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Evaluation of divided attention psychophysical task performance and effects on pupil sizes following smoked, vaporized and oral cannabis administration

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ABSTRACT: Establishing science-based driving *per se* blood Δ^9-tetrahydrocannabinol (THC) limits is challenging, in part because of prolonged THC detection in chronic, frequent users. Therefore, documenting observable signs of impairment is important for driving under the influence of drugs. We evaluated frequent and occasional cannabis smokers' performance on the modified Romberg balance, one leg stand (OLS), and walk and turn (WAT) tasks, and pupil size effects following controlled placebo (0.001% THC), smoked, vaporized and oral (6.9% [~50.4 mg] THC) cannabis administration. Significant effects following inhaled doses were not observed due to delayed tasks administration 1.5 and 3.5 h post-dose, but significant impairment was observed after oral dosing (blood THC concentrations peaked 1.5–3.5 h post-dose). Occasional smokers' odds of exhibiting ≥2 clues on the OLS or WAT following oral dosing were 6.4 (95% CI 2.3–18.4) times higher than after placebo, with THC and 11-hydroxy-THC blood concentrations individually producing odds ratios of 1.3 (1.1–1.5) and 1.5 (1.3–1.8) for impairment in these tasks, respectively. Pupil sizes after oral dosing under the direct lighting condition were significantly larger than after placebo by mean (SE, 95% CI) 0.4 (0.1, 0.2–0.6) mm at 1.5 h and 0.5 (0.2, 0.2–0.8) mm at 3.5 h among all participants. Oral cannabis administration impaired occasional cannabis users' performance on the OLS and WAT tasks compared to placebo, supporting other reports showing these tasks are sensitive to cannabis-related impairment. Occasional smokers' impairment was related to blood THC and 11-hydroxy-THC concentrations. These are important public health policy findings as consumption of edible cannabis products increases. Published 2017. This article is a U.S. Government work and is in the public domain in the USA.

Keywords: cannabis; Drug Evaluation and Classification Program; modified Romberg balance; one leg stand; walk and turn; pupil size; performance; edibles

Introduction

Cannabis prevalence among US weekend night-time drivers increased 48% from 2007 to 2013–2014 (Berning *et al.*, 2015). Increasing cannabis use among drivers poses a public health and safety risk due to an increased crash risk (Asbridge *et al.*, 2014; Hartman & Huestis, 2013; Li *et al.*, 2012; Ramaekers *et al.*, 2004). Establishing science-based *per se* limits for blood Δ^9-tetrahydrocannabinol (THC) is difficult, in part, due to prolonged THC detection following chronic, frequent intake; THC was detected at 0.3 μg l^{-1} in some chronic frequent cannabis smokers' blood 30 days after initiation of abstinence (Bergamaschi *et al.*, 2013). In other frequent cannabis users, blood THC was >1 μg l^{-1} up to 6.5 days after last reported use, and in some, THC was ≥5 μg l^{-1} (one currently implemented *per se* cutoff) up to 5.4 days after last reported use (Odell *et al.*, 2015). Another contributing factor is that THC rapidly distributes from blood. After vaporized cannabis administration to occasional-to-moderate smokers, maximum blood THC concentrations decreased a median 73.5% within 0.5 h post-dose and 90.3% by 1.4 h, with median concentrations <5 μg l^{-1} by 3.3 h post-dose (Hartman *et al.*, 2016d). Rapid decreases were similarly observed in frequent smokers (Newmeyer *et al.*, 2016), quickly returning to baseline concentrations. These factors contribute to the difficulty in relating blood THC concentrations to impairment.

When an officer stops an individual suspected of driving under the influence (DUI), standardized field sobriety tests (e.g., horizontal gaze nystagmus, walk and turn [WAT] and one leg stand [OLS]) are performed, leading to arrest if impairment is observed. If impairment based on standardized field sobriety test observations is not consistent with the suspect's blood alcohol concentration or the officer is unsure of naming an impairing agent, a drug recognition expert (DRE) evaluation may be requested. The DRE utilizes a standardized 12-step procedure combining physiological,

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psychophysical and observational evidence to form an opinion on which drug class(es) (central nervous system depressants, central nervous system stimulants, hallucinogens, dissociative anesthetics, narcotic analgesics, inhalants and cannabis) contribute(s) to the impairment.

Smoked cannabis can produce impairment on tasks associated with driving performance (Ramaekers *et al.*, 2006), with an approximate twofold increase in risk of involvement in a motor vehicle crash (Hartman & Huestis, 2013); however, partial tolerance to some impairing effects was demonstrated in frequent cannabis smokers (Desrosiers *et al.*, 2015; Hart *et al.*, 2001; Ramaekers *et al.*, 2009; Theunissen *et al.*, 2012). Following cannabis vaporization, an alternative inhalation route, occasional-to-moderate cannabis smokers demonstrated increased standard deviation of lateral position (lane weave), similar to impairing alcohol concentrations, with during-drive blood THC $\geq$8.2 $\mu g\ l^{-1}$ (Hartman *et al.*, 2015), while also demonstrating slower driving and greater headway (distance relative to a lead vehicle) (Hartman *et al.*, 2016a). Following various oral cannabis doses, the percentage of time spent in a pre-defined lane on a computerized tracking task was decreased (Ménétrey *et al.*, 2005). In another investigation, oral dronabinol increased the standard deviation of lateral position and time to speed adaptation in occasional smokers (Bosker *et al.*, 2012a). Oral THC produces delayed subjective and impairing effects and these are dependent on administered dose(s). Additionally, lower THC concentrations occur following oral dosing compared to inhaled cannabis. There is great uncertainty in THC content of commercial edible cannabis products, with 23% and 60% of tested products under-labeling and over-labeling THC content, respectively (Vandrey *et al.*, 2015). This is concerning as cannabis-containing edibles also are taken as medical cannabis and doses may be subtherapeutic, and because consumers may experience adverse effects if doses are larger than reported.

We sought to evaluate frequent and occasional cannabis users' performance on tasks from the Drug Evaluation and Classification Program (DECP) following controlled administration of placebo, smoked, vaporized and oral cannabis; chosen tasks previously demonstrated sensitivity to cannabis-related impairment (Bosker *et al.*, 2012b; Heishman *et al.*, 1996, 1998). The complex full study timeline only permitted psychophysical examinations at 1.5 and 3.5 h. Improving interpretation of observed DUI of drugs (DUID) impairment signs is critical, given the difficulty in establishing appropriate science-based *per se* THC limits for both occasional and frequent cannabis users and establishing relevant public health policy and legislation.

Materials and methods

Participants

Adults 18–50 years old provided written, informed consent to participate in this National Institute on Drug Abuse (NIDA) Institutional Review Board-, Federal Drug Administration- and Drug Enforcement Administration-approved study (Newmeyer *et al.*, 2016; Swortwood *et al.*, 2016). Inclusion criteria were the average self-reported cannabis intake frequency $\geq$ 2× per month but <3× per week (occasional smokers), or $\geq$5× per week (frequent smokers) for the previous 3 months, and a positive urine cannabinoid screen (frequent smokers). All participants underwent extensive medical and psychological evaluations before the study inclusion; anyone physically dependent on any drug other than cannabis, caffeine or nicotine or who could or would not discontinue use of contraindicated medications during the study were excluded.

Study design

This was a randomized, double-blind, placebo-controlled, crossover, double-dummy study. Participants entered the secure research unit ~19 h before dosing to preclude acute intoxication. Cannabis cigarettes were supplied from NIDA Research Technology Branch. Active (0.734 ± 0.05 g) and placebo (0.713 ± 0.05 g) cigarettes contained 6.9 ± 0.95% (~50.6 mg) and 0.001 ± 0.000% THC, respectively. Oral cannabis doses were prepared per Duncan Hines® Double Fudge cake-like brownie instructions. The contents of an active or placebo cigarette were ground, baked for 30 min at 121°C in aluminum foil, and mixed into equal portions of batter in a muffin tin. Following baking, individual doses were stored frozen, but allowed to thaw refrigerated overnight before dosing.

The study timeline is summarized in Fig. 1. Throughout four dosing sessions, participants were administered one active or placebo cannabis-containing brownie followed by one active or placebo cigarette or one active or placebo vaporized ground cannabis dose (210°C; Volcano® Medic; Storz & Bickel, Tuttlingen, Germany). Only one active dose was administered per session. Participants consumed the oral and smoked or vaporized dose ad libitum for 10 min. Frequent smokers remained on the unit 72 h post-dose and left the unit for $\geq$72 h between sessions to minimize withdrawal symptoms. Occasional smokers remained on the unit 54 h post-dose, but could stay or leave between sessions if dosing was no more frequent than self-reported intake. Previous controlled cannabis studies informed our choice of time between sessions for occasional cannabis users (Desrosiers *et al.*, 2014; Schwope *et al.*, 2011). Blood was collected on admission (if applicable) and at baseline of every session for proper result interpretation.

Psychophysical evaluations

Psychophysical tests challenge the ability to divide attention between remembering directions while performing a physical

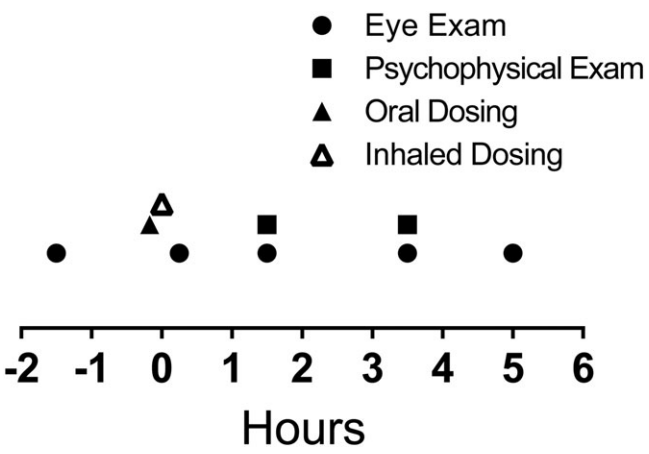

Figure 1. Summary of study procedures, including times of placebo (0.001% THC) or active (6.9% THC, ~50.6 mg) smoked and vaporized (inhaled) and oral cannabis administration, psychophysical exams (modified Romberg balance, one leg stand, and walk and turn), and eye exams. THC, Δ^9-tetrahydrocannabinol.

task. A certified DRE trained research staff on administering modified Romberg balance (MRB), OLS and WAT tests. Descriptions of the tasks and the impairment clues or observations are summarized in Table 1. Observation of ≥2 clues is the DRE "impairment" criteria, originally validated for 0.08% blood alcohol concentrations (Stuster, 2006). Owing to constraints on the busy study timeline and the required time for the psychophysical task presentation, the tests were administered 1.5 and 3.5 h post-dose.

Eye examinations

The cannabis' effects on pupil size and lack of convergence (LOC; inability to cross the eyes while focusing on a stimulus slowly approaching the bridge of the nose) were examined with the DAX™ Evidence Recorder (Ocular Data Systems LLC, Pasadena, CA, USA). The DAX recording device enables pupil size observation and video recording in room light (RL), near-total darkness (NTD) and direct light (DL). The goggle-like frame is placed against the participants' face and a pupilometer is centered between the eyes for measurement. After recording RL pupil size, a light-blocking cover was placed on the device to produce NTD, and an infrared camera enabled NTD pupil size measurement. A built-in light was shown separately into each eye for pupil measurement under DL. The cover and pupilometer were removed to evaluate LOC. Eye examinations were performed at baseline (−1.5 h) and 0.25, 1.5, 3.5 and 5 h post-dose.

Data analysis

Differences in demographic data between groups were evaluated with independent samples *t*-tests with SPSS® Statistics 20 for Windows (IBM Corp., Armonk, NY, USA). Differences in participants' estimation of 30 s during the MRB were analyzed via repeated-measures ANOVA; the Greenhouse–Geisser correction was utilized for sphericity violations. Between session differences in body sway in either direction during the MRB (defined here as any sway ≥1″) were evaluated by generalized estimating equations (GEE) with a binomial probability distribution, logit link function and a first-order autoregressive (AR(1)) correlation matrix. Differences in a number of observed clues during the OLS and WAT were analyzed by GEE but with a Poisson distribution and log link function. Participants were categorized as "impaired" if the number of clues exhibited during the OLS *or* the WAT was ≥2 (originally validated "impairment" criterion for 0.08% blood alcohol concentrations; Stuster, 2006). Differences in participants' categorization were analyzed via GEE as for body sway. In each analysis, effects of dosing session, time and smoking group were analyzed to find the best fit model. When possible, blood cannabinoid concentrations and relevant interactions were fit to the model instead of categorical dosing session. Finally, differences in pupil sizes between sessions were evaluated via repeated-measures ANOVA as for MRB time estimation; if significant dose × time interactions were observed, *post-hoc* tests comparing dosing sessions at each time point were conducted with a Bonferroni correction. Pupil sizes also were modeled with linear mixed models with dosing session and time set as repeated measures (AR(1) covariance structure); blood cannabinoid concentrations were included as fixed or random effects to best fit the model. Owing to differences in cannabinoid pharmacokinetics between routes (Newmeyer *et al.*, 2016), inhaled and oral data were compared against placebo separately. In all analyses, statistical significance was attributed to $P < 0.05$.

Table 1. Descriptions of administered divided attention psychophysical exams

Test	Description	Clues/observations
Modified Romberg balance	Participants were instructed to stand with their feet together, arms at their sides, head tipped back and eyes closed while estimating the passage of 30 s.	No validated clues. Observations included side-to-side and front-to-back body sway, eyelid tremors, and the actual elapsed time during participants' time estimation.
One leg stand	Participants were instructed to raise one leg ~6″ off the floor with their arms at their side and eyes watching their raised foot while counting aloud by thousands until told to stop (timed 30 s test).	Impairment clues were: swaying while balancing, using arms to balance, hopping, or putting their raised foot down.
Walk and turn	Participants were instructed to place their right foot on the starting line, then place their left foot in front of their right foot, making heel-to-toe contact; participants were to remain in that position until told to begin the test. Participants were then instructed to take nine heel-to-toe steps along a straight line, turn in a pre-defined manner (keeping the lead foot planted while taking small steps with the other foot to rotate), and return with nine heel-to-toe steps.	Impairment clues were: losing balance during instructions, beginning the test before being instructed to do so, stopping while walking, missing heel-to-toe contact (>0.5″), stepping off the line, raising arms for balance (>6″), taking an incorrect number of steps and turning incorrectly.

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Results

Participants

Table 2 summarizes demographics for 11 frequent and nine occasional cannabis smokers (ages 19–46 years, 75% male, 75% African American). Participants were in good physical health without any clinically significant electrocardiogram abnormalities, or histories of mental illness or clinically significant cannabis adverse events. Additionally, oral fluid screening tests conducted on admission and at baseline were all negative for other drug classes (amphetamine, benzodiazepines, cocaine, methadone, methamphetamine and opioids). Participant K was recruited as an occasional cannabis smoker, but reclassified as a frequent smoker when baseline THC and metabolite concentrations were consistent with published frequent smoker data (Desrosiers *et al.*, 2014; Schwope *et al.*, 2011). Participant H reported last use ~10 days before session 1, despite self-reporting smoking five times a week during screening; the participant reported smoking within 0.6–18.7 h of subsequent session admission. Occasional smokers began smoking at a significantly older age, smoked on a significantly fewer number of days out of the previous 14 and smoked significantly less per smoking occasion.

Blood cannabinoid concentrations

Table 3 summarizes THC and 11-hydroxy-THC (11-OH-THC) blood cannabinoid data collected 1.5 and 3.5 h post-dose. Median percentage decreases from maximum concentrations (C_{max}) after smoking or vaporization were large (≥93.7%) in both groups. Frequent smokers' decreases were less than occasional smokers were, and frequent smokers had greater THC concentrations than occasional smokers 1.5 and 3.5 h post-dose. Both frequent and occasional smokers' blood THC concentrations were greater at 1.5 and 3.5 h after oral dosing than after inhaled doses due to a longer absorption phase compared to inhaled

Table 2. Demographic data and cannabis smoking histories for 11 frequent and nine occasional smokers

Participant	Sex	Age (years)	Race and ethnicity[a]	BMI (kg m^{-2})	Age at first use[b]	Lifetime years smoked[b]	Cannabis intake frequency[b]	Time between last use and admission[c]	Number of days used in last 14[c]	Average joint equivalents per smoking occasion[c]
Frequent smokers										
A	M	21	AA	26.5	16	5	Daily	17.2 h	14	5
B	M	22	AA	31.0	15	7	Daily	19.3 h	10	4
C	M	19	AA	19.8	13	6	Daily	18.7 h	14	4
D	F	23	AA	31.9	13	10	Daily	7.9 h	14	10
E	M	38	AA	32.2	12	26	Daily	2.4 h	14	15
F	F	29	AA	31.0	11	18	Daily	1.9 h	14	20
G	M	38	AA	22.0	16	22	Daily	2.1 h	14	7
H	M	34	AA	23.0	14	20	5× a week	239.7 h[d]	2[d]	2[d]
I	M	21	AA	25.0	11	10	Daily	0.7 h	14	5
J	M	25	AA	19.0	13	12	5× a week	5.8 h	14	2
K	M	31	AA	16.8	15	16	2–3× a week[e]	5.1 h[e]	4[e]	2.5[e]
Mean		27.4		25.3	13.5*	13.9		8.4 h	13.6*	8.0*
SD		6.9		5.6	1.8	6.9		7.8 h	1.3	6.0
Median		25.3		25.0	13.0	12.3		5.8 h	14.0	5.0
Occasional smokers										
L	M	24	AA	36.3	17	7	2× a month	1.4 days	3	2
M	M	21	AA	23.0	13	8	2× a week	0.7 days	4	2
N	M	25	W	24.2	21	4	2× a week	13.0 days	1	3
O	M	40	W	28.3	18	22	2× a week	30.7 days	0	2
P	F	46	AA	31.0	26	20	2× a week	0.4 days	4	4
Q	M	33	AA	30.7	16	17	2× a month	22.8 days	0	3
R	F	22	W	22.0	16	6	2× a week	1.7 days	4	1
S	F	22	W	23.0	14	8	2× a week	1.1 days	10	2
T	M	31	W	21.7	22	9	1–2× a week	1.8 days	2	2
Mean		29.4		26.7	18.1*	11.3		8.2 days	3.1*	2.3*
SD		8.6		5.1	4.2	6.3		11.4 days	3.1	0.9
Median		24.9		24.2	17.0	8.5		1.7 days	3.0	2.0

[a]AA, African American; W, white.
[b]Data collected during screening.
[c]Data collected on admission to session 1.
[d]Self-reported data on admission inconsistent with data received at screening. Data excluded from statistics.
[e]Self-reported data inconsistent with biological sample concentrations. Data excluded from statistics.
* Significant difference between groups ($P < 0.05$).

Table 3. Median (range) THC and 11-OH-THC maximum blood concentrations (C_{max}), times of C_{max} (t_{max}), concentrations at 1.5 and 3.5 h ($C_{1.5h}$ and $C_{3.5h}$, respectively) following administration of smoked, vaporized and oral cannabis (6.9% THC [~50.6 mg]), and percentage differences between concentrations at either 1.5 or 3.5 h and C_{max}

		Smoking		Vaporization		Oral	
		THC	11-OH-THC	THC	11-OH-THC	THC	11-OH-THC
Frequent	C_{max}, μg l^{-1}	117 (52.8–471)	7.2 (1.9–30.9)	88.0 (24.7–170)	6.2 (1.6–10.7)	15.6 (4.7–34.8)	7.5 (2.2–14.3)
	t_{max}, h	0.13 (0.00–0.17)	0.20 (0.10–0.50)	0.10 (0.03–0.17)	0.17 (0.10–0.50)	2.5 (1.5–3.5)	2.5 (1.5–3.5)
	$C_{1.5h}$, μg l^{-1}	7.7 (4.1–14.8)	2.2 (1.2–6.7)	5.2 (3.4–10.7)	1.7 (1.0–2.6)	8.6 (4.5–20.1)	4.8 (2.2–9.3)
	% difference, 1.5 h[b]	93.9 (91.5–97.7)	72.7 (37.4–78.3)	93.7 (84.5–96.6)	69.5 (30.8–82.1)	41.1 (0.0–74.6)	32.1 (0.0–60.9)
	$C_{3.5h}$, μg l^{-1}	3.8 (2.2–6.5)	1.3 (0.9–2.6)	3.2 (1.2–6.3)	1.1 (0.0–2.0)	6.5 (3.7–20.9)	6.3 (1.5–11.0)
	% difference, 3.5 h[b]	96.4 (94.7–96.6)	83.2 (55.3–91.5)	94.9 (92.9–98.8)	79.3 (48.4–100)	58.3 (0.0–69.1)	37.1 (0.0–59.5)
Occasional[a]	C_{max}, μg l^{-1}	44.4 (1.3–174)	1.9 (0.5–8.7)	34.8 (5.2–137)	1.6 (0.7–3.5)	10.1 (3.6–22.5)	5.1 (2.4–11.0)
	t_{max}, h	0.10 (0.07–0.17)	0.19 (0.10–0.50)	0.10 (0.03–0.17)	0.15 (0.10–0.20)	2.5 (1.5–3.5)	2.5 (1.5–3.5)
	$C_{1.5h}$, μg l^{-1}	2.2 (0.0–4.1)	0.8 (0.0–2.1)	1.4 (0.0–2.5)	0.0 (0.0–1.2)	7.1 (2.5–10.1)	4.0 (2.2–5.8)
	% difference, 1.5 h[b]	96.0 (92.0–100)	75.0 (47.3–100)	97.5 (73.5–100)	100 (32.8–100)	29.2 (0.0–73.3)	10.9 (0.0–52.7)
	$C_{3.5h}$, μg l^{-1}	0.5 (0.0–1.2)	0.0 (0.0–0.6)	0.0 (0.0–0.9)	0.0 (0.0–0.6)	6.4 (1.9–22.5)	3.7 (2.2–11.0)
	% difference, 3.5 h[b]	98.9 (96.6–100)	100 (92.6–100)	100 (93.3–100)	100 (84.0–100)	42.2 (0.0–78.6)	17.9 (0.0–36.7)

11-OH-THC, 11-hydroxy-THC; THC, Δ^9-tetrahydrocannabinol.

[a]$n = 8$ for occasional smokers' 11-OH-THC concentrations because one participant was never positive after smoking or vaporization.

[b]For smoking and vaporization, this represents percentage decrease from C_{max}. For oral dosing, data at 1.5 h are during the absorption phase for most participants, while data at 3.5 h are during or after observed C_{max} were achieved; therefore, data at 1.5 h are percentage difference from what C_{max} *will be*, whereas data at 3.5 h are percentage decrease from what C_{max} *was*.

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routes (time of C_{max} [t_{max}] 2.5 [1.5–3.5] h). 11-OH-THC concentration percentage decreases at 1.5 and 3.5 h after inhaled doses also were high (≥69.5%), and 11-OH-THC concentrations at both time points were greater after oral compared to inhaled cannabis.

Psychophysical examinations

Overall, 158 tests (87 from frequent, 71 from occasional smokers) were conducted. Summaries of participants' performance are presented in Table 4. No significant effects on participants' MRB 30 s estimations were observed. A wide range of estimates was observed, with 20.0–31.6% <30 s, 0.0–20% equal to 30 s, and 55.0–80% >30 s. Sway ≥1″ in any direction was observed in 65.0, 87.5, 65.0 and 53.8% of tests (all participants and 1.5 and 3.5 h combined) following placebo, smoking, vaporization and oral dosing, respectively. The odds ratio (OR [95% CI]) of sway at either time point following smoking compared to placebo was 3.8 (1.5–9.5). There were no significant differences in sway after vaporization or oral dosing compared to placebo. Cannabis produced minimal impairment on the MRB task, with only smoked cannabis associated with increased sway.

The number of observed clues during the OLS and WAT in all participants at both time points are depicted in Fig. 2. No time effect was observed in any analysis, so data from both time points were combined. Oral cannabis produced an incidence rate for number of observed clues during the OLS 1.99 (1.06–3.71) times that following placebo. For the WAT, the incidence rate for observed clues was 1.60 (1.13–2.26) times higher after oral cannabis compared to placebo. Only oral cannabis produced significant increases compared to placebo in the number of observed clues on the OLS and WAT tasks.

Participants were grouped based on their performance on the OLS and WAT, with those who exhibited ≥2 clues on *either* test classified as "impaired." Significant overall effects of oral cannabis and an interaction with use history were observed; therefore, data from frequent and occasional smokers were analyzed separately. Frequent and occasional smokers classified as "impaired" in each dosing session are presented in Fig. 3. Occasional smokers' odds of being "impaired" following oral dosing were 6.43 (2.25–18.40) times higher after placebo. No significant differences between sessions were observed in frequent smokers. Oral cannabis significantly increased occasional smokers' odds of being impaired on either the OLS or WAT tasks compared to placebo, while active cannabis did not significantly affect frequent smokers' odds.

When modeling blood THC and 11-OH-THC concentrations to participants' classification of "impaired," significant concentration × group interactions were observed; therefore, occasional and frequent smokers were analyzed separately. Model parameters are summarized in Table 5 for occasional smokers only, as blood cannabinoid concentrations did not significantly relate to frequent smokers' classification as "impaired." Separate models were built for THC and 11-OH-THC as no model with THC and 11-OH-THC concentrations together yielded significant relationships. Time was not a significant covariate or factor in any model. THC and 11-OH-THC were similarly associated with "impairment," with OR of 1.30 (1.12–1.52) and 1.50 (1.25–1.79), respectively. THC and 11-OH-THC concentration increases were significantly associated with increased odds of occasional smokers being impaired on the OLS or WAT tasks.

Table 4. Participants' performance on the modified Romberg balance, one leg stand and walk and turn tasks at 1.5 and 3.5 h after placebo, smoked, vaporized and oral cannabis (6.9% Δ^9-tetrahydrocannabinol [~50.6 mg]) administration. Data are presented as median (range) for all participants (overall) and for frequent and occasional smokers separately

	Modified Romberg balance	
	Estimation 1.5 h post-dose(s)	Estimation 3.5 h post-dose(s)
Overall		
Placebo	34 (25–61)	34 (25–49)
Smoking	34 (26–51)	32 (24–42)
Vaporization	35 (18–52)	34 (19–51)
Oral	33 (24–49)	32 (18–39)
Frequent smokers		
Placebo	34 (25–44)	34 (25–45)
Smoking	33 (26–51)	36 (26–42)
Vaporization	35 (29–52)	35 (25–42)
Oral	34 (25–49)	33 (28–39)
Occasional smokers		
Placebo	34 (29–61)	34 (27–49)
Smoking	34 (26–41)	30 (24–40)
Vaporization	33 (18–46)	34 (19–51)
Oral	33 (24–38)	31 (18–39)
	One leg stand	
	Clues observed 1.5 h post-dose	Clues observed 3.5 h post-dose
Overall		
Placebo	0 (0–1)	0 (0–2)
Smoking	0 (0–2)	0 (0–2)
Vaporization	0 (0–2)	0 (0–2)
Oral	0 (0–1)	1 (0–3)
Frequent smokers		
Placebo	0 (0–1)	0 (0–2)
Smoking	0 (0–2)	0 (0–1)
Vaporization	0 (0–2)	0 (0–2)
Oral	0 (0–1)	1 (0–3)
Occasional smokers		
Placebo	0 (0–1)	0 (0–0)
Smoking	0 (0–2)	0 (0–2)
Vaporization	0 (0–1)	0 (0–1)
Oral	0 (0–1)	1 (0–2)
	Walk and turn	
	Clues observed 1.5 h post-dose	Clues observed 3.5 h post-dose
Overall		
Placebo	1 (0–3)	1 (0–2)
Smoking	1 (0–4)	1 (0–3)
Vaporization	1 (0–3)	1 (0–5)
Oral	2 (0–4)	1 (0–3)
Frequent smokers		
Placebo	1 (0–3)	1 (0–2)
Smoking	1 (0–3)	1 (0–3)
Vaporization	2 (0–3)	2 (0–5)
Oral	2 (0–3)	1 (0–2)
Occasional smokers		
Placebo	1 (0–2)	1 (0–2)
Smoking	0 (0–4)	1 (0–2)
Vaporization	1 (0–1)	1 (0–2)
Oral	2 (0–4)	2 (0–3)

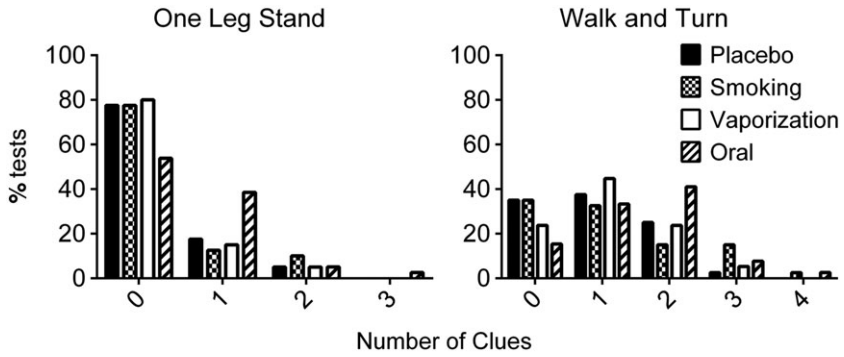

Figure 2. Distribution of the number of clues observed during the one leg stand and walk and turn tasks in 11 frequent and nine occasional cannabis smokers 1.5 and 3.5 h after placebo, smoked, vaporized and oral cannabis (6.9% Δ^9-tetrahydrocannabinol, ~50.6 mg) administration. Observation of ≥2 clues is the "impairment" criteria utilized by drug recognition experts, originally validated for 0.08% blood alcohol concentrations.

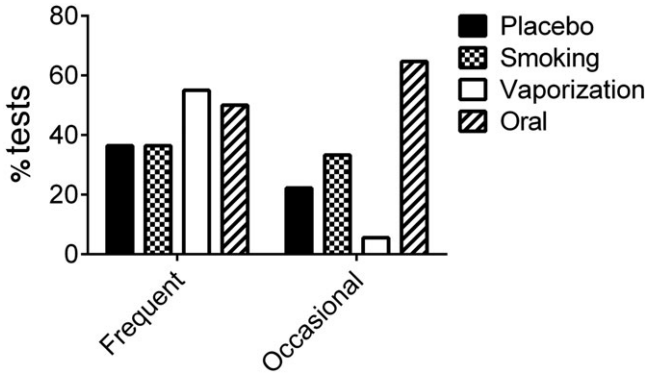

Figure 3. Percentage of 11 frequent and nine occasional smokers that displayed ≥2 clues on either the one leg stand *or* walk and turn tasks 1.5 and 3.5 h after placebo, smoked, vaporized and oral cannabis (6.9% Δ^9-tetrahydrocannabinol, ~50.6 mg) administration.

Eye examinations

Overall, 393 eye examinations (218 from frequent, 174 from occasional smokers) were conducted. Pupil sizes in the RL and NTD conditions were not significantly different between dosing sessions, times or smoking groups; overall (all participants and time points) mean (SD) pupil sizes after each dosing session are presented in Table 6. No significant effects were observed for pupil sizes in the DL condition following smoking or vaporization compared to placebo, but significant dose, time and dose × time effects were observed when comparing oral cannabis to placebo. *Post-hoc* tests revealed that mean (SE, 95% CI) pupil sizes 1.5 and 3.5 h after oral dosing were 0.4 (0.1, 0.2–0.6) and 0.5 (0.2, 0.2–0.8) mm larger, respectively. Significantly greater pupil sizes were observed after oral cannabis only compared to placebo at 1.5 and 3.5 h post-dose, within the range of t_{max} for participants' THC and 11-OH-THC concentrations.

Table 7 summarizes the results from modeling participants' pupil sizes and blood cannabinoid concentrations. Time was not a significant covariate or factor in any model. The best fitting model included a random intercept to account for variance in participants' baseline pupil sizes. Blood 11-OH-THC concentrations were significantly related to pupil sizes in all lighting conditions, with increases of 0.032, 0.052 and 0.052 mm unit^{-1} increase in 11-OH-THC concentration for RL, NTD and DL, respectively. Blood THC concentrations were a significant, but weak, covariate only for pupil sizes in the NTD condition ($b = -0.008$). 11-OH-THC concentration increases were significantly associated with increases in pupil sizes in all lighting conditions.

Table 5. Effects of blood THC and 11-OH-THC concentrations on occasional smokers exhibiting ≥2 clues on the one leg stand *or* walk and turn tasks following administration of smoked, vaporized and oral cannabis (6.9% THC [~50.6 mg])

	b (SE)	Wald χ^2 (1 df)	*P* value	OR (95% CI)
THC only				
Intercept	−1.342 (0.7130)	3.544	0.060	–
THC (μg l^{-1})	0.265 (0.0778)	11.556	**0.001**	1.30 (1.12–1.52)
11-OH-THC only				
Intercept	−1.221 (0.5654)	4.666	**0.031**	–
11-OH-THC (μg l^{-1})	0.402 (0.0907)	19.650	<**0.001**	1.50 (1.25–1.79)

11-OH-THC, 11-hydroxy-THC; 95% CI, 95% confidence interval; *b*, model parameter (coefficient); df, degrees of freedom; OR, odds ratio; SE, standard error; THC, Δ^9-tetrahydrocannabinol.
Data from nine occasional cannabis smokers who performed the one leg stand and walk and turn tasks at 1.5 and 3.5 h post-dose who were classified as either "impaired" or not (binary outcome variable). Models were built with either THC or 11-OH-THC concentrations as the predictor variable with generalized estimating equations with a binary probability distribution and a logit link function. The resulting equation is (in the case of blood THC, for example): logit(Y) = intercept + $b_{[THC]} \times$ [THC], where logit(Y) = ln (Y/1 − Y) or the log odds of being classified as "impaired." An odds ratio is obtained by calculating e^b and is interpreted as the change in odds of being classified "impaired" for each unit change in blood concentration. Bolded *P* values designate significance.

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Table 6. Pupil sizes (mm) in room light, near-total darkness, and direct light conditions after placebo, smoked, vaporized and oral cannabis (6.9% Δ^9-tetrahydrocannabinol [~50.6 mg]) administration. Data are presented as mean (SD) across all time points for all participants (overall) and for frequent and occasional smokers separately

	Room light	Near-total darkness	Direct light
Overall			
Placebo	4.2 (0.9)	5.0 (0.9)	3.3 (0.7)
Smoking	4.3 (0.8)	5.2 (0.8)	3.6 (0.7)
Vaporization	4.2 (0.9)	4.9 (0.9)	3.4 (0.7)
Oral	4.5 (0.9)	5.1 (0.8)	3.6 (0.8)
Frequent smokers			
Placebo	4.1 (0.7)	4.9 (0.7)	3.2 (0.7)
Smoking	4.2 (0.8)	5.0 (0.7)	3.5 (0.8)
Vaporization	4.1 (0.8)	4.9 (0.7)	3.4 (0.7)
Oral	4.4 (0.8)	5.1 (0.8)	3.5 (0.9)
Occasional smokers			
Placebo	4.3 (1.0)	5.2 (1.1)	3.5 (0.8)
Smoking	4.4 (0.8)	5.4 (0.7)	3.7 (0.5)
Vaporization	4.4 (1.1)	4.9 (1.1)	3.4 (0.7)
Oral	4.5 (1.0)	5.1 (0.9)	3.7 (0.6)

LOC was observed at baseline and all post-dose time points in all dosing sessions in five frequent and five occasional smokers (50% overall), while four frequent and one occasional smoker never exhibited LOC post-dose (25% overall); therefore, statistical evaluations could not be performed.

Discussion

We sought to evaluate performance impairment on three psychophysical tasks from the DECP – the MRB, OLS and WAT tasks – and effects on participants' pupil sizes and presence of LOC in frequent and occasional users following placebo, smoked, vaporized and oral cannabis administration.

Smoking is the most common cannabis administration route and is associated with increased crash risk (Hartman & Huestis, 2013; Ramaekers *et al.*, 2004), and exposes users to toxic pyrolytic by-products such as carbon monoxide (Hazekamp *et al.*, 2006). Smoking was deemed an inappropriate route for medical cannabis administration (Institute of Medicine, 1999). Vaporization is an attractive alternative route for recreational and medicinal administration because carbon monoxide exposure is reduced (Abrams *et al.*, 2007), and similar THC concentrations are achieved as found after smoking (Hartman *et al.*, 2016b; Newmeyer *et al.*, 2016). Cannabis administration via vaporization is also associated with impaired driving behavior (Hartman *et al.*, 2015, 2016a). Oral dosing is a popular route for recreational and medicinal cannabis, although bioavailability is lower than after inhaled doses and absorption is slow and erratic (Ohlsson *et al.*, 1980). Oral cannabis dosing is also associated with impaired driving (Bosker *et al.*, 2012a; Ménétrey *et al.*, 2005). An additional concern is mislabeled edible products (Vandrey *et al.*, 2015), which may increase the risk of adverse events occurring if users do not have accurate dosing information. Additionally, the risk of psychosis after oral doses appears to be greater based on the Colorado experience, although the mechanism for this effect is currently unknown.

Large decreases from C_{max} in participants' blood cannabinoid concentrations after smoking and vaporization were observed

Table 7. Effects of blood THC and 11-OH-THC concentrations on pupil sizes under room light, near-total darkness and direct lighting conditions following administration of smoked, vaporized and oral cannabis (6.9% THC [~50.6 mg])

	b	SE	df	*t*	*P* value	95% Confidence interval for *b*	
						Lower bound	Upper bound
Room light							
Intercept	4.308	0.182	21.186	23.667	**<0.001**	3.929	4.686
11-OH-THC	0.032	0.014	185.314	2.350	**0.020**	0.005	0.059
Subject variance in intercepts	0.593	0.203			**0.004**	0.302	1.161
AR1 rho	0.405	0.084			**<0.001**	0.228	0.555
Near-total darkness							
Intercept	4.954	0.160	21.542	30.982	**<0.001**	4.622	5.286
THC	–0.008	0.004	169.454	–2.218	**0.028**	–0.015	–0.001
11-OH-THC	0.052	0.018	107.815	2.862	**0.005**	0.016	0.087
Subject variance in intercepts	0.463	0.156			**0.003**	0.240	0.895
AR1 rho	0.079	0.084			0.345	–0.086	0.240
Direct light							
Intercept	3.437	0.149	21.495	23.080	**<0.001**	3.128	3.746
11-OH-THC	0.052	0.010	180.965	4.959	**<0.001**	0.031	0.072
Subject variance in intercepts	0.410	0.135			**0.002**	0.215	0.783
AR1 rho	0.214	0.093			**0.021**	0.027	0.387

11-OH-THC, 11-hydroxy-THC; *b*, model parameter (coefficient); df, degrees of freedom; SE, standard error; *t*, *t*-statistic; THC, Δ^9-tetrahydrocannabinol.

Data from 11 frequent and nine occasional cannabis smokers. Pupil sizes were measured at baseline (−1.5 h) and up to 5 h post-dose. Only time points where blood 11-OH-THC was measurable ($n = 207$) were included in linear mixed models; dosing session and time were set as within-subject repeated measures. The resulting equation (in the case of room light, for example) is: pupil size = intercept + $b_{11\text{-OH-THC}} \times$ [11-OH-THC]. Only significant terms were included in the final model. Bolded *P* values designate significance.

(73.5–100% for THC, 30.8–100% for 11-OH-THC). In contrast, the percentage differences from THC and 11-OH-THC C_{max} (0.0–78.6% and 0.0–59.5%, respectively) after oral dosing were lower, given the median (range) t_{max} for both analytes was 2.5 (1.5–3.5) h. Blood THC and 11-OH-THC concentrations at 1.5–3.5 h were greater after oral dosing than after either inhaled dose due to rapid absorption and distribution following inhaled doses – leading to large percentage concentration decreases – compared to the slow absorption and first pass metabolism following oral dosing, suggesting reasons why significant effects generally occurred only when comparing oral dosing to placebo. The timeline of administering tasks relative to the administration route is an important consideration when interpreting results.

Participants' MRB 30 s estimations varied widely after all doses with no significant dosing session, time or group effects. Although cannabis users report an altered sense of time, our data are inconclusive about how cannabis administration affects time perception; 70% of time estimation studies in one review reported overestimations, data from time production and reproduction studies were inconclusive due to large methodological variability and few available studies (Atakan *et al.*, 2012). In controlled drug administration studies in which DREs administered nearly complete evaluations, time estimation was not among the variables that best predicted the presence or absence of cannabis (Heishman *et al.*, 1996, 1998; Schechtman & Shinar, 2005). A significant difference in time estimations was observed in a comparison of toxicologically confirmed cannabis-only DRE opinions (median [range] 29 [4–90] s) and controls (30 [20–53] s), but time estimation was not among the optimized combination of measures for detecting cannabis-related DECP performance impairment (Hartman *et al.*, 2016c).

Oral cannabis dosing significantly increased the number of clues observed during the OLS and WAT compared to placebo. Additionally, a significant effect of oral dosing was observed only for occasional smokers on the observation of ≥2 OLS *or* WAT clues compared to placebo. Following paced smoking of 1.74 or 2.93% THC cigarettes, participants were significantly impaired (≥2 clues observed) on the OLS and WAT from 5 to 105 min after the completion of smoking (Papafotiou *et al.*, 2005). Performances on the OLS and WAT were not affected 4.5 or 5 h after 10 or 20 mg oral dronabinol dosing (Bosker *et al.*, 2012a), but OLS performance was impaired 2 h after paced smoking of a 400 μg THC kg^{-1} body weight cigarette with placebo alcohol (Bosker *et al.*, 2012b). Lack of impairment after the oral dronabinol dose may be due to a lower dose and the timing of the test relative to dosing. OLS (but not WAT) performance was impaired 2 h after paced cannabis smoking (Bosker *et al.*, 2012b), where we did not observe impairment on OLS after smoking, despite comparable blood THC concentrations between studies. Differences in observations may be due to comparing post-dose performance to baseline (Bosker *et al.*, 2012b) whereas we compared performance at the same time between active and placebo cannabis.

Hartman *et al.* (2016c) determined an optimized combination of measures for detecting cannabis-related impairment on the DECP – observing two of four of: ≥3 misses on the finger-to-nose task, eyelid tremors during the MRB; ≥2 clues on the OLS; and ≥2 clues on the WAT. The finger-to-nose task was not performed in this study, and eyelid tremors were not observed. However, oral dosing was shown to significantly increase the odds compared to placebo of observing ≥2 OLS *or* WAT clues, which supports Hartman *et al.* (2016c) that these tasks are sensitive to cannabis-related impairment.

Logan *et al.* (2016) found no significant correlations between blood THC concentrations and the number of either OLS or WAT clues, noting that blood was collected a mean (median, maximum) 74 (61, 225) min after arrest (Logan *et al.*, 2016). We observed significant effects of blood THC and 11-OH-THC concentrations on the OR of exhibiting ≥2 OLS *or* WAT clues. This is likely because in our controlled setting we could obtain blood specimens simultaneously with testing. This is an important observation, particularly the contribution of 11-OH-THC concentrations given it is an active metabolite (Lemberger *et al.*, 1973; Perez-Reyes *et al.*, 1972) and greater concentrations may be observed following oral compared to inhaled doses (Newmeyer *et al.*, 2016), which is a concern as consumption of cannabis-containing edibles is becoming increasingly popular (Schauer *et al.*, 2016).

Participants' pupil sizes were significantly different from placebo only in the DL condition 1.5 and 3.5 h after oral dosing; following placebo, mean (SD) pupil sizes were 3.3 mm (0.6) and 3.4 mm (0.7), respectively, and after oral cannabis 3.6 mm (0.8) and 3.8 mm (0.8), respectively. These values are above the average normal (unimpaired) value 3.0 mm but still within the normal range 2.0–4.5 mm for the DL condition utilized by DREs (International Association of Chiefs of Police, 2015). The magnitude of these increases is small compared to other evaluations; cannabis-positive drivers had a mean pupil size 5.4 mm in RL compared to 4.3 mm for controls (Logan *et al.*, 2016), and pupil sizes in cases were significantly greater and outside normal ranges in all conditions compared to controls (Hartman *et al.*, 2016c). Given the small effect size observed here it may be possible the administered dose was less than what was self-administered by those arrested for DUID. However, we did demonstrate that increases in blood 11-OH-THC concentrations were significantly related to increases in pupil sizes in all lighting conditions. THC concentrations were variably related to pupil sizes. The much larger variability in THC concentrations compared to 11-OH-THC concentrations may have affected the ability to identify significant THC effects (Table 3).

Finally, LOC was observed in 50% of participants at all time points. Previously, LOC was observed in significantly more cases compared to controls (Hartman *et al.*, 2016c; Logan *et al.*, 2016). Significant increases in LOC prevalence were not observed due to limited statistical power.

The timeline of task administration may have limited observation of significant effects following inhaled doses compared to placebo due to the rapid decreases in cannabinoid concentrations, but these data clearly demonstrate that oral cannabis administration can impair OLS and WAT performance. Double procedures (separate sessions for each placebo and active dose, resulting in six total sessions) were not performed, but this was offset by administering two doses per session where only one was active, except in the double-placebo session, which served as comparison for the active sessions. Baseline measures were not collected for the DECP tasks due to constraints in the study timeline, as this was one component of a larger clinical investigation; however, baseline data are not available when tests are administered by law enforcement personnel. Additionally, only a portion of the DECP was administered, limiting our conclusions on the utility of the overall exam in detecting cannabis-related impairment; however, the utility of the entire DECP was demonstrated elsewhere with actual cases,

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and optimized measures for detecting cannabis-related impairment were observed (Hartman *et al.*, 2016c; Logan *et al.*, 2016). Small sample size also possibly limited statistical power. Strengths of the study include the within-subject, placebo-controlled design, which allowed for the direct comparison of the effects of different cannabis administration routes on task performance, and the inclusion of both frequent and occasional cannabis users. The simultaneous collection of blood specimens was another strength; we demonstrated that performance on these physical tasks is affected by cannabinoid concentrations, which could not be demonstrated previously.

Conclusions

We present results of participant performance on divided attention psychophysical tasks and eye examinations from the DECP following controlled administration of placebo, smoked, vaporized and oral cannabis to frequent and occasional smokers. We demonstrated that oral cannabis administration impaired performance on the OLS and WAT tasks compared to placebo, supporting other data showing these tasks are sensitive to cannabis-related impairment. Occasional smokers' impairment was related to blood THC and 11-OH-THC concentrations. These are important findings as consumption of edible cannabis products increases. Our data suggest that at these administered doses, impairment following oral dosing was prolonged and occurred later compared to inhaled doses; earlier testing post-dose is needed to determine these relationships further. Because science-based *per se* THC limits in DUID cases are difficult to establish, increased importance may be placed on observable signs for documenting cannabis-related impairment, particularly for frequent users, as blood cannabinoid concentrations were not significantly related to impairment. These data provide guidance for the development of public health and safety policy and legislation.

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Conflict of interest

The authors did not report any conflict of interest.

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