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Cannabis effects on driving lateral control with and without alcohol

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ABSTRACT

Background: Effects of cannabis, the most commonly encountered non-alcohol drug in driving under the influence cases, are heavily debated. We aim to determine how blood Δ^9-tetrahydrocannabinol (THC) concentrations relate to driving impairment, with and without alcohol.
Methods: Current occasional (≥1×/last 3 months, ≤3days/week) cannabis smokers drank placebo or low-dose alcohol, and inhaled 500 mg placebo, low (2.9%)-THC, or high (6.7%)-THC vaporized cannabis over 10 min *ad libitum* in separate sessions (within-subject design, 6 conditions). Participants drove (National Advanced Driving Simulator, University of Iowa) simulated drives (~0.8 h duration). Blood, oral fluid (OF), and breath alcohol samples were collected before (0.17 h, 0.42 h) and after (1.4 h, 2.3 h) driving that occurred 0.5–1.3 h after inhalation. We evaluated standard deviations of lateral position (lane weave, SDLP) and steering angle, lane departures/min, and maximum lateral acceleration.
Results: In $N = 18$ completers (13 men, ages 21–37years), cannabis and alcohol increased SDLP. Blood THC concentrations of 8.2 and 13.1 μg/L during driving increased SDLP similar to 0.05 and 0.08 g/210 L breath alcohol concentrations, the most common legal alcohol limits. Cannabis-alcohol SDLP effects were additive rather than synergistic, with 5 μg/L THC + 0.05 g/210 L alcohol showing similar SDLP to 0.08 g/210 L alcohol alone. Only alcohol increased lateral acceleration and the less-sensitive lane departures/min parameters. OF effectively documented cannabis exposure, although with greater THC concentration variability than paired blood samples.
Conclusions: SDLP was a sensitive cannabis-related lateral control impairment measure. During drive blood THC ≥8.2 μg/L increased SDLP similar to notably-impairing alcohol concentrations. Despite OF's screening value, OF variability poses challenges in concentration-based effects interpretation.
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1. Introduction

Reducing drugged driving is a U.S. and worldwide priority (ONDCP, 2013). Cannabis is the most frequently detected illicit drug in drivers (Berning et al., 2015; Lacey et al., 2009; Legrand et al., 2013; Pilkinton et al., 2013); 12.6% of weekend nighttime drivers were positive for Δ^9-tetrahydrocannabinol (THC, primary psychoactive phytocannabinoid), in 2013–2014, a 48% increase since 2007 (Berning et al., 2015). Although blood THC is associated with increased crash risk and driver culpability (Asbridge et al., 2012; Drummer et al., 2004; Gjerde et al., 2011; Laumon et al., 2005; Li et al., 2012), cannabis effects on driving remain heavily debated. Road tracking and ability to remain within the lane are crucial driving skills. Lane weaving, an observable effect of drug-impaired driving, is a common measure for assessing driving performance. Standard deviation of lateral position (SDLP) is a sensitive vehicular control indicator, often employed in drugged driving research (Anderson et al., 2010; Lenné et al., 2010; Ramaekers et al., 2006a;

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Verster et al., 2006). In previous studies, cannabis increased SDLP and straddling lanes, but results were assessed by dose rather than blood THC concentrations (Ramaekers et al., 2000; Robbe, 1998; Downey et al., 2013).

To date, 23 states and the District of Columbia (DC) approved medical marijuana; four states and DC legalized recreational cannabis for adults (ProCon.org, 2014). Cannabis legalization is a crucial road safety issue. Since legalizing medical marijuana (2000), Colorado observed increased driving under the influence of cannabis (DUIC) cases (Urfer et al., 2014), and fatal motor vehicle crashes with cannabis-positive drivers; whereas no significant change was observed in 34 states without legalized medical marijuana (Salomonsen-Sautel et al., 2014). Establishing evidence-based *per se* laws for DUIC remains challenging, with varying laws across the US (Armentano, 2013; Grotenhermen et al., 2007; Lacey et al., 2010). Many are concerned that implementing concentration-based cannabis-driving legislation will unfairly target individuals not acutely intoxicated, because residual THC can be detected in blood for up to a month of sustained abstinence in chronic frequent smokers (Bergamaschi et al., 2013). Appropriate blood THC concentrations that universally reflect driving impairment remain elusive. Determining blood THC concentrations associated with lateral control impairment in occasional users would benefit forensic interpretation.

There is interest in linking driving impairment with oral fluid (OF) THC concentrations. OF is easy to collect, non-invasive, and associated with recent cannabis intake (Bosker and Huestis, 2009; Drummer, 2006; Wille et al., 2014). OF-based DUIC legislation exists in some jurisdictions (Drummer et al., 2007; Huestis et al., 2011; Van der Linden et al., 2012); however, limited simultaneous driving and OF concentration data preclude direct association with impairment.

Alcohol is the most common drug identified in drivers (Berning et al., 2015; Legrand et al., 2013). Cannabis and alcohol, frequently detected together (Legrand et al., 2013), produced greater impairing effects together than either separately (Robbe, 1998; Ronen et al., 2010), but it is unclear whether effects are additive or synergistic.

This is the first in a series of manuscripts evaluating cannabis' effects, with and without concurrent alcohol, on driving. We present here effects, relative to THC concentrations, on drivers' lateral control. We hypothesized cannabis and alcohol would each impair lateral control, with synergistic effects when combined.

2. Methods

2.1. Participants

Healthy adults provided written informed consent for this Institutional Review Board-approved study. Inclusion criteria were ages 21–55 years; self-reported cannabis consumption ≥1×/3 months but ≤3 days/week over the past three months (Cannabis Use Disorders Identification Test [CUDIT]; Adamson and Sellman, 2003); self-reported "light" or "moderate" alcohol consumption according to a Quantity-Frequency-Variability (QFV) scale (Sobell and Sobell, 2003); or, if "heavy", not more than 3–4 servings on a typical drinking occasion; licensed driver for ≥2 years with currently valid unrestricted license; and self-reported driving ≥1300 miles in the past year. Exclusion criteria included past or current clinically significant medical illness; history of clinically significant adverse event associated with cannabis or alcohol intoxication or motion sickness; ≥450 mL blood donation in two weeks preceding drug administration; pregnant/nursing; interest in drug abuse treatment within past 60 days; currently taking drugs contraindicated with cannabis or alcohol or known to impact driving; requirements for nonstandard driving equipment; and prior participation in a similar driving simulator study.

2.2. Study design/procedures

Participants entered the clinical research unit 10–16 h prior to drug administration to preclude acute intoxication. Participants drank 90% grain alcohol in fruit juice to reach approximately 0.065% peak breath alcohol concentration [BrAC], or placebo (juice with alcohol-swabbed rim and topped with 1 mL alcohol to mimic alcohol taste and odor) *ad libitum* over 10 min. After drinking, they inhaled 500 mg placebo (0.008 ± 0.002% THC), low (2.9 ± 0.14%)-, or high (6.7 ± 0.05%)-THC vaporized (Volcano® Medic, Storz & Bickel, Tuttlingen, Germany) cannabis (NIDA Chemistry and Physiological Systems Research Branch) *ad libitum* over 10 min. Participants received all six alcohol/cannabis combinations in randomized order, with sessions separated by ≥1 week.

Simulated drives occurred 0.5–1.3 h after start of cannabis dosing. Blood collection times were 0.17, 0.42, 1.4, and 2.3 h post-inhalation. Blood was collected via indwelling peripheral venous catheter into grey-top (potassium oxalate/sodium fluoride) Vacutainer® tubes (Becton, Dickinson and Company, Franklin Lakes, NJ), and stored on ice ≤2 h. Specimens were stored in 3.6 mL Nunc® cryotubes (Thomas Scientific, Swedesboro, NJ) at −20 °C, and analyzed within three months, based on known cannabinoid stability (Scheidweiler et al., 2013). OF was collected simultaneously with blood (except 0.42 h), with the Quantisal™ collection device (Immunalysis, Pomona, CA). BrAC was measured via Alco-Sensor® IV (Intoximeters, St. Louis, MO) at the same times as blood, reporting alcohol in g/210 L breath (limit of quantification [LOQ] 0.006 g/210 L), equivalent to approximate blood alcohol concentration (BAC).

2.3. National Advanced Driving Simulator

Driving simulations were conducted in NADS-1, the high-fidelity, full-motion simulator at the National Advanced Driving Simulator (NADS), Iowa City, IA (Fig. 1). A 1996 Malibu sedan is mounted in a 7.3 m-diameter dome with a motion system providing 400 m^2 acceleration space, ±330° rotation, and high-frequency motion (Lee et al., 2010). Drivers experience acceleration, braking, steering cues, road conditions (e.g., gravel), and realistic sounds (e.g., wind, motor). NADS-1 produces a complete record of vehicle state (e.g., lane position) and driver inputs (e.g., steering wheel position).

2.4. Drives

The 45 min drive challenged multiple driving skills affected by cannabis, including SDLP. Each drive had urban, interstate, and rural nighttime segments. The urban segment involved a two-lane city roadway with posted speed limits 25–45 miles/h (40–72 km/h) and signal-controlled and uncontrolled intersections; interstate, a four-lane divided expressway with posted 70 miles/h (113 km/h) speed limit; rural, two-lane undivided road with curves, a gravel portion, and a 10 min timed straightaway. Because each participant drove six times, three scenarios with varied event orders were utilized to minimize practice effects. Each scenario contained the same number of curves and turns, in varied order and position. Other traffic, pedestrians, and potential hazards were present throughout the drive. Hundreds of performance variables were monitored; the lateral control (necessary for road tracking, lane keeping) subset is presented here.

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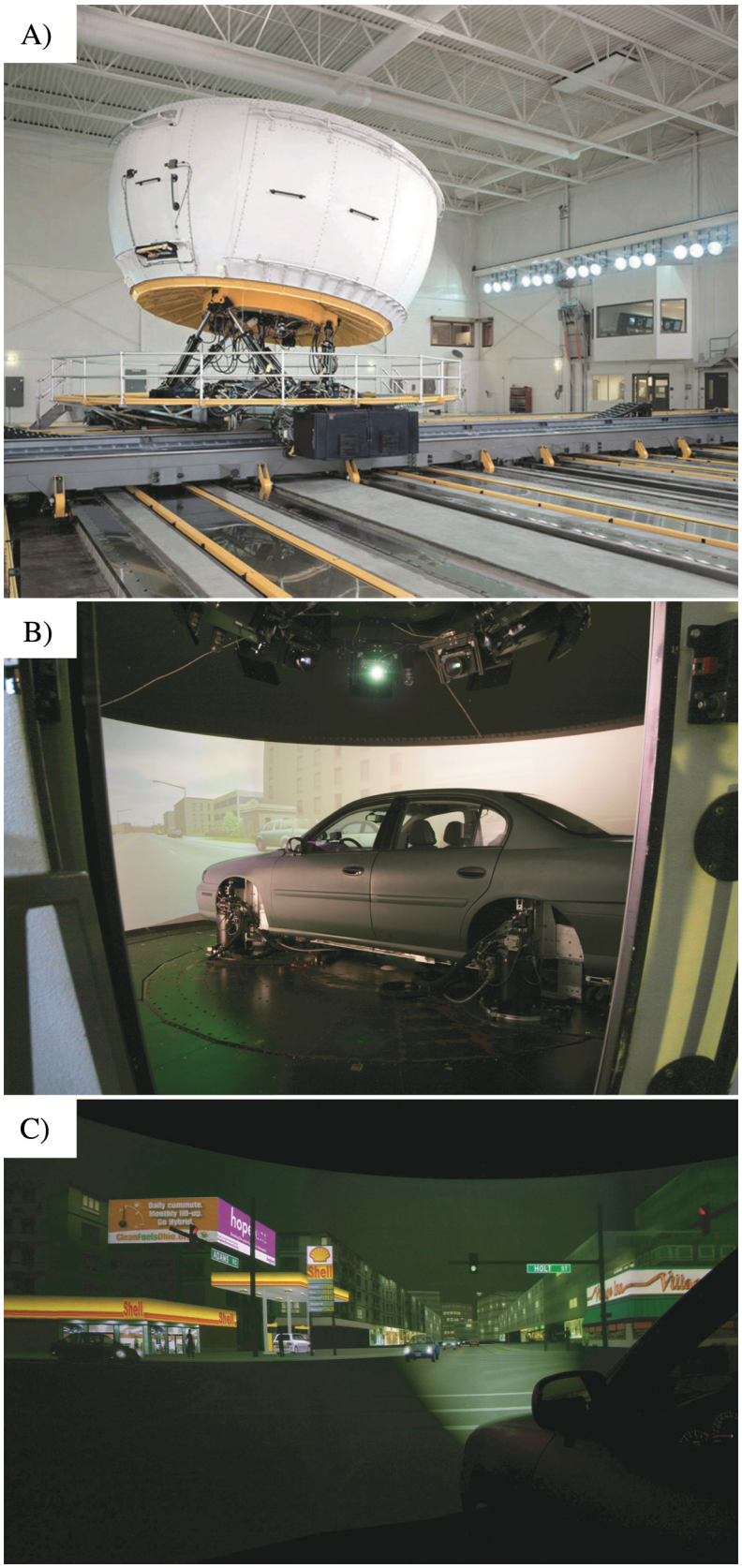

Fig. 1. The National Advanced Driving Simulator: (A) exterior, dome mounted in room; (B) dome interior with car mounted inside; (C) view of night-drive simulation.

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2.5. Specimen analysis

Blood THC concentration was quantified by a previously-published method (Schwope et al., 2011). Briefly, 0.5 mL blood was protein-precipitated with ice-cold acetonitrile, and supernatants diluted and solid-phase extracted. THC's linear range was 1–100 μg/L. Inter-assay (n = 30) analytical bias and imprecision were ≤3.7% and ≤8.7%, respectively. OF THC quantification is described in detail elsewhere (Hartman et al., 2015a). We utilized a published validated method (Milman et al., 2010), modified by adding 0.4 mL hexane to solid-phase extraction columns before the initial elution solvent. THC's linear range was 0.5–50 μg/L. Inter- and intra-assay imprecision were ≤6.6%; analytical bias, ≤14.4% (n = 21). If concentrations exceeded the upper LOQ, OF specimens were diluted with drug-free Quantisal™ buffer to achieve concentrations within the method's linear range.

2.6. Data analysis

Blood THC concentrations during drives were modeled via individual power-curve regression from pre-drive (0.17 and 0.42 h) and post-drive (1.4 and 2.3 h) specimens. BrAC concentrations during drives were modeled by linear interpolation, as alcohol was in the post-absorptive phase, during which its pharmacokinetics are linear (Jones and Andersson, 2003). Driving data were analyzed by participants' modeled concentrations during drives.

Data were reviewed to determine which events were suitable for analysis. Events for which dependent measures were not meaningful (e.g., SDLP during turn), were excluded. For each dependent measure, events with similar means were grouped for analytic purposes. Data were analyzed using SAS v9.4 General Linear Model (GLM) Select function to identify appropriate regression models. This procedure was selected due to its ability to accommodate continuous dependent measures and combinations of continuous and categorical independent measures (Neerchal et al., 2014). The stepwise selection method was chosen; the Schwarz Bayesian Information Criterion determined model entry/removal (Schwarz, 1978). Effect hierarchy was not enforced on model parameters. Available model parameters were blood THC, BrAC, interaction term THC × BrAC, speed limit, inverse curvature, and subject. Dependent measures of drivers' lateral control included SDLP, standard deviation of steering wheel angle, lane departures/min ("lane departure" defined as edge of vehicle crossing a lane boundary; per minute allowed for normalization across drive events), and maximum lateral acceleration in events without sharp turns. For final regression models, the analysis of variance for the model fit is presented, along with estimates, t-values, and p-values for model parameters.

3. Results

3.1. Participants

Nineteen healthy adults (13 men, ages 21–37 years, 74% white) participated (Table 1). Most consumed cannabis ≥2×/month (but ≤3 days/week), and reported last intake within a week prior to admission. Participants self-reported driving 6–23 years, and all reported driving ≥1×/week. Data review revealed one participant (#12) was consistently an extreme outlier in almost all measures and dosing conditions, including placebo cannabis/placebo alcohol. Driving videos indicated markedly erratic and abnormal driving behavior, inattention, and distractibility in all conditions, suggesting invalid data. These data were excluded from all driving analyses, yielding N = 18 completing drivers.

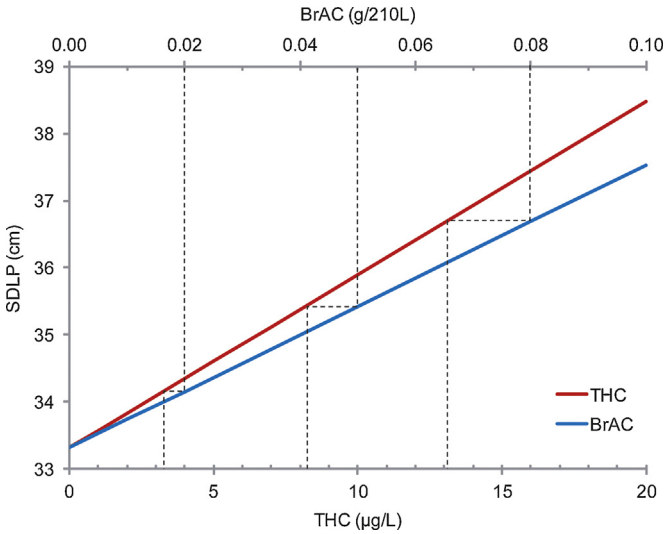

Fig. 2. GLM Select modeled standard deviation of lateral position (SDLP) versus blood Δ^9-tetrahydrocannabinol (THC) concentration (lower x-axis) and versus breath alcohol concentration (BrAC, upper x-axis). Note x-axis scales are different so slopes cannot be directly compared; dotted lines indicate THC concentrations producing equivalent SDLP to 0.02, 0.05, and 0.08 g/210 L BrAC.

3.2. Driving

GLM Select model results are depicted in Table 2. THC concentration and BrAC significantly associated with SDLP, but the interaction (THC × BrAC) was not selected into the model. This indicates additive, rather than synergistic, cannabis and alcohol effects. To account for a possible ceiling effect of increasing concentrations, quadratic terms THC^2 and $BrAC^2$ were added to the list of potential predictors; neither was included in the resultant model. The model predicts that blood THC and BrAC increased SDLP 0.26 cm per μg/L THC and 0.42 cm per 0.01 g/210 L BrAC (Table 3), representing 0.8% and 1.3% increases relative to median baseline (drug-free) SDLP per μg/L THC or 0.01 g/210 L BrAC, respectively. Participants displayed high inter-individual variability in baseline (drug-free) SDLP (Supplemental Fig. 1). BrAC concentrations of 0.05% and 0.08%, the most common *per se* alcohol limits worldwide, were associated with similar SDLP to 8.2 and 13.1 μg/L THC concentrations, respectively (Fig. 2). Low (1 and 2 μg/L) blood THC concentrations were associated with SDLP increases similar to 0.01 g/210 L BrAC. At 5 μg/L THC, a 4.1% increase in SDLP was observed; at 10 μg/L, SDLP increased 8.2%. This change was comparable to 0.05 g/210 L BrAC (6.7% increase) and 0.08 g/210 L BrAC (11% increase).

Natural-log SDLP transformation is common analytical practice due to non-normal distribution. Results obtained from ln SDLP (Supplemental Tables 1 and 2) were similar to untransformed SDLP; therefore, we report the more straightforward and conservative SDLP results.

BrAC significantly increased lane departures/min and maximum lateral acceleration; these measures were not sensitive to cannabis. Neither THC nor BrAC affected standard deviation of steering wheel angle.

THC concentration-based statistical analysis was utilized because of substantial overlap in achieved THC blood C_{max} across the active-THC dose groups (Fig. 3): six participants achieved higher C_{max} after the low than high-THC dose and four had low and high C_{max} within 20% of one another despite a two-fold dose difference. This overlap makes statistical analysis by dose group (Table 4) not scientifically meaningful, illustrating the importance of analyzing effects by actual blood THC. THC concentration peaks prior to finishing inhalation (Huestis et al., 1992), and inhalation variability causes THC concentration variability (Azorlosa et al., 1995, Hartman

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Table 1
Self-reported demographic characteristics, recent cannabis and alcohol consumption and driving history of 19 healthy adult occasional cannabis smokers.

Participant	Sex	Age (years)	Race and ethnicity	BMI (kg/m^2)	Alcohol intake frequency	Typical drinks per occasion	Cannabis intake frequency	Hours "stoned" on typical cannabis occasion[a]	Time since last cannabis consumed (days)	Amount last consumed[b] (joint or joint equivalent)	Years of driving experience	Driving frequency
1	M	23.7	W	24.3	2–3×/wk	2–4	2–4×/m	1–2	1	1	7	≥1×/d
2	F	28.4	AA	23.8	≥4×/wk	2–4	2–4×/m	3–4	14	1	–[c]	–[c]
3	M	21.9	W	24.7	2–3×/wk	5–6	2–4×/m	1–2	6	1	7	≥1×/d
4	M	37.8	W	26.1	2–3×/wk	2–4	2–3×/wk	1–2	3	2.5	23	≥1×/d
5	M	26.6	W	21.6	≤1×/m	2–4	≤1×/m	1–2	11	3.5	12	≥1×/d
6	F	26.3	W	20.0	2–3×/wk	2–4	2–3×/wk	3–4	1	0.25	12	≥1×/d
7	M	25.8	W	40.6	2–4×/m	2–4	2–3×/wk	1–2	0.3	0.5	11	≥1×/d
8	M	26.1	H	31.5	2–4×/m	1–2	2–3×/wk	1–2	3	1	10	≥1×/d
9	M	23.2	W	19.5	2–3×/wk	2–4	2–3×/wk	3–4	2	1	7	≥1×/wk
10	M	23.1	W	23.9	2–4×/m	2–4	≤1×/m	1–2	2	0.25	9	≥1×/d
11	M	32.3	O, H	28.9	2–3×/wk	2–4	2–3×/wk	1–2	4	1	16	≥1×/d
12[d]	F	23.4	W	23.3	2–3×/wk	2–4	2–4×/m	3–4	4	1	8	≥1×/wk
13	F	30.3	AA	24.1	2–3×/wk	2–4	≤1×/m	<1	120	1	14	≥1×/d
14	M	24.6	W	23.3	2–3×/wk	2–4	2–4×/m	1–2	7	0.8	8	≥1×/wk
15	M	21.8	W	32.7	≤1×/m	1–2	2–4×/m	1–2	7	0.13	6	≥1×/d
16	F	21.7	AA, W	23.0	2–4×/m	1–2	2–3×/wk	1–2	1.1	1.5	7	≥1×/d
17	M	28.7	W	18.3	2–3×/wk	2–4	≤1×/m	3–4	45	0.5	12	≥1×/wk
18	M	28.1	W	48.3	2–4×/m	2–4	2–4×/m	3–4	5	1	12	≥1×/d
19	F	22.9	W	21.6	2–4×/m	5–6	2–3×/wk	3–4	1	1	6	≥1×/d
Median (all)		25.8		23.9					4.0	1.0	10	
Mean (all)		26.1		26.3					12.5	1.0	10	
StDev (all)		4.1		7.5					27.9	0.8	4	
Median (N = 18)		25.9		24.0					3.5	1.0	10	
Mean (N = 18)		26.3		26.5					13.0	1.1	11	
StDev (N = 18)		4.2		7.7					28.6	0.8	4	

Abbreviations: W, White; AA, African American; H, Hispanic or Latino; As, Asian; O, Other; AI, American Indian/Native American; StDev, standard deviation.

[a] 'Hours "stoned"' wording originates from Cannabis Use Disorders Identification Test, source of self-reported cannabis frequency data.

[b] Cannabis amount last consumed is based on empirically-normalized joint consumption, to account for various administration routes and self-reported "sharing" between multiple individuals.

[c] Participant did not provide response.

[d] Participant excluded from driving analyses due to consistently outlying behavior.

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Table 2
General Linear Model (GLM) Select results of effects on lateral control measures in 18 volunteer drivers after controlled vaporized cannabis with or without oral alcohol.

Parameter	DF	Estimate (*b*)	*t*	Standard Error	*p*-value
Standard Deviation of Lateral Position (SDLP)					
THC	1	0.26	3.6	0.07	0.0004
BrAC	1	0.42	2.9	0.15	0.0037
THC × BrAC					
Speed limit	1	0.50	19	0.03	<0.0001
Inverse curvature	1	464	9.5	49	<0.0001
Intercept	1	17.3	8.3	2.1	<0.0001
Subject	17				
Model df:	21				
Model F-value	28.24				
Error df:	1916				
Standard deviation of steering angle (curvy)					
THC					
BrAC					
THC × BrAC					
Speed limit	1	0.07	5.4	0.01	<0.0001
Inverse curvature	1	−122	−7.7	16	<0.0001
Intercept	1	5.2	9.0	0.6	<0.0001
Subject					
Model df:	2				
Model F-value	29.59				
Error df:	427				
Standard deviation of steering angle (straight)					
THC					
BrAC					
THC × BrAC					
Speed limit	1	−0.40	−17	0.02	<0.0001
Inverse curvature	1	1389	27	51	<0.0001
Intercept	1	25	21	1.2	<0.0001
Subject					
Model df:	2				
Model F-value	657.9				
Error df:	1936				
Lane departures/min					
THC					
BrAC	1	0.030	2.8	0.009	0.0055
THC × BrAC					
Speed limit	1	0.010	6.8	0.001	<0.0001
Inverse curvature	1	10.9	5.2	2.1	<0.0001
Intercept	1	1.4	10.3	0.14	<0.0001
Subject	17				
Model df:	20				
Model F-value	19.59				
Error df:	840				
Maximum lateral acceleration (non-sharp events)					
THC					
BrAC	1	0.0023	3.5	0.0007	0.0005
THC × BrAC					
Speed limit	1	0.0012	11.4	0.0001	<0.0001
Inverse curvature					
Intercept	1	0.091	10.0	0.0091	<0.0001
Subject	17				
Model df:	19				
Model F-value	17.37				
Error df:	2026				
Maximum lateral acceleration (sharp events)					
THC					
BrAC					
THC × BrAC					
Speed limit					
Inverse curvature	1	−1.8	−4.3	0.43	<0.0001
Intercept	1	0.45	17	0.027	<0.0001
Subject	17				
Model df:	18				
Model F-value	8.61				
Error df:	304				

Driving occurred 0.5 h after drinking placebo or active alcohol (calculated to produce approximate peak 0.065% BrAC) and inhaling placebo, 2.9% THC, or 6.7% THC vaporized bulk cannabis (500 mg, Volcano® Medic vaporizer). Estimate represents parameter (coefficient) estimate [effect size scaled to the unit] for each factor (negative b indicates the parameter decreases the effect; positive b indicates the parameter increases the overall effect).
Boldface indicates parameter included in the final GLM Select model. All *p*-values for final overall analysis of variance of model fits were <0.0001.
Abbreviations: DF, degrees of freedom; THC, blood Δ^9-tetrahydrocannabinol concentration; BrAC, breath alcohol concentration.

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Table 3
GLM Select model estimates for predicted standard deviation of lateral position (SDLP), lane departures/min, and maximum lateral acceleration associated with specific blood Δ^9-tetrahydrocannabinol (THC) concentrations and breath alcohol concentrations (BrAC) during driving.

During-drive concentration		Standard Deviation of Lateral Position (SDLP)			Lane departures/min			Maximum lateral acceleration (non-sharp events)		
THC (μg/L)	BrAC (g/210 L)	Median [range] predicted SDLP (cm)	Difference (cm)	Percent increase[a] (%)	Median [range] predicted lane departures/min (*N*)	Difference (*N*)	Percent increase[a] (%)	Median [range] predicted maximum lateral acceleration (m/s^2)	Difference (m/s^2)	Percent increase[a] (%)
0	0	31.4 [24.7–44.8]	–	–	0.38 [0.05–1.95]	–	–	1.17 [0.87–1.54]	–	–
1	0	31.7 [25.0–45.1]	0.26	0.8	0.38 [0.05–1.95]	0	0	1.17 [0.87–1.54]	0	0
2	0	32.0 [25.3–45.4]	0.52	1.6	0.38 [0.05–1.95]	0	0	1.17 [0.87–1.54]	0	0
5	0	32.7 [26.0–46.1]	1.3	4.1	0.38 [0.05–1.95]	0	0	1.17 [0.87–1.54]	0	0
7	0	33.3 [26.5–46.7]	1.8	5.8	0.38 [0.05–1.95]	0	0	1.17 [0.87–1.54]	0	0
10	0	34.0 [27.3–47.4]	2.6	8.2	0.38 [0.05–1.95]	0	0	1.17 [0.87–1.54]	0	0
20	0	36.6 [29.9–50.0]	5.2	16	0.38 [0.05–1.95]	0	0	1.17 [0.87–1.54]	0	0
0	**0.01**	31.9 [25.2–45.3]	0.42	1.3	0.41 [0.08–1.97]	0.026	6.9	1.19 [0.90–1.56]	0.022	1.9
0	**0.02**	32.3 [25.6–45.7]	0.84	2.7	0.43 [0.11–2.00]	0.053	14	1.21 [0.92–1.58]	0.045	3.8
0	**0.05**	33.6 [26.8–47.0]	2.1	6.7	0.51 [0.19–2.08]	0.13	35	1.28 [0.98–1.65]	0.11	9.5
0	**0.08**	34.8 [28.1–48.2]	3.4	11	0.59 [0.26–2.16]	0.21	55	1.35 [1.05–1.72]	0.18	15
0	**0.10**	35.7 [29.0–49.1]	4.2	13	0.64 [0.32–2.21]	0.26	69	1.39 [1.10–1.76]	0.22	19
2	**0.05**	34.1 [27.4–47.5]	2.6	8.4	0.51 [0.19–2.08]	0.13	35	1.28 [0.98–1.65]	0.11	9.5
5	**0.05**	34.9 [28.1–48.3]	3.4	11	0.51 [0.19–2.08]	0.13	35	1.28 [0.98–1.65]	0.11	9.5

Data generated from 18 healthy occasional cannabis smokers 0.5–1.3h after ingesting placebo or active oral alcohol and inhaling placebo or active vaporized bulk cannabis. Values obtained by assessing general linear model (GLM) Select results of each measure at specific THC concentrations and BrAC. All estimates are for speed 55 miles/h (89 km/h), straight road.

[a] Relative to median baseline (blood THC 0 μg/L, BrAC 0 g/210 L) value.

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Table 4
Participant distribution into 3 (placebo, low, high cannabis) × 2 (placebo, alcohol) repeated measures design and results of repeated measures linear mixed model, accounting for achieved Δ^9-tetrahydrocannabinol (THC) blood maximum concentration. Due to inhaled dose self-titration and interindividual variability, some participants are represented multiple times in certain cells (e.g., THC <8.6 μg/L/placebo, alcohol) and not at all in others.

Structural problem with analysis by condition	Placebo cannabis	THC C_{max} < 8.6 μg/L (median) "Low"	THC C_{max} > 8.6 μg/L (median) "High"
Placebo alcohol	18 data points 0 repeating points 18 unique cases	17 data points 6 repeating points (same participant falls into this category for low and high administered doses) 11 unique cases	19 data points 7 repeating points (same participant falls under this category for low and high administered doses) 12 unique cases
Active alcohol	18 data points 0 repeating points 18 unique cases	19 data points 1 repeating point (same participant falls into this category for low and high administered doses) 18 unique cases	17 data points 1 repeating point (same participant falls into this category for low and high administered doses) 16 unique cases
Results of analysis by condition[a]	Standard Deviation of Lateral Position (SDLP)	Lane departures/min	Maximum lateral acceleration (non-sharp events)
$p_{THC\ group\ (P,L,H)}$	0.2801	0.4537	0.2543
$p_{alcohol\ (P,A)}$	0.0673	0.1286	0.0918
$p_{THC\text{-}alcohol}$	0.2398	0.1245	0.4949
$p_{drive\ event}$	<0.0001	<0.0001	<0.0001

[a] Due to unequal cells and resultant invalid statistical assumptions for within-subjects (repeated measures) design and "missing" or duplicate data, linear mixed model analysis (for which resultant *p*-values are displayed) has low power and uncertain interpretation.

et al., 2015b). Table 5 presents mean (SD) results by THC and alcohol condition.

3.3. Pre- and post-drive blood and OF THC concentrations

Table 6 presents pre- and post-drive blood and OF concentrations. Full blood and OF pharmacokinetic data are presented in Hartman et al. (2015a,b) respectively). Between-subject blood concentration variability (coefficient of variation) was substantially lower than matched OF concentration variability at all time points: 45–65% vs. 125–207%, respectively, immediately post-dose; 39–69% vs. 129–184% at 1.4 h; and 61–82% vs. 139–174% at 2.3 h (Table 6).

4. Discussion

Using a sophisticated driving simulator and rigorous placebo-controlled, within-subject design, we found a positive association between blood THC concentration and one (SDLP) of three alcohol-sensitive lateral control impairment measures (SDLP, normalized lane departures, maximum acceleration). Cannabis-alcohol combination effects were additive, not synergistic.

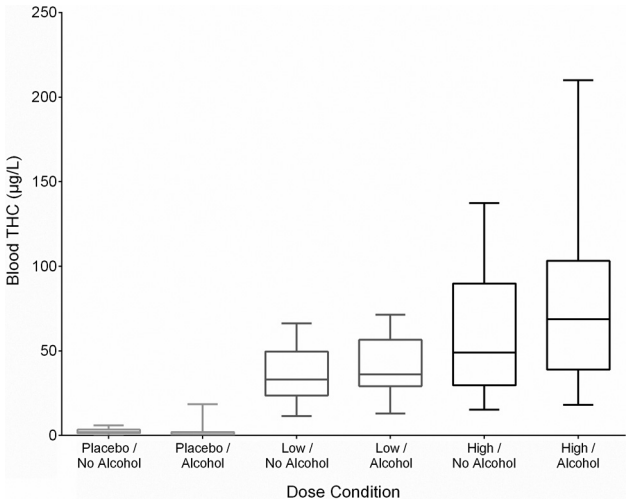

Fig. 3. Box plot of maximum blood Δ^9-tetrahydrocannabinol (THC) concentration by administered cannabis (placebo, 0.008% THC; low, 2.9% THC; high, 6.7% THC) and alcohol (placebo, active) doses for 18 participants.

Decreased lateral control was associated with blood THC concentrations and BrAC, based on descriptive models. SDLP is among the most sensitive and consistently utilized driving impairment measures (Charlton and Starkey, 2013; Ramaekers et al., 2006a; Verster and Roth, 2011, 2012). Given that most countries have 0.05 or 0.08% BAC *per se* laws, the observed SDLP increase may be substantial enough to be considered impairment. Although SDLP (experimental measure) is not directly validated to predict crash risk (epidemiological measure), it is an objective measure of continuous behavior while driving (Lococo and Staplin, 2006). The lowest criterion of drug-induced driving impairment is considered to be SDLP consistent with 0.05 BAC, approximately 2.4 cm (Lococo and Staplin, 2006). In this study, ≥8.2 μg/L THC met that criterion. The increase associated with 10 μg/L THC also was similar to 2 μg/L THC + 0.05 g/210 L BrAC (8.4% increase). At higher 20 μg/L THC, SDLP increased 16%, comparable to 0.10 g/210 L BrAC (13% increase). In an on-road study (Ramaekers et al., 2000; Robbe, 1998), 100, 200, and 300 μg/kg THC doses (~7 mg, ~14 mg, ~21 mg) significantly increased SDLP 1.7–3.5 cm relative to placebo. These increases are consistent with our 7–10 μg/L during-drive THC (5.8–8.2% increase) or 0.05–0.08 g/210 L BrAC (6.7-10.7% increase, Table 3). Our final lane departures/min and maximum lateral acceleration GLM Select models did not include THC, indicating increasing THC concentrations did not increase these measures. Alcohol concentration-dependently increased lane departures/min and maximum lateral acceleration, with 0.05 g/210 L corresponding to 35% and 9.5% increases, respectively.

Combining cannabis with alcohol produced an additive – rather than synergistic – effect on SDLP, with no interaction term. Past simulator studies were inconsistent regarding SDLP cannabis–alcohol interactions. Ronen et al. (2010) observed significant increases in lane position variability when 13 mg THC and 0.05% (BAC) alcohol were combined, despite neither producing an independent significant effect. Conversely, Lenné et al. (2010) observed significant main effects of cannabis and alcohol independently, but no interaction (combined effects not synergistic), similar to our findings. Combining 100 or 200 μg/kg THC with

Table 5
Mean (standard deviation) results for standard deviation of lateral control (SDLP), lane departures/min, and maximum lateral acceleration during driving, grouped by achieved THC/alcohol concentration conditions and by administered THC and alcohol dose conditions.

Achieved THC, alcohol conditions (THC grouped by median blood concentration)			Standard Deviation of Lateral Position (SDLP)				Lane departures/min				Maximum lateral acceleration			(non-sharp events)
THC Group	Alcohol dose	*N*	Mean (cm)	St Dev (cm)	Difference (cm)	Percent increase[a] (%)	Mean (*N*)	St Dev (*N*)	Difference (*N*)	Percent increase[a] (%)	Mean (m/s^2)	St Dev (m/s^2)	Difference (m/s^2)	Percent increase[a] (%)
Placebo	Placebo	18	28.8	17.8	–	–	0.52	0.71	–	–	0.115	0.080	–	–
<Median (<8.6 μg/L)	Placebo	11	32.3	21.7	3.5	12	0.69	0.93	0.17	33	0.112	0.083	–0.003	-3
>Median (>8.6 μg/L)	Placebo	12	29.8	16.4	1.0	3	0.54	0.70	0.02	4	0.110	0.079	–0.005	-4
Placebo	Active	18	32.3	21.7	3.5	12	0.74	0.98	0.22	42	0.130	0.091	0.015	13
<Median (<8.6 μg/L)	Active	18	34.6	22.0	5.8	20	0.76	0.90	0.24	46	0.126	0.086	0.011	10
>Median (>8.6 μg/L)	Active	16	32.2	17.8	3.4	12	0.77	0.98	0.25	48	0.121	0.088	0.006	5
Administered dose conditions			SDLP				Lane departures/min				Maximum lateral acceleration (non-sharp events)			
THC	Alcohol	N	Mean (cm)	St Dev (cm)	Difference (cm)	Percent Increase[a] (%)	Mean (N)	St Dev (*N*)	Difference (*N*)	Percent Increase[a] (%)	Mean (m/s^2)	St Dev (m/s^2)	Difference (m/s^2)	Percent Increase[a] (%)
Placebo	Placebo	18	28.8	17.8	–	–	0.52	0.71	–	–	0.115	0.080	–	–
Low	Placebo	18	31.3	20.3	2.5	9	0.64	0.85	0.12	23	0.116	0.084	0.001	1
High	Placebo	18	31.2	19.1	2.4	8	0.61	0.84	0.09	17	0.106	0.078	-0.009	-8
Placebo	Active	18	32.3	19.3	3.5	12	0.74	0.98	0.22	42	0.130	0.091	0.015	13
Low	Active	18	34.2	21.6	5.4	19	0.73	0.94	0.21	40	0.123	0.083	0.008	7
High	Active	18	32.2	17.4	3.4	12	0.80	0.96	0.28	54	0.123	0.092	0.008	7

Data are from 18 healthy occasional cannabis smokers 0.5–1.3h after ingesting placebo or active oral alcohol and inhaling placebo or active (low/2.9%, high/6.7% Δ^9-tetrahydrocannabinol [THC]) vaporized bulk cannabis. Due to the resultant unbalanced design in low- and high-THC conditions imposed by participants' self-titration, statistical analysis of variance could not be conducted by dose condition.

[a] Relative to placebo–placebo condition.

0.04% target BAC in the on-road study described above significantly increased SDLP by 5.3 and 8.5 cm, classified as "severe" performance decrements (Ramaekers et al., 2000; Robbe, 1998). In our model, this increase is similar to ≥20 μg/L blood THC alone. Although epidemiological studies do not quantify crash risk by SDLP, increases in lane weave may lead to more lane departures (detected by Downey et al., 2013) and, in turn, more crashes. Cannabis approximately doubled crash risk in two recent epidemiological meta-analyses (Li et al., 2012; Asbridge et al., 2012).

Unlike cannabis, alcohol affected additional lateral control parameters besides SDLP. Lane departures/min and maximum lateral acceleration also increased with BrAC, consistent with prior NADS alcohol findings (Lee et al., 2010). This suggests more extreme reaction to lateral position when DUI alcohol, compared to DUIC. Cannabis-influenced drivers may attempt to drive more cautiously to compensate for impairing effects, whereas alcohol-influenced drivers often underestimate their impairment and take more risks (Sewell et al., 2009). Alcohol's strong effects on driving are well-established (Charlton and Starkey, 2013, 2015; Moskowitz and Fiorentino, 2000; Van Dyke and Fillmore, 2014). Alcohol increased center and edge lane crossings, and time over the edge line in a simulated drive (Charlton and Starkey, 2013). Lack of observed cannabis effects on lane departures contrasts with prior findings. Downey et al. (2013) observed dose-dependent cannabis effects on straddling lane barrier or solid lines, with or without alcohol, in simulated nighttime driving. That study had more participants (80), possibly providing higher power to detect weak effects. In one on-road study, only cannabis–alcohol combinations significantly increased time out of lane (Ramaekers et al., 2000; Robbe, 1998); neither cannabis nor alcohol (0.04% BAC) alone produced a significant effect. Because increasing lane departures and "time out of lane" require more substantial lane weaving than SDLP, this discrepancy may result from the low alcohol dose administered in that study. SDLP is more sensitive, with observable impairment at BACs as low as 0.04% (Moskowitz and Fiorentino, 2000).

Neither cannabis nor alcohol affected standard deviation of steering angle. To our knowledge, only one prior simulator study found a significant alcohol effect on this parameter: 0.6 g/kg alcohol (peak BACs ~0.05%) produced a significant but small increase in standard deviation of steering angle (Lenné et al., 2010). Lower 0.4 g/kg (peak BACs ≤ 0.025%) had no effect. Although cannabis alone (19, 38 mg) did not significantly increase steering angle variability (main effect), there was significant interaction with driver experience. Experienced drivers (≥7 years driving) showed unchanged or decreased steering angle variability with increasing cannabis dose relative to placebo; inexperienced drivers (<2 years) had increased variability (Lenné et al., 2010). All of our participants had ≥6 years of driving experience, perhaps accounting for this discrepancy. Lenné et al. (2010) also analyzed effects by dose rather than concentration, possibly resulting in greater apparent effect size because dose-wise (categorical) variable analyses generally have higher power than continuous variables. Multiple other studies found no cannabis-only effect on steering wheel position variability (Anderson et al., 2010; Ronen et al., 2010), although one observed increased steering variability in occasional smokers after alcohol alone and alcohol-cannabis combination (Ronen et al., 2010). Standard deviation of steering angle appears insensitive, due to the amplifying effect of steering mechanisms. Minor steering adjustments can substantially alter course and change lane position due to forward motion, despite re-straightening the wheel.

By controlling *ad libitum* inhalation topography (e.g., inhalation rate, depth, hold time), smokers can self-titrate cannabis dose to achieve desired pharmacological response (Azorlosa et al., 1995). We infer self-titration from the observed disjunction between dose and THC concentration; there is often poor correlation between THC dose and blood concentration, making concentration-based

Table 6
Blood and oral fluid THC and variability prior to and after driving ($N = 19$) after controlled vaporized active (2.9% THC and 6.7% THC) cannabis with or without alcohol.

Time post-dose (h)		Blood THC (μg/L)				OF THC (μg/L)			
		No alcohol		Alcohol		No alcohol		Alcohol	
		2.9%	6.7%	2.9%	6.7%	2.9%	6.7%	2.9%	6.7%
−0.8 (baseline)	Median	0	0	0	0	0.5	0	0	0.6
	range	0–6.2	0–5.4	0–4.9	0–6.3	0–30.7	0–11.7	0–72.9	0–34.2
	Mean (SD)	0.5 (1.5)	0.4 (1.3)	0.5 (1.2)	0.6 (1.5)	4.6 (8.7)	2.6 (4.0)	6.3 (17.0)	4.7 (8.9)
	%CV	284%	332%	245%	282%	191%	157%	272%	189%
0.17 (pre-drive 1)	Median	32.7	42.2	35.3	67.5	848	764	735	952
	range	11.4–66.2	15.2–137	13.0–71.4	18.1–210	32.1–18,230	25.1–23,680	72.9–7,494	22.7–66,200
	Mean (SD)	35.9 (16.7)	56.2 (36.4)	40.5 (18.2)	75.0 (48.1)	2,101 (4,142)	3,220 (5,645)	1,599 (2,005)	7,652 (15,842)
	%CV	46%	65%	45%	64%	197%	175%	125%	207%
0.42 (pre-drive 2)	Median	10.0	13.2	10.6	16.2	–	–	–	–
	range	1.6–17.9	2.4–40.8	5.5–17.4	5.3–43.9				
	Mean (SD)	10.0 (4.5)	16.8 (10.9)	10.4 (3.4)	19.0 (11.9)	–	–	–	–
	%CV	45%	65%	33%	63%	–	–	–	–
1.4 (post-drive 1)	Median	3.7	4.6	3.6	6.2	52.5	91.0	69.5	138
	range	0–10.7	0–14.7	1.4–6.3	1.3–18.4	3.0–662	9.3–1,028	7.0–1,822	5.2–3,940
	Mean (SD)	3.9 (2.3)	5.7 (3.9)	3.6 (1.4)	6.8 (4.6)	91.3 (145)	213 (275)	228 (418)	637 (1,097)
	%CV	59%	69%	39%	68%	159%	129%	184%	172%
2.3 (post-drive 2)	Median	1.9	2.6	1.8	3.2	33.1	46.9	35.4	91.0
	range	0–8.5	0–9.6	0–4.9	0–9.5	1.8–374	1.9–542	8.7–473	1.6–1,541
	Mean (SD)	2.2 (1.8)	3.2 (2.6)	1.8 (1.1)	3.2 (2.5)	47.7 (81.1)	92.1 (128)	86.4 (124)	263 (458)
	%CV	82%	82%	61%	77%	170%	139%	144%	174%

Abbreviations: THC, Δ^9-tetrahydrocannabinol; OF, oral fluid; SD, standard deviation; CV, coefficient of variation.

analysis more meaningful and robust than dose-based analysis (see Tables 4–5, Fig. 3). In our sample, 52.6% of participants showed evidence of self-titration (Hartman et al., 2015b). Substantial concentration variability was observed, consistent with prior cannabis research (Desrosiers et al., 2014). This further underscores the robustness of concentration-based – rather than dose-based – analysis.

There is substantial interest in relating driving performance directly to OF concentrations due to screening advantages. THC enters OF primarily by oromucosal contamination during inhalation, and consequently is less representative of systemic concentrations shortly after intake. OF concentration variability was 2–5-fold higher than for paired blood concentrations, making interpretation of effects more challenging. Similar to blood, low OF THC concentrations are difficult to interpret because intake history and individual variability affect detection time and later concentrations. However, in this sample, OF THC > 1600 μg/L indicated intake within the last 1.4 h, and >600 μg/L indicated intake within the last 2.3 h. In a roadside study, the percentage of people displaying observable cannabis-related impairment increased with increasing OF concentrations when aggregated into wide ranges (≤3 μg/L, 3–25 μg/L, 25–100 μg/L, >100 μg/L) (Fierro et al., 2014).

4.1. Strengths and limitations

Major study strengths include the double-blind, placebo-controlled, within-subject design; drive scenarios controlling for other road conditions (speed limit and curvature), which potentially affect drivers' lateral control and road tracking performance; administration of multiple doses of cannabis (THC) with/without alcohol; concentration-based analysis; and multiple specimen collections before and after driving (allowing during-drive pharmacokinetic modeling), to better relate driving impairment to THC concentrations.

In authentic DUIC cases, measured THC concentrations do not reflect those present during driving. Blood collection is typically delayed 90 min to 4 h after the event (Biecheler et al., 2008; Jones et al., 2008). During this delay, there is rapid THC distribution from blood into highly-perfused tissues, resulting in rapid blood THC concentration decrease in the first hour post-inhalation. Later, THC concentration continues to decrease, albeit more slowly. This results in lower measured THC concentrations than were present during driving. In contrast, we examined driving performance relative to THC concentrations and BrAC that were present during driving. Thus, to our knowledge, the current study is among the most robust analyses of cannabis and alcohol effects on lateral control at specific THC concentrations. For context, we report driving performance results at concentrations typically considered or established for *per se* laws around the world (1, 2, 5, 7 μg/L THC; 0.02, 0.05, 0.08% BrAC) (Armentano, 2013; Grotenhermen et al., 2007; Karakus et al., 2014; Lacey et al., 2010; Ramaekers et al., 2006b; Verstraete et al., 2011). However, these *per se* limits are applied to THC concentrations that may substantially underestimate concentrations during driving. Thus, our reported THC 1–5 μg/L SDLP changes may be understated compared to forensic DUIC cases. In the present study, median blood and OF THC concentrations immediately post-dose were >30 μg/L and >700 μg/L, respectively. Blood THC ≥ 20 μg/L indicated intake within the last 0.42 h and THC ≥ 10 μg/L indicated intake within the last 1.4 h. Thus, if people drive during or soon after cannabis inhalation, during-drive THC concentrations could exceed 20 μg/L. Our SDLP increase associated with THC ≥ 20 μg/L (~5.2 cm) was considered "severe" by other researchers (Ramaekers et al., 2000; Robbe, 1998), representing a 16% increase in our observed lane position variability. Despite lack of significant THC effect on lane departures/min, our results suggest substantial lateral control performance decrements, consistent with effects produced by known impairing alcohol concentrations. Verster and Roth (2014) determined that lane departures alone were not sufficiently sensitive to experimentally detect impaired driving or effect size differences. SDLP is a sensitive marker, serving as experimental proxy for rarer events such as lane departures. Even minor lateral control decrements may be dangerous in narrow or winding roads, or in heavy traffic where navigational precision or defensive driving may be required.

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This study has several limitations. We approached data analyses via a stepwise GLM Select procedure, with the goal of describing data without assumptions of which parameters (THC, BrAC, other) would produce fixed effects. In research settings, participants are aware driving is constantly under observation, and may drive with greater caution or focus. Other participants may have wanted to demonstrate that cannabis does not affect driving; public attitudes toward DUIC are less negative than for DUI alcohol (McCarthy et al., 2007; Terry and Wright, 2005). However, self-perception of driving performance or impairment – even without drugs – may be unreliable (Van Dyke and Fillmore, 2014; Verster and Roth, 2012).

This study was limited to occasional smokers. Frequent cannabis smokers demonstrate tolerance to some acute cannabis intoxication effects (Ramaekers et al., 2011), but tolerance did not compensate for all effects (Downey et al., 2013). There is currently substantial interest in comparing occasional to frequent smokers and assessing potential tolerance (Ramaekers et al., 2009; Toennes et al., 2008; Wright and Terry, 2002), especially as medical and recreational cannabis becomes more commonplace.

We do not believe that conducting this study in a driving simulator, rather than on the road, represents a significant limitation. Rather, simulators offer advantages for assessing impaired driving. Participants can engage in risky driving behavior without endangering themselves or others. Simulators provide controlled reproducible research environments and ability to make detailed real-time measurements. Modern simulators produce highly realistic driving scenarios (Hartman and Huestis, 2013). The NADS-1 is the world's most sophisticated simulator, and was successfully utilized to assess distracted and drugged driving (Garrott et al., 2005; Lee et al., 2010).

4.2. Conclusion

In this rigorous, double-blind, placebo-controlled study, cannabis and alcohol were significantly associated with impaired driving lateral control. Cannabis only affected SDLP; whereas alcohol affected SDLP, lane departures/min, and maximum acceleration. During-drive 8.2 μg/L blood THC was associated with SDLP increases similar to 0.05 g/210 L BrAC (~0.05% BAC), and SDLP at 13.1 μg/L THC approximated 0.08 g/210 L BrAC. Combining alcohol and cannabis produced an additive effect on SDLP; 5 μg/L THC with 0.05 g/210 L BrAC was similar to 0.08 g/210 L SDLP impairment. These THC concentrations during driving are higher than those generally measured hours later during sample collection. OF concentration variability was substantially greater than blood concentration variability, suggesting better performance as a screening tool than impairment gauge.

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Contributors

Authors Hartman, Brown, Gorelick, Gaffney, and Huestis participated in the research design. Authors Hartman, Brown, Milavetz, Spurgin, and Gaffney participated in research conduct, under oversight from Author Huestis. Authors Hartman, Brown, Milavetz, Spurgin, Pierce, Gaffney, and Huestis participated in data analysis, under the substantial guidance of Author Pierce. Author Hartman wrote the initial draft of the manuscript, Authors Gorelick and Huestis contributed substantially to the draft revision process, and all authors contributed to the finalized version.

Conflicts of interest

Volcano® and Quantisal™ devices and supplies (Storz & Bickel, Tuttlingen, Germany and Immunalysis, Pomona, CA) were provided by manufacturers through Materials Transfer Agreements. No commercial entity played any role in study design and conduct, data analysis, manuscript drafting, or the decision to publish. The authors declare no personal conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2015.06.015

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