely recognized, they may have some disadvantages for measuring deficits to working memory storage. Most critically, based on our down-sampling analysis, we believe that the very short task length of digit span (forward and backward conditions, <5 min) critically reduces its sensitivity. In addition, simple span tasks (e.g., the forward digit span condition) load onto a general working memory factor at the latent level [46] relatively weakly, and typically do not predict individual differences in general fluid intelligence [47–51], but also see [52]. *N*-back tasks correlate somewhat weakly with other working memory

tasks [53–55] and have relatively poor statistical reliability [51], potentially making it difficult to detect effects across treatment conditions. On the other hand, *n*-back tasks still load well onto a general WM factor at the latent level [46] and are particularly useful for investigating the executive function component of WM (vs. the storage component).

Here, we used the "Discrete Whole-Report" task, a visuospatial working memory task in which participants encode many items simultaneously and recall them at test. This and similar visuospatial working memory tasks are reliable [32,56], correlate well with other measures of working memory [46,47], and predict individual differences in general fluid intelligence [47]. Thus, we believe that visuospatial working memory tasks (i.e., whole-report, partial-report, and change detection) are well-suited for characterizing deficits in the ability to temporarily store information in mind. In addition, the short trial length of these tasks makes them well-suited for future neural studies that will help to deepen our understanding of the mechanisms underlying THC's effects on working memory performance, and the relatively simple nature of these tasks allows for direct comparisons in performance of humans and non-human primates [57].

Limitations and implications for future studies of THC and cognition

There in an intense public interest in the effects of cannabis on cognition and an urgent need for practical information that will guide use. Our findings offer important new leads on how the drug affects memory, but the studies also had limitations and suggest future avenues for research. First, we were able to test working memory at only one, relatively late time-point after oral consumption of a THC capsule (160 – 220 minutes), and at two moderate doses. It will be important to characterize the effects of THC on working memory performance over the full time-course of the drug, and, importantly when it is taken at higher doses and by different routes of administration (especially smoked and vaped). Second, we need more information on the severity of working memory disruption and the extent to which the effect depends on initial performance. Although the effect we observed was relatively large (d = .65), this effect is smaller than, for example, normal variation in working memory performance across individuals. The behavioral performance difference between the placebo and drug conditions was 0.29 items, but the difference between the top- and bottom-half of individuals within the placebo condition was .80 items. Further, the effects of the drug may be especially pronounced in certain at-risk populations, including those with initially poor working memory performance.

Our literature search revealed the importance of statistical power in studies of THC on cognition. Here, we used one relatively long task (~30 minutes, 90 trials). In contrast, many earlier studies used several shorter tasks (e.g. ten 3-minute tasks), presumably to assess a range of potential deficits. However, because task time and statistical power have direct tradeoffs, this approach may miss important effects. Similar problems of inadequate power may exist in other studies of effects of drugs on working memory and other aspects of cognition. Thus, we recommend that longer tasks be used to determine the effects of drugs on cognition.

Methods

Participants

Healthy occasional cannabis users, aged 18-35, were recruited for the study. Screening included a physical examination, an electrocardiogram, and a semi-structured interview by a clinical psychologist. Exclusion criteria included any current Axis I DSM-IV disorder including substance dependence, current use of >5 cigarettes per day, history of psychosis or mania, less than a high school education, lack of English fluency, a body mass index outside 19-33 kg/m2, high blood pressure (>140/90), abnormal electrocardiogram, daily use of any medication other than birth control, pregnancy, or lactating. Participants were eligible if they reported having used cannabis at least 4 times, but no more than 100 times (Exp 1) or daily (Exp 2). We enrolled 24 participants in Exp 1 (12 female; M = 23.0 years old, SD = 3.6) and 24 in Exp 2 (12 female; M = 23.4 years old, SD = 4.3), but one participant was excluded from each study because of poor behavioral performance (>3 SDs below the mean). Procedures were approved by the University of Chicago Institutional Review Board, and participants provided written, informed consent.

Drug

THC (15 mg Exp 1; 7.5 or 15 mg Exp 2; Marinol®; Solvay Pharmaceuticals) was placed in opaque, size 00 capsules with dextrose filler. Placebo capsules contained only dextrose. These doses produce reliable subjective and cardiovascular effects without adverse effects [19,58].

Design

Both experiments used double-blind, within-subjects, counterbalanced designs. In both experiments, sessions were conducted at least 1 week apart, in a laboratory setting. Subjects were screened for recent drug use and pregnancy before each session. The drugs (THC 15 mg or placebo in Exp 1; placebo 7.5 and 15 mg in Exp 2) were administered in mixed order under double-blind conditions. On each session participants performed a discrete whole-report working memory task [13,14,59] and completed questionnaires regarding drug effects and self-reports of their level of concentration (Exp 1) or their level of performance (Exp 2). In Exp 1, participants also performed a long-term memory task that was reported by Doss and colleagues [60]. In Exp 2, participants also performed a cognitive test battery that was reported by Pabon and colleagues [61].

Procedures

Pre-session. During an orientation session subjects received instructions, signed a consent form, and practiced the tasks. They were instructed to consume their normal amount of caffeine and nicotine, but to abstain from alcohol, prescription drugs (except contraceptives), over-the-counter-drugs, cannabis, and other illicit drugs for at least 48 hours before session. Participants were informed that they would be tested for recent drug use at the beginning of each session, and positive tests would result in rescheduling or dismissal. Finally, they were advised to get their normal amounts of

sleep and to not eat for 2 hours prior to each experimental session. To minimize expectancy effects, participants were informed that they may receive a stimulant, sedative, cannabinoid, or placebo during the sessions.

Experimental sessions. At the beginning of each laboratory visit, subjects provided breath and urine samples for breath alcohol level (Alco-sensor III, Intoximeters, St. Louis, MO), a urine drug test (ToxCup, Branan Medical Co., Irvine, CA), and a pregnancy test (females only; Aimstrip, Craig Medical, Vista, CA). Those testing positive were rescheduled or dropped from the study. Baseline cardiovascular and mood measures were also taken, and participants consumed the capsule (placebo or THC, double-blind). During the first 120 min, participants relaxed with magazines and music (but were not allowed to eat, sleep, work, or browse the internet) while the drug was absorbed. Cardiovascular and mood measures were taken approximately every 30 minutes during this baseline absorption period and at multiple points during the cognitive testing period.

Cognitive testing began at 120 min. Before performing the working memory task, participants completed other cognitive tests. In Exp 1, participants completed long-term memory tasks for stimuli they had encoded 48 hours earlier (SI Methods) as previously reported in [60]. In Exp 2, participants completed a series of cognitive tasks on a desktop computer and on a mobile phone [61]. The working memory task was performed at around 160 min post-capsule in Exp 1 (M = 159.4, SD = 14.5, Range = [126,193]) and around 220 min post-capsule in Exp 2 (exact time not recorded).

Physiological and Subjective Measures

Heart rate and blood pressure were measured with portable monitors in Exp 1 (A&D Medical/Life Source, San Jose, CA) and Exp 2 (Omron 10 Plus, Omron Healthcare). Cardiovascular measures were taken at baseline (immediately preceding capsule administration) and at 30, 60, 90, 120, 190 and 210 min post-capsule in Exp 1, and at baseline and at 30, 60, 90, 150 and 240 min post-capsule in Exp 2. Subjective measures were taken at the same time-points as the cardiovascular measures, with the exception that the 210 minute time point was not collected in Exp 1. Exp 1 included the Addiction Research Center Inventory [ARCI] [62,63], the Visual Analog Scales [VAS] [64], and the Drug Effects Questionnaire [DEQ] [65], and the End of Session Questionnaire (ESQ; given only at end). Exp 2 included only the ARCI and DEQ. See SI Methods for more details.

Working Memory Task

In both Experiments, participants performed 90 trials (3 blocks of 30) of a discrete whole report task [13,14]. On each trial, participants briefly viewed (200 ms) an array of 6 brightly colored squares, and remembered the colors and locations of the squares across a blank delay (1,000 ms). Colors for each trial were chosen without replacement from a set of 9 highly-discriminable colors [14]. At test, “response grids” appeared at each location (3x3 grid of all 9 colors). Participants freely recalled the color-location pairing of each item by clicking the color in each response grid that

corresponded to the color remembered at that location. They were required to make a response to all 6 squares before moving on to the next trial.

Task-Unrelated Thoughts. In Exp 1, participants were occasionally probed (20% of trials) about the contents of their thoughts at the moment of the probe. Participants could choose between the categories of "on task", "mind wandering", or "zoning out". If mind wandering, they were asked to further classify whether their mind had wandered toward the future, the past, "other", or "I don't know". Participants were given instructions and examples of each category during the orientation pre-session.

Item-level Confidence Judgements. In Exp 2, participants made a binary confidence judgement for each response. If they felt they had "some information" in mind about the item, they should click the color with the left mouse button. If they felt they had "no information" in mind, they should click the color with the right mouse button. The number of confident items was calculated for each trial by summing the number of left click responses (out of 6).

Statistical Analysis

To assess subjective and physiological measures at the time of the working memory test, we calculated a change score from baseline (timepoint immediately before consuming the capsule). In Exp 1, we used the time-point closest in time to the WM test (120 min for 4 participants who started the WM task at ~130 min; 190 min for remaining participants who started the WM test at 160 min). In Exp 2, we used the time-point immediately following the WM Test (240 min). In Exp 1, one participants' heart rate and blood pressure could not be collected due to device malfunction, leaving 22 participants, and one participants' subjective measures could not be collected due to a computer malfunction, leaving 22 participants.

Significance of placebo versus THC (15 mg) in Exp 1 was tested by paired *t*-test (2-tailed) of the 2 conditions. Significance of a THC effect in Exp 2 was tested by 1-way Repeated Measures ANOVA, with the within-subjects factor Drug containing 3 levels (Placebo, 7.5 mg THC, 15 mg THC).

Literature Review and Power Analysis

We reviewed the literature to find within-subjects, randomized, placebo-controlled studies testing the acute effect of THC on working memory performance (SI Methods). By far the most common test of working memory was the Digit Span (Forward/Backward) Task. We found 15 papers meeting our inclusion criteria that reported the results of a standard Digit Span task [17–31]. Together, these papers reported a total of 57 different conditions that were tested (e.g. Forward vs. Backward span, differing doses of THC). We did not include conditions from papers that reported only combined Digit Span [66], or conditions measuring Digit Recall instead of Span [67–71]. These and other tasks show consistent patterns, but we chose to focus on only Digit Span conditions for our core arguments because this task (1) is the single most-used task and (2) is administered in a highly consistent manner. See SI Results for the p-values across conditions for other working measures in the literature.

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