

Psychomotor Performance, Subjective and Physiological Effects and Whole Blood Δ^9 -Tetrahydrocannabinol Concentrations in Heavy, Chronic Cannabis Smokers Following Acute Smoked Cannabis

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Δ^9 -tetrahydrocannabinol (THC) is the illicit drug most frequently observed in accident and driving under the influence of drugs investigations. Whole blood is often the only available specimen collected during such investigations, yet few studies have examined relationships between cannabis effects and whole blood concentrations following cannabis smoking.

Nine male and one female heavy, chronic cannabis smokers resided on a closed research unit and smoked *ad libitum* one 6.8% THC cannabis cigarette. THC, 11-hydroxy-THC and 11-nor-9-carboxy-THC were quantified in whole blood and plasma. Assessments were performed before and up to 6 h after smoking, including subjective [visual analog scales (VAS) and Likert scales], physiological (heart rate, blood pressure and respirations) and psychomotor (critical-tracking and divided-attention tasks) measures.

THC significantly increased VAS responses and heart rate, with concentration-effect curves demonstrating counter-clockwise hysteresis. No significant differences were observed for critical-tracking or divided-attention task performance in this cohort of heavy, chronic cannabis smokers. The cannabis influence factor was not suitable for quantifying psychomotor impairment following cannabis consumption and was not precise enough to determine recent cannabis use with accuracy.

These data inform our understanding of impairment and subjective effects following acute smoked cannabis and interpretation of whole blood cannabinoid concentrations in forensic investigations.

Introduction

An estimated 125–203 million persons aged 15–64 worldwide smoked cannabis at least once in the previous year (1), with 16.7 million Americans and 18.1% of individuals aged 18–25 years smoking cannabis in the previous 30 days (2). Additionally, cannabis is the most common illicit substance detected in blood and oral fluid of nighttime drivers (3). Although impairment cannot be assumed from drug presence, detection windows in these matrices are relatively short for less than daily cannabis smokers (4–6), increasing impairment probability following a positive test.

The primary psychoactive chemical in cannabis, Δ^9 -tetrahydrocannabinol (THC), is metabolized *in vivo* to several phase I metabolites, most prominently the equipotent 11-hydroxy-THC (11-OH-THC) and non-psychoactive 11-nor-9-carboxy-THC (THCCOOH) (7–8). Several studies have investigated cannabinoid metabolism and urine, plasma and

oral fluid pharmacokinetics following acute and chronic oral, smoked and intravenous THC administration (9–14). Recently, we investigated whole blood cannabinoid pharmacokinetics with direct liquid chromatography tandem mass spectrometry (LC–MS–MS) analysis for the first time, providing valuable data regarding cannabinoid detection in this matrix following cannabis smoking (15).

THC is detectable in plasma within seconds after the first puff of a cannabis cigarette, with dose-related tachycardia, subjective “high” and conjunctival injection (9, 10, 12, 16). Cannabis impairs psychomotor performance, cognition and driving ability in both driving simulators and on-the-road driving tests (17–25). Hunault *et al.* examined cognitive and psychomotor effects following smoked cannabis containing up to 69 mg THC and observed significant, dose-related impairing effects following paced smoking in primarily occasional cannabis smokers (26). Papafotiou examined cannabis-induced impairment in a driving simulator in cannabis smokers with unknown histories after one week of abstinence; significant impairment was observed 80 min but not 30 min after smoking a 1.74 or 2.93% THC cannabis cigarette (27). However, Ramaekers *et al.* studied effects of cannabis smoking (13% THC, 500 μ g/kg) in heavy (>4 days/week) and occasional (\leq 1x/week) smokers and found significant impairment in tracking performance, divided attention, and inhibitory control in occasional, but not heavy smokers (28).

The cannabis influence factor (CIF), described by Daldrop as a predictor of cannabis-induced impairment, is calculated as molar blood [THC] + [11-OH-THC] divided by [THCCOOH] (29). A CIF > 10 was proposed to predict cannabis-induced impairment analogous to a 0.11 g/dL blood alcohol concentration. Menetrey *et al.* examined this model following controlled oral cannabis decoction (hemp extracted into hot milk) administration (30), yet none, to our knowledge, examined this following controlled cannabis smoking.

The present study examined relationships between whole blood cannabinoid concentrations and pharmacodynamic effects in heavy, chronic cannabis smokers. Cannabis-induced effects were determined in critical tracking and divided attention task performance, subjective and physiological measures, as well as the CIF, following cannabis smoking. These data should facilitate interpretation of whole blood cannabinoid results, often the only specimen available in driving under the influence of drugs (DUID), accident and other forensic investigations.

Materials and Methods

Participants

Participants provided written informed consent for this National Institute on Drug Abuse Institutional Review Board-approved protocol and this study was performed in accordance with the Declaration of Helsinki. Inclusion criteria were cannabis use at least twice monthly for three months before study entry, positive urine cannabinoid test, 18–45 years old, normal cardiac function and veins suitable for intravenous catheter placement. Clinically significant medical or psychiatric disease, history of clinically significant adverse event associated with cannabis intoxication, current interest in drug abuse treatment, pregnancy or nursing, or blood donation in the previous 30 days were exclusionary. Participants were heavy (>4 days/week) and chronic (>2 years) cannabis smokers admitted to the secure research unit 15–20 h before dosing; no cannabis use restrictions were enforced prior to admission. All participants underwent an immunoassay-based urine drug screen (iScreen™, Instant Technologies, Inc, Norfolk, VA) on admission and were negative for all substances other than THC. Cigarette smoking was permitted up to 30 min before and after 90 min following THC dosing.

Smoked cannabis administration and blood collection

The NIDA Chemistry and Physiological Systems Research Branch supplied cannabis cigarettes containing $6.8 \pm 0.2\%$ THC, $0.25 \pm 0.08\%$ CBD and $0.21 \pm 0.02\%$ CBN (w/w). Mean cigarette weight was 0.79 ± 0.16 g, yielding total THC, CBD and CBN content of 54, 2.0 and 1.7 mg per cigarette, respectively. Participants smoked a single cigarette *ad libitum* for 10 min while seated with legs elevated, and remained in this position during the data collection period. Whole blood and plasma were collected on ice into sodium heparin blood tubes via indwelling intravenous catheter 0.5 h before and 0.25, 0.5, 1, 2, 3, 4 and 6 h after the start of smoking. Blood collected for plasma was centrifuged (1,600 x g, 15 min) and plasma separated within 2 h.

Cannabinoid analysis

Cannabinoids were quantified by a previously validated LC–MS–MS method (31). Briefly, 1.5 mL acetonitrile was added to 0.5 mL specimen to precipitate proteins. After mixing and centrifugation, the supernatant was diluted and subjected to solid-phase extraction (SPE). Extracts were evaporated, reconstituted and chromatographed; detection was via electrospray ionization. Imprecision was < 10.5% coefficient of variation (CV), recovery was > 50.5% and bias within $\pm 13.1\%$ of target across the linear range. Limits of quantification (LOQ) were 1.0 $\mu\text{g/L}$ for THC, 11-OH-THC and THCCOOH.

Subjective scales

Visual analog scales (VAS) were presented on a computer screen –0.5, 0.25, 0.5, 1, 2, 3, 4 and 6 h after the start of smoking. Participants indicated the magnitude of “Good Drug Effect,” “High,” “Stoned,” “Stimulated,” “Sedated,” “Anxious” and “Restless” on a 100-mm line anchored with “not at all” and

“most ever.” Position on the scale was converted to a percentage between 0 and 100.

5-point Likert scales for “Difficulty concentrating,” “Altered sense of time,” “Slowed or slurred speech,” “Body feels sluggish or heavy,” “Feel hungry,” “Feel thirsty,” “Shakiness/tremulousness,” “Nausea,” “Headache,” “Palpitations,” “Dizzy” and “Dry mouth or throat” were presented on a computer screen immediately following VAS. Participants selected the response best characterizing their condition: 1, none; 2, slight; 3, mild; 4, moderate; or 5, severe.

Cardiovascular measures

Blood pressure (systolic and diastolic), heart rate and respiratory rate were measured before and after smoking at –0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5 and 6 h.

Cannabis influence factor

CIF was calculated as $100 \times ([\text{THC}] + [11\text{-OH-THC}]) / [\text{THCCOOH}]$ (29, 30) for all whole blood and plasma samples; analytes detected below LOQ were considered to have 0.0 nmol/mL.

Impairment assessments

The “critical tracking task” (32) measures a participant’s ability to control a displayed error signal in a first-order compensatory tracking task. Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements null the error by returning the cursor to the midpoint. The frequency of cursor deviations, and, therefore, its velocity, increases as a stochastic, linear function of time. Control is lost at the point where the compensatory response lags the cursor’s last movement by 180 degrees. The response frequency at this point is defined as the critical frequency or lambda-c (λ_c). The test includes five trials. The average of the middle three scores (i.e., deleting the highest and lowest) is taken as the final score. This 2-min task was performed before smoking and 1.5, 3 and 5.5 h after starting smoking.

The “divided attention task” (33) measures a participant’s ability to divide attention between two simultaneous tasks. The primary task is the same as the critical tracking task described previously, with the exception that the velocity of the error signal is kept constant at 50% of the participant’s optimal performance ($\lambda_c/2$). Tracking error is measured by the absolute distance (mm) between the cursor’s position and the center of the scale. The secondary task involves monitoring 24 single-digit numbers (0–9) displayed in the four corners of a central screen that change asynchronously every five seconds. The participant is required to remove his/her foot from a pedal-switch as quickly as possible any time the target numeral “2” appears. Mean absolute tracking error (mm), number of correct detections (hits) and number of control losses are the primary performance measures. This 15-min task was performed before smoking and at 1.6, 3.1 and 5.6 h after starting smoking.

Participants were trained before the study session to achieve stable task performance and minimize practice effects. Critical tracking task training continued until participants performed

with < 10% variance from the average measured over three trials. The divided attention task was practiced for 12 minutes, regardless of final performance.

Calculations and statistical analysis

SPSS 15.0 for Windows (SPSS, Chicago, IL) was utilized for statistical evaluations. GLM repeated-measures ANOVA were conducted to investigate changes in participants' VAS scores over time, with a Huynh-Feldt epsilon correction applied to counter sphericity violations. Bonferroni post-hoc testing determined differences between specific time points. Wilcoxon signed-rank tests evaluated differences between whole blood and plasma CIF values at each time point. Areas within concentration-effect curves were calculated in a manner similar to Galeazzi *et al.* (34) by subtracting the total area under the lower limb of the curve from that under the upper limb, determined by the trapezoidal rule. *P* values ≤ 0.05 were considered significant. Other statistical calculations were performed with GraphPad Prism 5.2 for Windows (GraphPad Software, La Jolla, CA).

Results

Samples

Participant demographics and self-reported smoked cannabis histories are detailed in Table I. Ten participants (nine male, one female) completed the protocol. Age ranged from 18.5–45.7 years and BMI ranged from 18.1–32.0 kg/m². Mean (standard deviation; SD) self-reported joints smoked in the previous 14 days was 11.7 (2.2), with a range of 10–168 joints. Only one scheduled blood sample (Participant I at 0.25 h) was not collected, due to catheter dislodgement.

Subjective effects following smoked cannabis

Cannabis smoking significantly increased "Good drug effect" [$F(2.37, 21.36) = 17.6, P < 0.001$], "High" [$F(2.78, 25.02) = 26.03, P < 0.001$], "Stoned" [$F(2.94, 26.49) = 13.29, P < 0.001$], "Stimulated" [$F(3.25, 29.30) = 8.54, P < 0.001$] and "Sedated" [$F(4.70, 42.34) = 3.35, P = 0.014$], but did not significantly

change "Anxious" [$F(4.82, 43.35) = 1.15, P = 0.349$] or "Restless" [$F(2.55, 22.91) = 2.58, P = 0.086$] VAS scores.

Mean blood concentration-effect curves for each of the seven VAS scales are shown in Figures 1A–H. For all scales, observed peak THC blood concentration and peak VAS scores occurred 0.25 h after starting smoking, at the time of the first blood collection. Blood THC concentrations decreased rapidly, although subjective effects persisted. Starting approximately 1 h after smoking, subjective effects decreased linearly through 6 h, with THC concentrations changing more slowly during this period. This pharmacodynamic-pharmacokinetic relationship described a counterclockwise hysteresis for all VAS measures, demonstrating the lack of correlation between blood concentrations and observed effects until after the initial distribution phase.

While group mean blood concentration-VAS relationships yielded consistent hysteresis effects, concentration-effect curves for individual subjects varied substantially (Figures 2A–L). All participants (except I) reported peak subjective "High" between 66 and 85; with peak whole blood THC concentrations at the time of these responses ranging from 13 (Participant A) to 63 µg/L (Participant L). There was no apparent relationship between hysteresis areas and age or self-reported frequency or chronicity of cannabis intake.

Five-point Likert scales displayed varied effects. Participants reported significant increases compared to baseline for "Slowed or slurred speech" [$F(2.10, 18.9) = 4.35, P = 0.026$], "Feel Hungry" [$F(5.86, 52.7) = 22.0, P < 0.001$], "Feel thirsty" [$F(5.37, 48.3) = 19.2, P < 0.001$], "Shakiness/tremulousness" [$F(1.81, 16.3) = 4.19, P = 0.037$] and "Dry mouth or throat" [$F(6.34, 57.0) = 20.6, P < 0.001$], with no significant increases observed for other Likert scales.

Cardiovascular measures

Cannabis smoking significantly increased heart rate only at 0.5 h [$F(1, 9) = 11.99, P = 0.007$]. Diastolic blood pressure decreased significantly only from 0.5 to 1 h, [$F(1, 9) = 8.95, P = 0.015$]. Systolic blood pressure and respiratory rate were unaffected at all times during the session.

Table I

Demographics and Self-Reported Cannabis Smoking Characteristics for 10 Adult Cannabis Smokers*

Subject	Sex	Race	Age (y)	BMI [†] (kg/m ²)	Mean available dose [‡] (µg/kg)	Days since last cannabis use	Typical joints/day	Days cannabis use/last 14	Age 1 st cannabis use (y)
A	M	White	37.1	18.1	1,000	2	6	14	22
B	M	African American	26.5	30.6	560	3	2	10	16
C	M	White	45.7	32.0	480	1	5	14	12
D	F	White	27.7	22.3	980	1	6	8–9	15
F	M	White	34.1	23.0	720	2	1	10	16
G	M	White	22.2	22.9	560	1	12	14	15
H	M	African American	18.5	22.3	740	2	6	9	13
I	M	African American	41.5	25.5	690	3	6	12	19
K	M	White	22.5	20.9	710	4	2	13	16
L	M	African American	30.7	30.6	590	1	3	9	15
		Mean	30.6	24.8	700	2.0	4.9	11.7	15.9
		SD	8.9	4.7	170	1.1	3.2	2.2	2.8

*Adapted from Schwoppe *et al.* (15).

[†]BMI = weight (kg)/height² (m).

[‡]Average amount of THC contained in cigarette (µg) divided by participant weight (kg).

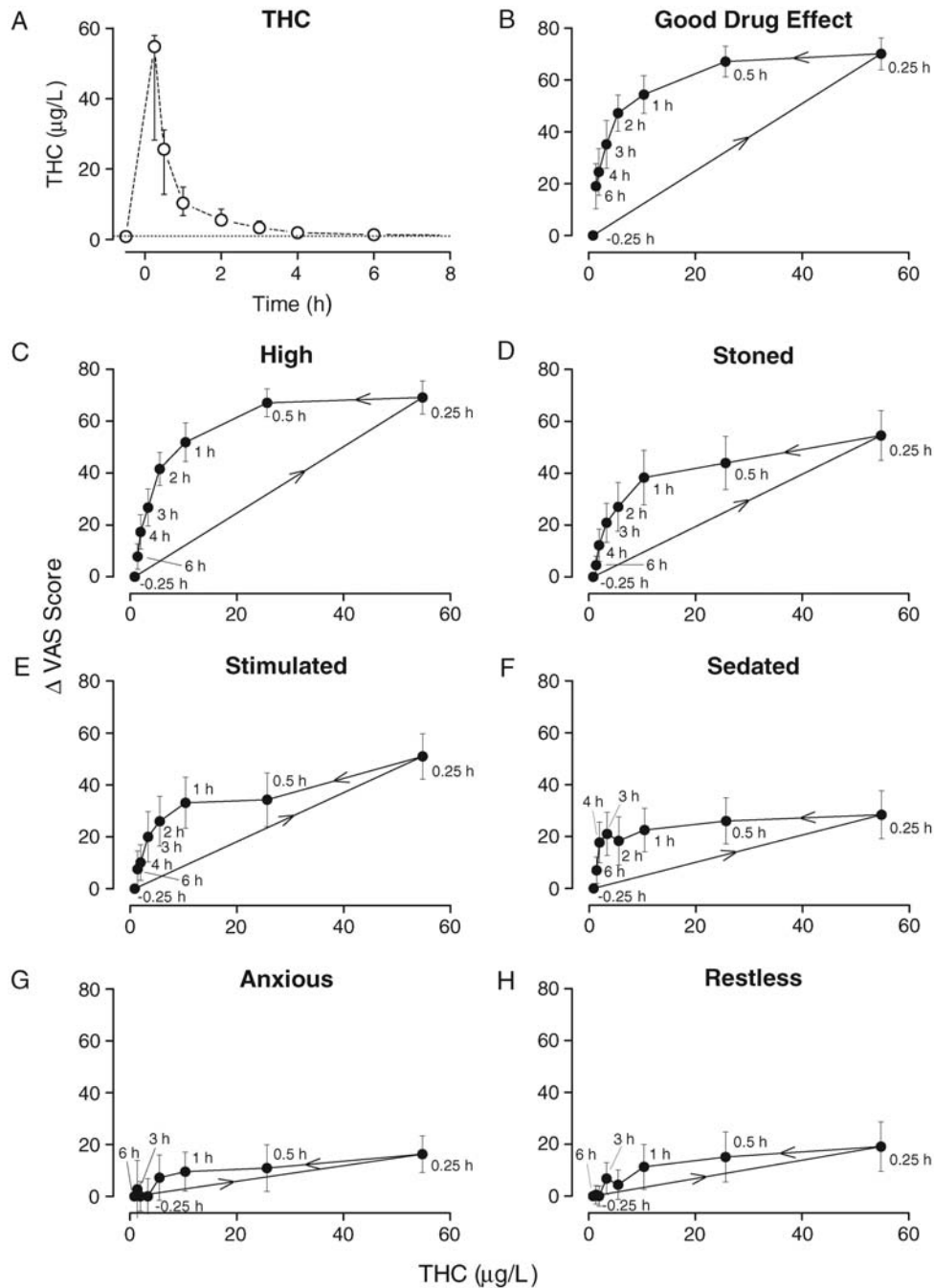


Figure 1. Median (inter-quartile range) whole-blood THC concentrations (A) and mean (SEM) hysteresis plots for seven VAS scales (B–H) following smoking of a 6.8% THC cannabis cigarette ($n = 10$). VAS scores are calculated as change from baseline (-0.5 h). Samples collected at -0.5 , 0.25 , 0.5 , 1.0 , 2.0 , 3.0 , 4.0 and 6.0 after starting smoking. Dotted line in THC plot indicates limit of quantification ($1 \mu\text{g/L}$). Arrows in hysteresis plots indicate samples collected over increasing time.

Cannabis influence factor

CIF increased substantially immediately following cannabis smoking, reaching a median peak (range) of 150 (93–250) in whole blood and 170 (79–270) in plasma 0.25 h after starting smoking (Figure 3). CIF then rapidly decreased, although the rate of change lessened over time. Median (range) whole blood CIF was 13 (0.0–32) 4 h after smoking and 8.0 (0.0–27) 6 h after smoking; plasma CIF was 14 (6.9–34) at this final observation. Six-hour plasma CIF was significantly higher than baseline

[$F(1, 9) = 19.24$, $P = 0.002$], although whole blood CIF was not [$F(1, 9) = 4.35$, $P = 0.067$]. No significant differences were observed between plasma and whole blood CIF at any time other than 6 h ($T = 2$, $P = 0.037$).

Critical tracking task/divided attention task

Cannabis smoking had no significant effects on critical tracking task performance in this population of almost-daily,

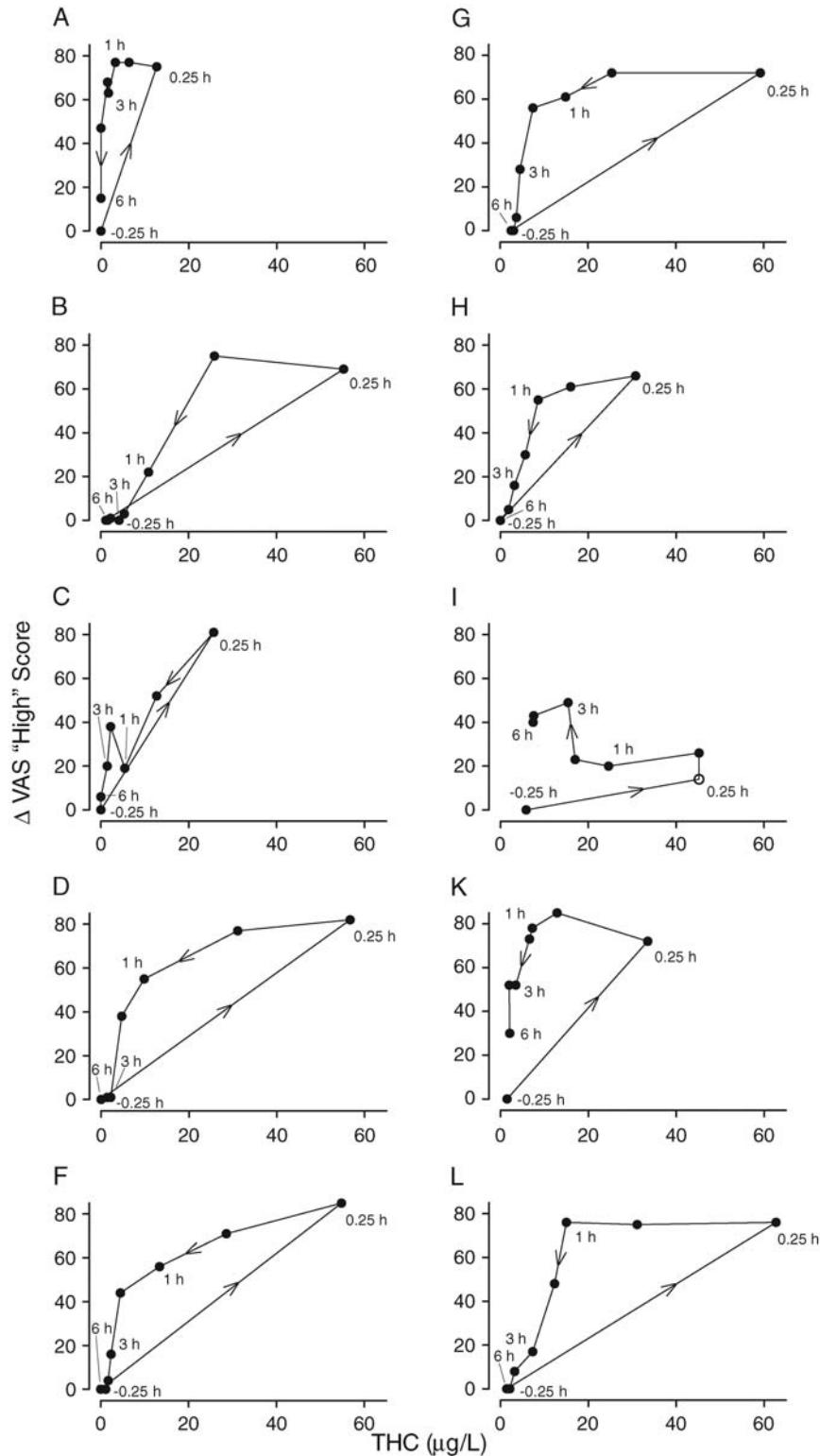


Figure 2. Individual ($n = 10$) hysteresis plots for “High” VAS scales following smoking of a 6.8% THC cannabis cigarette. VAS scores are calculated as change from baseline (-0.5 h). Samples collected at -0.5 , 0.25 , 0.5 , 1.0 , 2.0 , 3.0 , 4.0 and 6.0 after starting smoking (\bullet), except for Participant I, which did not have blood at 0.25 h (\circ). Arrows in hysteresis plots indicate direction of plot.

chronic cannabis smokers (Figure 4). For the divided attention task, significant differences were observed between baseline and 3 h, $F(3, 27) = 2.4$, $P = 0.022$ for the number of

correct identifications (hits) in the secondary peripheral stimuli task, although no significant differences were observed 1.5 h after smoking. No significant effects due to

cannabis smoking were observed for control losses, reaction time or tracking error.

Discussion

The present study characterizes acute cannabis effects over 6 h after smoking a 6.8% THC cigarette containing approximately

54 mg THC in a sample of heavy, chronic cannabis smokers. Robust subjective and cardiovascular effects were observed, while psychomotor performance changes were modest. THC potency was selected to closely represent current mean illicit cannabis potency in seized US drugs, which increased from 3.4% in 1993 to 8.8% in 2008 (35). Thus, these data provide insight into the pharmacodynamics and pharmacokinetics of the higher-potency cannabis currently prevalent in the US.

As expected, smoking a single cannabis cigarette significantly increased positive effects such as “Good drug effect,” “High,” “Stoned,” “Stimulated” and “Sedated,” while having no significant effect on negative effects such as “Anxious” or “Restless.” The frequency and chronicity of cannabis smoking in our population may have minimized negative effects and adverse events.

When VAS subjective effects were compared to simultaneously collected whole blood THC concentrations, counter-clockwise hystereses were observed. Cocchetto *et al.* (36) first detailed hysteresis following cannabis smoking, indicating a delay in the onset of subjective effects as compared to plasma concentrations. Barnett *et al.* (37) also observed a counter-clockwise hysteresis for heart rate and THC plasma concentrations, and Chiang *et al.* (38) described differences in hysteresis areas for oral, smoked and intravenous THC based on differences in administration route or cannabis potency. In 1993, Cone and Huestis detailed hysteresis for “How much drug effect do you feel?” (measured by VAS) with multiple measurements of subjective effects and plasma concentrations obtained with a continuous blood withdrawal pump during cannabis smoking (10, 39). Data from the present study also documented a counter-clockwise hysteresis starting immediately after the end of smoking, and during the initial distribution and elimination phases.

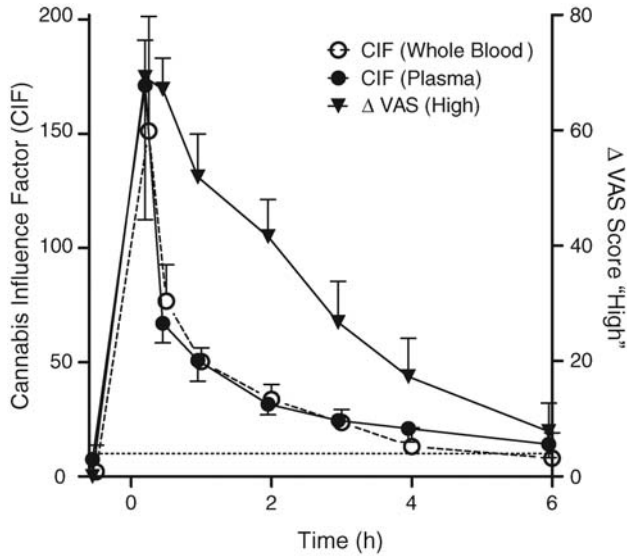


Figure 3. Mean (SEM) CIF and VAS “High” score following *ad libitum* smoking of a 6.8% THC cannabis cigarette ($n = 10$). VAS score is calculated as change from baseline (-0.5 h). CIF calculated from molar whole blood concentrations as $100 \times ([THC] + [11-OH-THC]) / [THCCOOH]$. Samples collected at $-0.5, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0$ and 6.0 after starting smoking. Dotted line at $CIF = 10$ indicates “impaired,” as proposed by Daldrop.

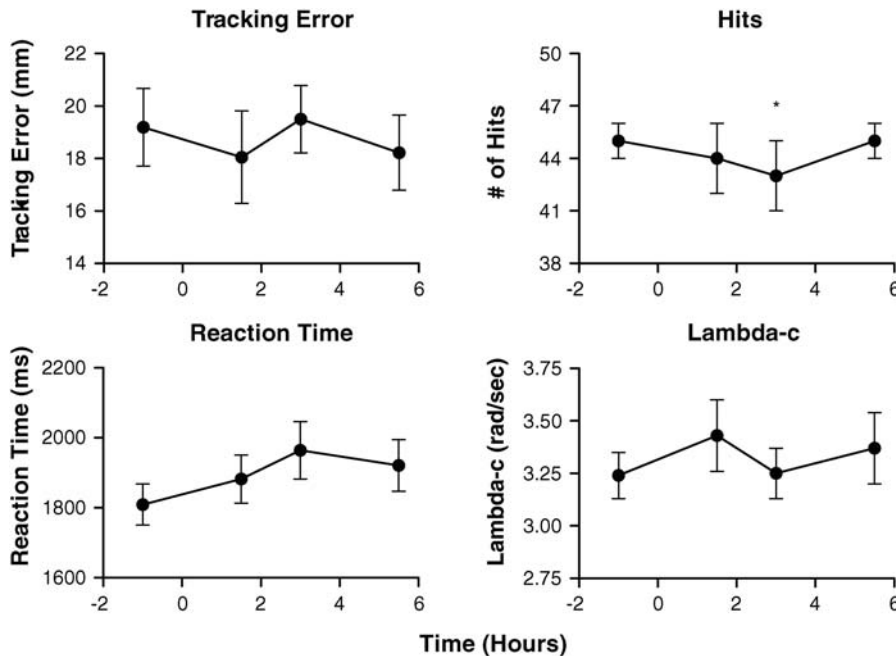


Figure 4. Mean (SEM) values ($n = 10$) for lambda-c in the critical tracking task (CTT) and tracking error, hits and reaction time in the divided attention task (DAT) as a function of time after smoking *ad libitum* a single 6.8% THC cannabis cigarette. Samples collected after smoking at 1.5, 3 and 5.5 h for CTT and 1.6, 3.1 and 5.6 h for DAT; * $P < 0.05$ compared to baseline, repeated-measures ANOVA.

Counter-clockwise hystereses are typically observed for drugs with a larger volume of distribution, drugs with active metabolites, or an indirect mechanism of drug action (40). Highly lipophilic THC, with 2- or 3-compartment pharmacokinetics and an equipotent metabolite (11-OH-THC), is a likely candidate for counter-clockwise hysteresis. Here, for the first time, we report hystereses for whole blood THC concentrations and several VAS scores, improving our understanding of subjective THC effects following ad libitum smoked cannabis. Yet, as demonstrated in Figures 2A–L, inter-individual variability is high for these concentration-effect curves. Hystereses may vary substantially depending on dose, experimental setting or prior chronicity or frequency of use (40).

Significant impairment differences were observed in tracking and divided attention tasks in frequent and occasional users following 500 µg/kg smoked cannabis (28). The authors suggested tolerance development to acute THC-induced impairment in the heavy smoker group, similar to the findings of Hart *et al.* (20). In the present study, we found minimal performance changes in critical tracking and divided attention tasks 1.5–5.5 h after smoking 700 µg/kg (range 480–1,000) THC (Table 1). Most participants in the present study smoked cannabis almost daily for a mean (SD) of 7.2 (5.3) years, with several self-reporting numerous smoked joints per day. These findings support those reported by Ramaekers *et al.* and Hart *et al.*, documenting significant subjective response and minimal impairment in driving-related psychomotor tasks in chronic daily cannabis smokers. Additional research is needed to determine whether tolerance develops to the impairment of complex driving skills in chronic daily cannabis smokers compared those who use cannabis occasionally.

Menetrey *et al.* investigated whole blood CIF following a cannabis decoction in milk containing 45.7 mg THC (30). A mean peak CIF of approximately 50 was achieved, decreasing to approximately 18 after 5.5 h, and 5 after 24 h. The present study examined CIF in whole blood and plasma following smoked cannabis intake, yielding peak median CIF of 150 and 170, respectively. CIF in whole blood and plasma were similar (Figure 3), with absolute CIF decreasing much more quickly than subjective “high.” This was expected, because blood cannabinoid concentrations decreased much more rapidly than subjective response (Figure 1A–H). Because we observed minimal impairment on tracking and divided attention tasks through 4 h after smoking, this model does not appear suitable for quantifying impairment following cannabis consumption in heavy, chronic cannabis smokers. Additionally, four participants had whole blood CIF > 10 in the baseline sample 0.5 h before smoking despite residence for more than 12 h on the closed clinical unit, precluding CIF as a definitive marker for recent cannabis intake.

As described by Schwöpe *et al.* (15), Mareck *et al.* (41), and Kelly *et al.* (42), detection of minor cannabinoids, CBD, CBN or THC-glucuronide may be beneficial in identifying recent cannabis intake. Our data indicated that these markers occurred during the period of strong subjective effects and potential impairment. Unfortunately, the frequent lengthy delay between cannabis smoking and sample collection during DUID and other investigations may preclude this approach, because concentrations may fall below current limits of quantification (15).

Concentration-effect curves for whole blood THC and subjective effects produced counter-clockwise hysteresis following *ad libitum* smoking of a single 6.8% THC cannabis cigarette. Despite whole blood THC concentrations of 13–63 µg/L 15 min after the start of cannabis smoking, little psychomotor impairment was observed, although there were robust cardiovascular and subjective responses. These data suggest differential tolerance to the psychomotor, but not other effects of THC in heavy, chronic cannabis smokers, as previously reported by others (20, 28). CIF did not accurately predict impairment or subjective response following a single cannabis cigarette, but a high value (≥ 30) may suggest recent cannabis intake. These data advance our understanding of whole blood pharmacodynamic-pharmacokinetic relationships following cannabis smoking in heavy, chronic cannabis smokers. Additional research is needed to provide insight into pharmacodynamic-pharmacokinetic relationships in occasional cannabis smokers, because impairment may differ with less frequent exposure.

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