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Acute and residual effects of smoked cannabis: Impact on driving speed and lateral control, heart rate, and self-reported drug effects

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ABSTRACT

Background: Although driving under the influence of cannabis is increasingly common among young adults, little is known about residual effects on driver behavior. This study examined acute and residual effects of smoked cannabis on simulated driving performance of young cannabis users.

Methods: In this double-blind, placebo-controlled, parallel-group randomized clinical trial, cannabis users (1–4 days/week) aged 19–25 years were randomized with a 2:1 allocation ratio to receive active (12.5% THC) or placebo (0.009% THC) cannabis in a single 750 mg cigarette. A median split (based on whole-blood THC concentrations at the time of driving) was used to divide the active group into low and high THC groups. Our primary outcome was simulated driving performance, assessed 30 min and 24 and 48 h after smoking. Secondary outcomes included blood THC concentrations, subjective drug effects, and heart rate.

Results: Ninety-six participants were randomized, and 91 were included in the final analysis (30 high THC, 31 low THC, 30 placebo). Mean speed (but not lateral control) significantly differed between groups 30 min after smoking cannabis ($p \leq 0.02$); low and high THC groups decreased their speed compared to placebo. Heart rate, VAS drug effect and drug high increased significantly immediately after smoking cannabis and declined steadily after that. There was little evidence of residual effects in any of the measures.

Conclusion: Acutely, cannabis caused decreased speed, increased heart rate, and increases in VAS drug effect and drug high. There was no evidence of residual effects on these measures over the two days following cannabis administration.

1. Introduction

Cannabis is a very commonly used drug, and as more jurisdictions legalize its medicinal and recreational use, there is increasing concern with its effects. Many studies have examined the acute effects of the drug, showing that cannabis influences cognitive and psychomotor function, affect, and cardiovascular measures among others (e.g., Broyd et al., 2016; Spindle et al., 2018). Some research also suggests that an acute dose of cannabis may have residual effects 24 h and perhaps longer following use (e.g., Pope et al., 1995). As more jurisdictions consider changing laws in ways that will allow increased access to the drug, a better understanding of both acute and residual effects is

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needed.

Understanding these acute and residual effects is particularly relevant for young cannabis users. For example, data suggest that driving under the influence of cannabis (DUIC) is now more common than driving under the influence of alcohol (DUIA) among young drivers in North America (Adlaf et al., 2003; O'Malley and Johnston, 2013). Recent meta-analyses have confirmed that cannabis increases collision risk, with reported pooled odds ratios ranging from 1.36 to 2.66 (Asbridge et al., 2012; Li et al., 2012; Rogeberg and Elvik, 2016). In Canada, DUIC-related motor vehicle collisions (MVCs), injuries and fatalities were estimated to cost more than $1 billion in 2012 and are most common among younger drivers (Wettlaufer et al., 2017). Driving simulator studies indicate that cannabis-related effects most commonly reported are decreased speed (Anderson et al., 2010; Downey et al., 2013; Hartman et al., 2015; Lenne et al., 2010; Ronen et al., 2010) and poorer lane control (Downey et al., 2013; Hartman et al., 2015, 2016; Lenne et al., 2010). However, the impact of the drug on driver behavior and collision risk of young drivers specifically has received little attention. Young drivers are more likely to be involved in distraction-related MVCs (Buckley et al., 2014) due to a combination of developmental factors that may relate to a lower comprehension of driving safety (Keating, 2007), inexperience allocating attentional resources to different aspects of the driving environment (Hosking et al., 2009), and a greater propensity to engage in distracting activities while driving (Lee, 2007). This is particularly relevant given that experimental studies of adult drivers found that performance under the influence of cannabis may deteriorate under conditions of divided attention or increased complexity (Anderson et al., 2010; Lenne et al., 2010; Ogourtsova et al., 2018).

Pope and colleagues reviewed the literature and concluded that residual effects of cannabis on attention, psychomotor function, and memory may be observed at periods of up to 24 h following administration (Pope et al., 1995). However, results are not consistent. Heishman et al. (1990), in a sample of 3 cannabis users ranging in age from 27 to 29 who reported using an average of 4.7 joints per month, observed residual effects of smoking 2–4 cannabis cigarettes containing 2.57% THC 24 h after smoking on measures of cognitive performance, but not on measures of subjective effects and heart rate. Yesavage et al. (1985) examined flight simulator performance 24 h after smoking a cigarette containing 19 mg of THC in a sample of 10 pilots with an average age of 29 years who were experienced marijuana smokers and observed significant performance impairment. Similarly, Leirer et al. (1991) examined flight simulator performance following smoking a cigarette containing 20 mg of THC in a sample of 11 pilots who were experienced cannabis users with an average age of 31.1 years and observed significant impairment of performance 24 h later. However, Leirer et al. (1989) examined flight simulator performance in two samples of 9 pilots each aged 25.5 years and 37.6 years on average, respectively, who were experienced cannabis users and had smoked a cigarette containing 0, 10 or 20 mg of THC, and found no significant impairment 24 or 48 h later. Ronen et al. (2008) examined driving simulator performance in a group of 14 students with an average age of 26.1 years who were recreational cannabis users (used 1–4 times per month). Twenty-four hours after smoking a dose of 17 mg of THC, no significant impact on performance measures was found. Subsequently, Ronen et al. (2010) examined the effects of both alcohol and cannabis on driving simulator performance in a group of 12 students with an average age of 26.1 years who were recreational cannabis users (used 1–4 times per month). No residual effects of a dose of 13 mg THC, or THC plus alcohol, on performance measures were observed 24 h after smoking.

A better understanding of acute and residual effects of cannabis may be particularly relevant to young cannabis users. If they drive, they are still acquiring experience with both driving and the effects of cannabis. However, no studies examining acute and residual effects of cannabis on driving and other measures among young individuals have been reported. The aim of this study was to examine the acute and residual (24 and 48 h after smoking) effects of smoked cannabis on simulated driving measures (driving speed, lateral control), self-reported drug effects and heart rate in young adults aged 19–25 years.

2. Methods

2.1. Study population and design

Healthy young adults (aged 19–25 years) with a valid driver's license were recruited from community advertisements in Toronto between July 2012 and August 2016. All participants were regular cannabis users (1–4 days/week) and evidence was required of recent cannabis use (based on qualitative urine THC-COOH determination; point-of-care cut-off of 50 ng/mL or laboratory assay cut-off of 15 ng/mL); the intention was to recruit participants who were regular recreational (non-medical) cannabis users who were not dependent on cannabis and thus would not experience withdrawal during the study sessions. Participants were excluded if they regularly used psychoactive medications that could impact their driving performance (e.g. antidepressants, benzodiazepines), met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria for lifetime substance dependence (including lifetime cannabis dependence), had severe psychiatric or medical conditions, had a family history of schizophrenia, or were pregnant, trying to become pregnant, or breastfeeding.

The study was a double-blind, placebo-controlled, parallel-group design randomized clinical trial conducted at a single site in Ontario, the Centre for Addiction and Mental Health (CAMH). Participants were randomized to receive either active or placebo cannabis using a 2:1 allocation ratio to maximize the number of participants in the active group. The study involved a total of five sessions (after initial telephone pre-screening): an eligibility assessment, a practice session to allow participants to familiarize themselves with testing procedures (and to collect some self-report data, e.g. past 12-month impaired driving), an acute drug exposure session, and two sessions at 24 and 48 h after drug exposure to assess residual effects. Breathalyser (Alert™ J5 model, Alcohol Countermeasure Systems) readings and urine samples for point-of-care toxicology screening (Quickscreen™ CLIA-Waived 10-Panel Multi Drug Test) were obtained at the beginning of each session to aid in assessing compliance with the requirement that participants do not use cannabis, alcohol or other drugs not medically required for 48 h prior to the practice session and for the duration of the study. These tests were used in addition to self-reported last use to monitor abstinence (thus, it is possible that some participants may not have remained abstinent for at least 48 h).

2.2. Study intervention

All participants received a single cannabis cigarette with a mass of approximately 750 mg. The Δ^9-tetrahydrocannabinol (THC) content in the active condition was 12.5% (approximately 93.75 mg) and 0.009% in the placebo condition (approximately 0.07 mg). The cannabidiol (CBD) content was negligible (< 0.5%). Active cannabis (as loose plant material) was obtained from Prairie Plant Systems Inc., a producer licensed by Health Canada, while placebo cannabis was obtained from the National Institute of Drug Abuse (NIDA) in the United States and arrived as pre-made cigarettes that had to be disassembled and re-weighed. The CAMH Research Pharmacy prepared the cannabis cigarettes and maintained the randomization codes. A computer-generated list of random numbers was used to allocate participants to active or placebo cannabis in blocks of 9; the allocation sequence was generated by the Research Pharmacy and concealed from personnel involved in running the trial. Prepared cigarettes were stored in a secure, locked freezer at −20 °C. Prior to each drug administration session, cigarettes were removed from the freezer and re-humidified for approximately 12 h. Active and placebo cigarettes were visually indistinguishable, had

the same mass, and were rolled using the same rolling paper. Cigarettes were weighed before and after smoking to estimate dosage. The estimated dose was calculated as the difference in mass of the cigarette multiplied by the potency of THC in the active plant material (12.5%).

Participants were instructed to smoke *ad libitum,* i.e. to their desired level, over the course of 10 min in a dedicated reverse airflow room with external ventilation and were observed through a one-way mirror to monitor any behavioral signs of discomfort and to ensure correct timing of cigarette smoking. The end of smoking marked time 0. Study personnel observing the participant noted the duration of smoking. To help maintain the blind, separate personnel who were not involved in administering driving trials collected the cigarette remnants and all potentially unblinding data (e.g. urine toxicology results). Participants were asked at the end of the session to guess whether they had received active or placebo cannabis in order to examine the success of the blinding procedures.

2.3. Driving simulator

The CAMH Virage VS500 M simulator consists of the driver's side instrument cluster, steering wheel, controls, and center console of a General Motors compact car. The steering wheel provides dynamic force feedback, as do the brake and accelerator pedals. The visual system consists of three 50-inch screens providing a 180° field of view in the front, and two 17-inch side displays providing visual feedback for the left and right blind zones. Custom scenarios used for the drives were all programmed on the same 9-km stretch of rural highway, along with periodic driving interactions (e.g. slowly moving vehicle, disabled vehicle at roadside) that differed for each scenario. Participants were instructed to drive as they normally would, allowing for assessment of driver behavior (i.e. how a driver *chooses* to operate the vehicle) as opposed to one's ability to perform certain driving skills. Posted speed limits were 80 km/hr.

2.4. Outcome measures

Our driving outcome variables of interest were mean speed and lateral control, the two measures most commonly affected by cannabis in previous research (Anderson et al., 2010; Downey et al., 2013; Hartman et al., 2015, 2016; Lenne et al., 2010; Ronen et al., 2010) assessed on a straightaway (i.e. a straight stretch of road without any traffic control signals or other moving vehicles). Lateral control was operationalized as the standard deviation of the absolute distance between the center of the simulated vehicle and the center of the lane in which the participant was driving. Both variables were assessed under both single task and dual task scenarios (the dual task scenario always immediately followed the single task scenario). In the dual task condition, the participant counted backwards from a number between 700 and 999 by 3's while driving (Lansdown and Saunders, 2012; North and Hargreaves, 1999). The addition of a counting backward task has a long history of use to increase the complexity of cognitive and other tasks (e.g., Peterson and Peterson, 1959). Driving trials occurred at baseline (i.e. before cannabis administration), and then again at +30 min, +24 h, and +48 h.

We also assessed subjective drug effects, whole-blood concentrations of THC, and heart rate (cognitive functioning measures were also included but will be reported elsewhere). At each data collection time point (baseline, +5, +15, +30 min, +1, +2, +3, +4, +5, +6 h), vital signs, a 7-item visual analogue scale (VAS) for assessment of cannabis-specific drug effects, and a blood sample for quantitative measurement of THC concentrations were collected. Measures of cognitive functioning, the Addictions Research Centre Inventory (ARCI) short form (Haertzen et al., 1963) and the Profile of Mood States (POMS) (Spielberger, 1972), were collected at baseline and +1 h. In addition, participants were asked to rate how willing they would be to drive a real vehicle on a scale of 1 (very unwilling) to 5 (very willing) just after driving simulation trials. Blood samples were collected via an indwelling intravenous catheter that was inserted by a registered nurse during the acute drug exposure session and was removed at the end of the acute drug exposure session. For the 24 and 48 h sessions, participants were escorted to the CAMH Clinical Laboratory for single blood draws.

At the end of each study session, the EDTA-blood specimens were transferred from the collection tubes to cryovials and stored at -80 ^{0}C until analyzed at the CAMH Clinical Laboratory. THC quantification was performed by GC−MS (gas chromatography coupled with mass spectrometry) as described by Sears RM in the application note 00315 (Agilent Technologies, Solid Phase extraction of THC, THC-COOH and 11-OH-THC from Whole Blood) with slight modifications. Briefly, 1 mL whole blood specimens spiked with deuterated internal standard (THC-D3) were solid phase extracted using the Bond Elut Certify II (200 mg) cartridges (Agilent Technologies). The extracts were evaporated under nitrogen and BSTFA-derivatized prior to GC−MS analysis using the ISQ, single quadrupole mass spectrometer (ThermoFisher). The THC quantification was in SIM mode using the target ion of 386 Da. Calibration with internal standardization was performed with linear regression curve fits with 1/X weighting. Detection (LOD) and quantification (LOQ) limits for THC were 0.2 ng/mL and 0.5 ng/mL, respectively.

Throughout the study, participants were monitored for any adverse events (AEs) using a modified version of the Systematic Assessment for Treatment Emergent Effects (SAFTEE) questionnaire (Guy et al., 1986; Rabkin and Markowitz, 1986). AEs were coded based on a list of preferred terms, and the date of onset, duration, severity, relationship to study drug, and action taken were recorded. In the event that an AE did not match the SAFTEE preferred terms, an alternate term was used. Some participants experienced multiple AEs; each AE was coded separately.

2.5. Sample size

Relatively little research is available to guide effect size estimations of cannabis' residual effects on driving simulator performance, and a major goal of the proposed research was to provide information needed for a more comprehensive investigation of this question. The sample size needed to achieve the power necessary to detect a residual effect of cannabis that corresponds to a medium effect size of 0.5 (Cohen's $d = 0.5$) is 114 (76 receiving cannabis and 38 receiving placebo). Data collection continued until funds were expended.

An interim analysis was conducted with n = 54 participants enrolled as of April, 2015. This analysis was conducted to determine if there were final adjustments that were needed to the study procedures, given the novelty of the study design. No adjustments were made as a result.

2.6. Statistical analysis

SPSS 24.0 for Windows was used for all statistical analyses. Initially, all data were subject to inspection and descriptive analyses (means, proportions). Subsequent analyses employed general linear model (GLM) ANOVA. Inspection of the blood THC data revealed substantial variability among the active cannabis group, similar to that seen in other studies, which could be due to variations in smoking practices or self-titration of effects (Newmeyer et al., 2014). As a result, the active cannabis group was divided into two groups based on a median split at 7.3 ng/mL blood THC concentration at +30 min (the beginning of the driving trials), yielding low and high THC groups. Analyses of the THC, heart rate, and VAS data employed mixed (split-plot) ANOVA comparing the three groups from baseline until +48 h. For the driving simulator data, we were specifically interested in change from baseline, and thus derived change scores (post-pre). These data were then examined with a 3 (group) by 3 (time) ANOVA. Because of our specific interests in the acute and residual effects of cannabis, we report here

Table 1
Participant characteristics by group (mean (SD) unless noted).

	Placebo n = 30	Low THC n = 31	High THC n = 30	p
Age (years)	21.9 (2.2)	22.2 (1.8)	22.3 (2.0)	n.s.
Sex	**30.0[a,b]**	**41.9[b]**	**13.3[a]**	**0.046**
Female %				
BMI (kg/m^2)	24.6 (4.3)	23.9 (4.7)	25.4 (4.4)	n.s.
Frequency of cannabis use (days/week)	2.8 (1.1)	2.4 (0.9)	2.6 (0.8)	n.s.
Blood THC concentration at baseline (ng/mL; mean, median [range])	**0.3[a], 0 [0-2.9]**	**0.06[a], 0 [0-0.7]**	**1.2[b], 0.6 [0-7.0]**	**0.001**
Blood THC concentration at time of driving (+30 min; ng/mL; mean, median [range])	**0.3[a], 0 [0-2.0]**	**2.9[a], 2.5 [0-6.7]**	**15.4[b], 12.2 [7.3-42.0]**	**< 0.001**
DUIC past 12 months (% yes within group)	70.0	41.9	60.0	n.s.
DUIA past 12 months (% yes within group)	13.3	9.7	6.7	n.s.

Columns with the same superscript letter are not significantly different at the 0.05 level.

results of the groups by time interactions and main effects of groups. When assumptions of sphericity were violated, Greenhouse-Geisser corrections were reported. Significant group by time interactions were further assessed with simple main effects tests, with Bonferroni *post hoc* tests. Because of the substantial interest in the association of dose and THC levels with driving performance (Chow et al., 2019), we conducted some additional analyses of the driving measures. First, due to the disproportionate number of females in the low THC group (see Table 1), we added sex to the models as a covariate. Then, in order to further explore the relationship between blood THC concentrations and driving performance, we ran bivariate correlations between THC concentrations at the time of driving (+30 min) and change in performance for each driving variable. For descriptive purposes, all tabulated data are presented as mean ± standard deviation (SD).

2.7. Ethics approval

Written informed consent was obtained by trained study personnel from all participants before initiation of study-related procedures. This study was approved by the CAMH Research Ethics Board (Protocol #125/2011) and the Health Canada Research Ethics Board (Protocol #2011-0024).

3. Results

3.1. Enrolment and participant characteristics

Five unblinded pilot participants received active cannabis and were not included in the final analysis. Of the 96 participants randomized to receive active or placebo cannabis, 91 were included in all the final analyses (30 high THC, 31 low THC, 30 placebo; see Fig. 1). Two participants (1 active, 1 placebo) missed the 24 and/or 48 h sessions and were included only in analyses of acute data. There were no statistically significant differences between groups in mean age, BMI, or frequency of cannabis use (Table 1). However, sex was found to differ significantly between groups [$\chi^2(2) = 6.2$, $p < 0.05$]. A Z test revealed that the low THC group had significantly more females than the high THC group.

3.2. Driving outcome measures

Driving data are presented in Table 2. Groups did not differ in baseline performance of any driving outcome measure ($p > 0.47$, data not shown).

Change in Mean speed (kilometers per hour). The interaction of group and time was significant for mean speed under both single [$F(3.5, 151.6) = 3.2$, $p = 0.02$] and dual task conditions [$F(3.2, 136.3) = 3.6$, $p = 0.014$]. Group differences were found at +30 min for both measures [single task $F(2, 88) = 3.9$, $p = .022$; dual task $F(2, 88) = 5.4$, $p = .006$], but not at +24 or +48 h ($p > 0.09$). At +30 min, in the single task condition, the high THC group was different than placebo (-4.8 vs. + 1.5 km/h, $p = 0.019$), but the low THC group did not differ from the other two. For the dual task condition, both the high and low THC groups were different than placebo, but not from one another (respectively, -2.1 km/h, -1.5 km/h vs +6.6 km/h, $p \leq 0.02$). To further explore these results, we added sex as a covariate and conducted ANCOVAs. This did not change the group main effects or interactions, though there was a significant main effect of sex on mean speed in the dual task condition [$F(1,85) = 7.2$, $p = 0.009$], which was due to females having a negative mean change score (i.e. tending to slow down), while males had a positive mean change score (i.e. tending to speed up). We also examined the correlations, in the active groups, between blood THC concentration in the acute session at the time of driving and change in mean speed, but none of the correlations were statistically significant (single task r=-0.18, $p = 0.15$; dual task r=-0.083, $p = 0.53$).

Change in Lateral control (mean absolute deviation in meters from the centre of the lane). There was a main effect of group for lateral control in the single task condition [$F(2, 86) = 3.7$, $p = .03$]. The high THC group was marginally different from the placebo group at +30 min (+0.04 vs. + 0.08 m, $p = 0.05$), and this difference reached statistical significance at +48 h (+0.04 vs. + 0.08 m, $p = 0.044$), though no difference was observed at +24 h. There was no effect of cannabis on lateral control in the dual-task condition. Similar to mean speed, there was no difference in results when including sex as a covariate in the model, though there was a main effect of sex on lateral control in the single task condition [$F(1,85) = 7.2$, $p = 0.008$]. The main effect of sex was due to the changes scores for females being smaller across all three times. There was also no significant correlation between blood THC concentration at the time of driving in the acute session and change in lateral control in the active groups (single task r=-0.16, $p = 0.21$; dual task $r = 0.16$, $p = 0.22$).

3.3. THC concentrations, heart rate, and VAS results

Mean (SD) smoking duration was 5.7 (1.6) min for the placebo, 6.0 (2.0) min for the low THC, and 7.0 (2.1) min for the high THC groups. The high THC group smoked for a longer duration than the placebo group (mean difference [95% CI]: 1.3 [0.06–2.5] min, $p = 0.036$). The mean (SD, range) estimated dose for the low THC group was 70.3 (21.3, 29.9–103.8) mg THC and for the high THC group 94.0 (16.4, 57.0–122) mg THC, which was a significant difference (mean difference [95% CI]: 23.7 [14.0–33.4] mg, $p < 0.001$). In the placebo group, 90% of participants (27/30) correctly guessed they had received placebo cannabis. Similarly, in the high THC group, 93.3% (28/30) correctly guessed they had received active cannabis, while only 71% (22/31) of participants in the low THC group correctly guessed they had received active cannabis. Overall, there was a significant difference between groups in how willing participants would be to drive a real vehicle [$\chi^2(8) = 23.0$, $p = 0.003$]. In the placebo group, 80% of participants indicated a 5 (very willing to drive a real car), compared to 29% of participants in the low THC group and 26.7% of participants in the high THC condition.

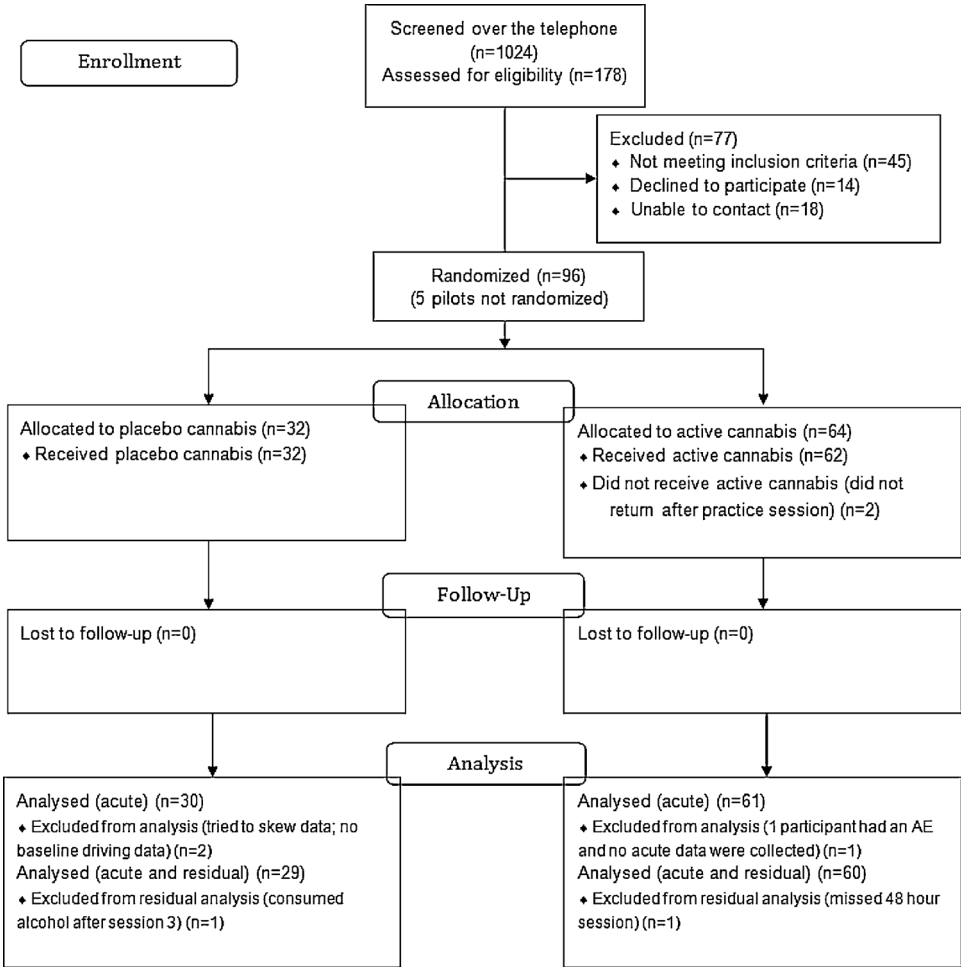

Fig. 1. Study flow chart, according to the consolidated standards of reporting trials (CONSORT).

Conversely, only 3.3% of participants in the placebo group indicated a 1 (very unwilling to drive a real car), compared to 12.9% of participants in the low THC group and 13.3% of participants in the high THC group.

THC concentrations in whole blood for each group are presented in Fig. 2. The overall group by time interaction was significant [$F(2.2, 92.9) = 78.8$, $p < 0.001$]. Mean THC concentrations were highest at +5 min for both the low and high THC groups. The high THC group remained significantly different from both the low THC and placebo groups throughout all data collection points, while the low THC group was significantly different than placebo only at +5 min and lost statistical significance thereafter.

Heart rate data are presented in Fig. 3. The overall time by group interaction was significant [$F(10.3, 434.4) = 13.4$, $p < 0.001$]. Peak heart rate occurred at +5 min for the low THC and high THC groups. The difference in heart rate remained significantly different until +4 h ($p < 0.005$) but was no longer significantly different from +5 h onwards.

Visual analogue scale data are presented in Fig. 4. The overall group by time interaction was significant for VAS *drug effect* [$F(4.7, 179.4) = 21.8$, $p < 0.001$] and VAS *high* [$F(4.6, 173.0) = 24.5$, $p < 0.001$]. Mean VAS *drug effect* and *drug high* scores peaked at +5 min for both the low and high THC groups.

Table 2
Primary driving outcome measures (presented as change from baseline, mean (SEM)).

	Placebo			Low THC			High THC		
	30 min	24 h	48 h	30 min	24 h	48 h	30 min	24 h	48 h
n	30	29	29	31	31	30	30	30	30
Mean Speed	1.5	2.7	3.1	−0.9	0.3	1.8	−4.8	1.7	3.5
	(7.4)	(6.6)	(6.3)	(7.8)	(5.9)	(7.1)	(10.6)*	(7.0)	(8.6)
Mean Speed	6.6	6.2	4.6	−1.5	0.3	0.9	−2.1	3.5	4.1
(DT)	(10.1)	(9.4)	(7.3)	(13.7)*	(10.4)	(6.1)	(10.1)*	(10.9)	(8.1)
Lateral Control	0.08	0.01	0.08	0.07	0.001	0.06	0.04	−0.008	0.04
	(0.07)	(0.06)	(0.08)	(0.06)	(0.04)	(0.06)	(0.04)	(0.05)	(0.06)
Lateral Control	0.05	0.1	0.008	0.05	0.1	0.003	0.06	0.1	0.02
(DT)	(0.05)	(0.08)	(0.04)	(0.05)	(0.05)	(0.05)	(0.05)	(0.04)	(0.04)

Bold text indicates significant group by time interaction in the split-plot ANOVA; DT = dual task condition; Mean speed in km/h; Lateral control in m.
* $p < 0.05$, different from placebo.

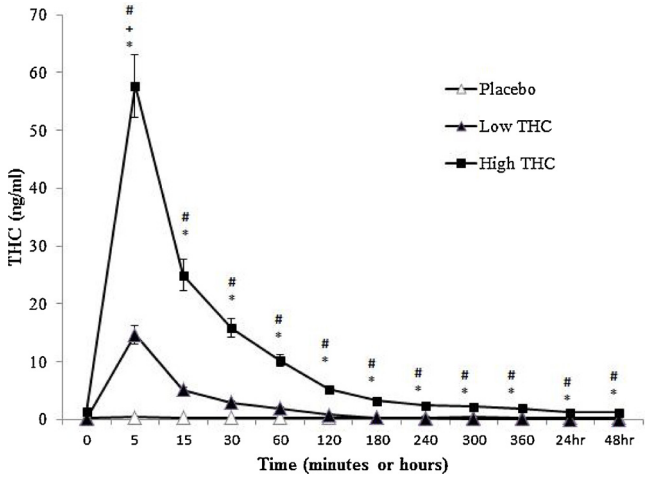

Fig. 2. Whole blood concentrations of THC from baseline to 48 h after cannabis exposure. Data are presented as mean ± SEM. *p < 0.05 high THC vs. placebo; +p < 0.05 low THC vs. placebo; #p < 0.05 high THC vs. low THC.

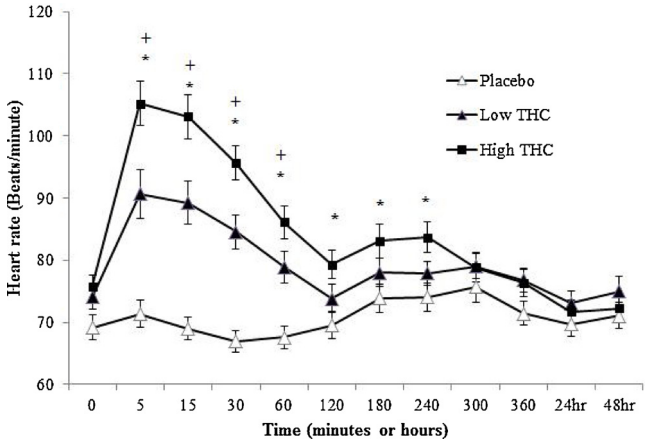

Fig. 3. Heart rate from baseline to 48 h after cannabis exposure. Data are presented as mean ± SEM. *p < 0.05 high THC vs. placebo; +p < 0.05 low THC vs. placebo; #p < 0.05 high THC vs. low THC.

3.4. Safety

A total of 66 AEs were recorded in the active groups, and 26 in the placebo group (see Table 3). The most common AEs in the active groups were headache (14.9%), insomnia (9.0%), dizziness (7.5%), and tiredness/fatigue (7.5%). The most common AEs in the placebo group were tiredness/fatigue (9.4%), headache (6.2%), dizziness (6.2%), and muscle/joint pain (6.2%). All AEs were of mild or moderate severity; no AEs were severe, and no serious adverse events (SAEs) occurred. Of the 66 AEs reported for the active group, 31 (44.9%) were considered as possibly or probably related to the study drug or related procedures. For example, of the 6 instances of insomnia in the active group, 3 reported experiencing insomnia in the two days prior to the practice session.

4. Discussion

In this randomized clinical trial, we examined the acute and residual effects of smoked cannabis on driving measures (speed and lateral control), heart rate and self-reported drug effects in a group of young drivers who were regular, but not dependent, cannabis users. Both the high and low THC groups drove significantly slower than placebo after smoking cannabis, relative to baseline. The significant reductions in mean speed observed here following acute administration of cannabis, ranging from 0.9 to 4.8 km/h, are comparable to the decreases in mean speed ranging from 0.2 to 4.1 km/h following acute cannabis administration recently reported by Hartman et al. (2016). The difference in lateral control was significant at the 48 h session, but this was the only suggestion of a residual effect. Group differences in VAS scores and heart rate generally persisted until the end of the acute effects session (which confirms that participants were feeling a drug effect and supports the viability of the drug administration procedure) but were no longer significant at the residual effects sessions. In addition, over a quarter of participants in both the low and high THC groups indicated that they would be very willing to drive a real vehicle at the time of their driving simulation trial (30 min after smoking cannabis). Overall, we found significant evidence of differences in driver behavior, heart rate, and self-reported drug effects 30 min after smoking cannabis, but like Ronen et al. (2008), we found little evidence to support residual effects. However, we caution that residual effects might be more consistently observed among other types of cannabis users (e.g. naïve or inexperienced users) or under other administration conditions (e.g. after the use of cannabis edibles).

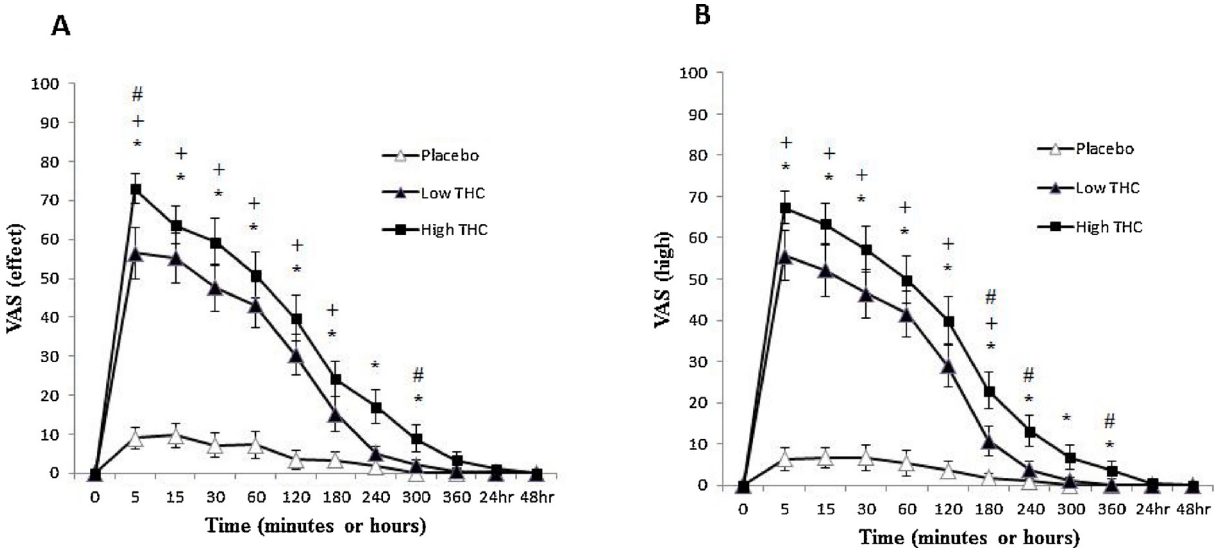

Fig. 4. VAS ratings of A) "drug effect" and B) "high" from baseline to 48 h after cannabis exposure. Data are presented as mean ± SEM. *p < 0.05 high THC vs. placebo; +p < 0.05 low THC vs. placebo; #p < 0.05 high THC vs. low THC.

Table 3
Number of adverse events (AEs) in the 2 treatment groups[1].

	Active (n = 67)	Placebo (n = 32)
No. of AEs reported[2]	66	26
Severe AEs, no. (% of AEs per group)[2]	0 (0)	0 (0)
Possibly or probably related to study drug or study procedures, no. (% of AEs per group)[2]	31 (44.9%)	7 (26.9%)
No. of participants reporting AEs (% of participants per group)	38 (56.7%)	15 (46.8%)
Most common AEs, no. (% of participants per group)		
Headache	10 (14.9%)	2 (6.2%)
Insomnia	6 (9.0%)	0 (0)
Dizziness	5 (7.5%)	2 (6.2%)
Tiredness/fatigue	5 (7.5%)	3 (9.4%)
Muscle/joint pain	3 (4.5%)	2 (6.2%)

Note: [1]AEs are reported for all participants who received study drug, including participants not included in the analyses. [2]Some participants had more than one AE.

It has been suggested that drivers under the influence of cannabis may be aware of the effects of the drug on their behavior (e.g. driving) and may try to compensate for it (Fischer et al., 2006; Lamers and Ramaekers, 2001; Ronen et al., 2008; Sutton, 1983). The finding of reduced speed observed in the active THC groups supports this suggestion. Reduced speed is similarly observed following an increase in task complexity, such as when engaging in a secondary task like using a mobile phone (Haigney et al., 2000) or texting (Caird et al., 2014). Young and Regan (2007) note that this change could reflect either a reduction of cognitive resources available for the driving task, or that drivers are willing to accept sub-optimal driving under these circumstances, both of which are undesirable from a road safety perspective. Any deviations from predictability in road safety behavior, including slower drivers, likely pose a risk to roadway safety (Aarts and van Schagen, 2006). The acute effects of cannabis in reducing speed may also explain the general absence in this study of cannabis effects on lateral control, since research demonstrates that reduced speed is associated with reduced lane deviation (Zhou et al., 2008). Participants were instructed to drive as they normally would, in order to maximize generalizability to real world conditions. Studies observing cannabis effects on lateral control have often employed instructions that involved maintaining specific speeds (e.g., Hartman et al., 2015; Lenne et al., 2010).

The results of the present study are particularly relevant in light of recent efforts to develop evidence-based *per se* laws to deter impaired driving. Because of the *ad libitum* smoking procedure (which has the advantage of being more naturalistic than cued procedures), the dose of THC (and resultant blood concentrations) was quite variable amongst the active groups, which prompted the division of the active group into two based on a median split. At +30 min, coinciding with the time of driving assessment after cannabis smoking, blood THC concentrations ranged from 7.3 to 42 ng/mL in the high THC group and from 0 to 6.7 ng/mL in the low THC group. A 2007 expert panel suggested that 7–10 ng/mL of THC in serum (approximately 3.5–5 ng/mL in whole blood) was a defensible legal limit (Grotenhermen et al., 2007). We observed in several instances that the high THC group differed from placebo, while the low THC group did not.

A few limitations should be kept in mind. Given the lack of consequences associated with simulated driving, participants in the study may not have taken the driving task as seriously as they would have if driving a real car. However, a recent within-subjects study found that performance in simulated and on-road driving was comparable after consumption of oral THC, at least for measures of lateral control (Veldstra et al., 2015). Our driving course involved a relatively uncomplicated rural highway, and a more complicated driving environment may provide different results. As well, we are unable to say if the amount of impairment observed on driving measures would constitute mild or more serious impairment. In addition, there was substantial variability of blood THC concentrations in the active groups; in fact, the range of THC concentrations in the placebo group overlapped with the range in the low THC group. Thus, a lack of significant group differences on certain measures could be due to the fact that some participants in the active group achieved relatively low blood THC concentrations. This limitation was largely mitigated by our decision to split the active group into two; however, as this was not an *a priori* decision, this may have limited our power to detect group differences. Choosing a between-subjects design may also be seen as a limitation, as there may have been group differences not accounted for that confounded the results. We chose not to use a within-subjects design in order to encourage participant retention and to minimize the number of times participants drove in the simulator (to minimize practice effects). Finally, we did not collect information on the age at which participants initiated cannabis use (i.e. how long participants had been using cannabis), which is important given that previous research suggested an earlier age of onset of cannabis use is associated with an increased risk of DUIC (Le Strat et al., 2015).

5. Conclusion

Among young regular but non-dependent cannabis users, smoked cannabis led to a significant reduction in driving speed, increases in heart rate and increases in VAS ratings of drug effects in the acute effects phase, but there was little evidence of residual effects. More research on the acute and residual effects of cannabis is needed, including studies on the effects of differing doses of cannabis on driving performance measures, a comparison of the effects of the drug on younger and older participants, and an assessment of the role of experience with the drug on acute and residual effects.

Contributors

BB, REM, and BLF conceptualized the study. BB, REM and BLF were responsible for obtaining trial funding. BB and BLF supervised the study and data collection. GSS, JB, JFP, and JM recruited participants and collected data. REM, GS, and JM carried out the statistical analysis. BB, REM, GS, and JM drafted the manuscript, which was reviewed and revised by all authors. BB is the guarantor. All authors read and approved the final manuscript.

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anything to disclose.

Declaration of Competing Interest

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