Received: 16 April 2024 | Revised: 26 March 2025 | Accepted: 27 March 2025

DOI: 10.1111/dar.14060

ORIGINAL PAPER

Drug and Alcohol REVIEW APSAD WILEY

Elucidating the acute effects of medically prescribed oral and vaporised delta-9-tetrahydrocannabinol on cognitive functions important for driving

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Funding information
This research was funded by the Motor Accident Insurance Commission. The funders did not have any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript

Abstract

Introduction: This program of research investigated the acute effects of orally ingested (Study 1) and vaporised (Study 2) cannabis containing delta-9-tetrahydrocannabinol (THC) on cognitive functions relevant for driving in two samples of medicinal cannabis patients (Study 1 $N = 41$ oral users; Study 2 $N = 37$ flower users).

Method: Participants completed counterbalanced baseline (no cannabis) and cannabis consumption (post-cannabis) appointments scheduled approximately 1 week apart. During each session, participants were administered a cognitive battery assessing information processing speed, sustained and divided attention, inhibitory control and mental flexibility. In the post-cannabis condition, the battery was completed 90 min after consuming one dose of cannabis oil (Study 1) or 15 min after vaporising one dose of cannabis flower (Study 2).

Results: In both samples, acute cannabis oil and flower administration did not induce a change in information processing speed, divided and sustained attention, or inhibitory control performance (after excluding participants with a positive drug indication at the start of either session), highlighting the moderating role of tolerance. However, significant reductions in TMT B performance were observed. Further, TMT ratio was significantly reduced post consumption of cannabis oil.

Discussion and Conclusions: TMT B may be sensitive to acute cannabis consumption in medicinal cannabis patients. However, further research is needed to determine the nature and duration of these effects, and whether such effects vary depending on the population studied (e.g., regular vs. new users).

KEYWORDS
cannabis, cognition, delta-9-tetrahydrocannabinol, neuropsychology, THC

1 | INTRODUCTION

The use of cannabis for both recreational and medicinal purposes is increasing globally [1]. With a growing number of jurisdictions legalising the possession and use of cannabis, increasing attention is being paid to the implications of these legislative changes (e.g., [2–4]). On the one hand, cannabis can be used to relieve a number of health conditions/symptoms, including chronic pain, insomnia, nausea/vomiting and epilepsy [5–8]. However, at the same time, the psychoactive constituent of cannabis (Delta-9-Tetrahydrocannabinol, THC) may acutely influence neurocognitive functioning and hence the ability to undertake complex and safety-sensitive tasks, such as driving [9, 10]. Despite this, inspection of the literature indicates that the nature and extent of neurocognitive changes are yet to be clearly elucidated, particularly among medicinal cannabis patients who have developed a tolerance to the substance through frequent and ongoing use. Knowledge of how THC affects cognition is vital for identifying the mechanisms underpinning THC intoxication as well as the development of behavioural tools to identify the magnitude and temporal duration of neurocognitive impairment.

Driving with THC in one's system (as indicated by oral fluid or blood samples) is illegal in Queensland, where the present study was conducted [11]. However, concerns have been raised about a zero-tolerance approach, given there is minimal correspondence between biological markers (either plasma or oral fluid samples) and changes in performance on cognitive and driving measures [12–14]. In addition, research indicates that residual THC can remain detectable in the blood and oral fluid samples of frequent cannabis users for several days after abstinence [15]. As a result, there is a dilemma in the treatment of medicinal cannabis patients who may provide a positive roadside THC indication without having recently consumed their medication [15]. This issue is further complicated by a lack of validated measures for assessing reductions in driving-related skills, leading to the current reliance on presence-based biological detection methods (i.e., detection though oral fluid). Consequently, it is vital that valid and reliable tools are developed to identify THC impairment, thereby enabling the identification of the time at which the intoxication subsides (and hence when an individual is able to undertake safety-sensitive tasks such as driving). However, it should be emphasised that research is urgently needed to first understand how THC affects different domains of neurocognitive function before the validity of such tests can be established.

Cannabis is known to adversely affect neural networks implicated in cognitive functions relevant for driving, including sustained and divided attention, working memory, reaction time, information processing speed, visuomotor abilities and inhibitory control (e.g., [16, 17]). However, there is variability in the nature and extent of these changes across domains, studies or populations, rendering the development of an assessment tool extremely difficult. Several factors appear to moderate the effect of THC on neurocognitive functioning, including (but not limited to) dosage, tolerance, symptom relief and route of administration [17]. First, while the dose-dependent relationship between cannabis and cognition may not be completely linear (owing to the fact that cannabis is lipophilic), a recent meta-analysis concluded that higher doses of THC may increase the extent and duration of impairment [16]. Second, there is evidence to suggest that acute cognitive deficits resulting from cannabis ingestion may be less pronounced in frequent users compared to occasional or new users (e.g., [16, 18–20]). Further, there is potential for improved cognitive functioning arising from THC-related mitigation of symptoms (e.g., pain, anxiety) that can exert independent negative effects on cognitive performance [17]. Finally, the timing of acute cognitive effects of THC varies depending on the route of administration, peaking at 90 min post-consumption for orally ingested routes and 15 min post-consumption for vaporised routes [16]. While numerous studies have examined the effect of cannabis on cognition among healthy, infrequent cannabis users, these effects among medicinal cannabis patients remain understudied. This population may be less susceptible to the acute neurocognitive effects of THC due to the alleviation of symptoms and tolerance developed through the daily use of their medication.

Given these points, the present research investigated the acute effects of orally ingested cannabis oil (Study 1) and vaporised cannabis flower (Study 2) on cognitive function in adults prescribed medicinal cannabis. In addition, these studies aimed to identify measures that may be sensitive to potential subtle changes in cognition secondary to cannabis consumption in medicinal patients. Using within-subject designs, performance across measures of information processing speed, divided and sustained attention, inhibitory control, and mental flexibility were compared between a no cannabis condition (baseline) and 90 min post-consumption of cannabis oil (Study 1) or 15 min post-vaporisation of cannabis flower (Study 2) (post-cannabis conditions).

2 | METHOD

2.1 | Study design and participants

Within-subjects designs were used to examine changes in neuropsychological function following the acute

consumption of medicinal cannabis oil or flower containing THC. Participants took part in two separate assessment sessions (baseline and post-cannabis), scheduled approximately 7 days apart. In the baseline (no cannabis) condition, participants refrained from any cannabis use prior to the assessment. In the post-cannabis session, participants were required to self-administer a single dose of their prescribed product before completing neuropsychological tests after a 90-min (Study 1) or 15-min (Study 2) delay. The cannabis/no-cannabis session order was counterbalanced across participants. Prior to both sessions, participants were asked to abstain from consuming any cannabis for at least 11.5 h to minimise the likelihood of residual neurocognitive effects from prior THC consumption [16]. Participants were required to attend both of their assessment sessions at the same time of day, being offered morning (8:30 AM) or afternoon (1:00 PM) sessions. Participants were also advised to consult with their GP to ensure the conditions of the study were suitable for their current treatment plan (e.g., whether the testing procedures were suitable and would not be contraindicated for their medical condition).

2.2 | Study 1

A total of 41 medicinal cannabis patients (*M*age years = 46, SD = 13, range = 21–67) from the Sunshine Coast (Queensland, Australia) were included in this study as part of a larger project investigating the effects of orally ingested THC on cognitive functions relevant for driving as well as driving performance/behaviour. Participants were recruited primarily via paid Facebook advertising, as well as through the distribution of brochures to local medicinal cannabis clinics and pharmacies. Participants were eligible for this study if they were aged 18 years and older, held a current Queensland driver's licence, drove at least once per week, resided within 50 km of the University of the Sunshine Coast Sippy Downs Campus, and held a valid prescription for orally ingested cannabis oil containing THC. Exclusion criteria for this study included the following (current) conditions: uncorrected visual or hearing impairments; neurocognitive impairment due to traumatic brain injury or dementia; diagnosis of major psychiatric illness (schizophrenia, panic disorder or delusional disorder); epilepsy; or pregnancy.

2.3 | Study 2

Thirty-eight participants (*M*age = 43, SD = 12, range 24–67 years) holding a valid prescription for medicinal cannabis flower were recruited for this study. Participants were recruited via paid Facebook advertising and promotional materials dispersed at known cannabis clinics on the Sunshine Coast (Queensland, Australia). A snowball sampling technique was also used, whereby participants could refer other known medicinal cannabis patients. The same exclusion criteria were applied from Study 1, with the exception of respiratory conditions, which were excluded from participation in Study 2. In addition, participants were not eligible to take part in Study 2 if they had taken part in Study 1.

Eligibility screening for both studies was conducted via an online screening form and confirmed via an online medical questionnaire. Informed consent was obtained both online and in writing prior to commencement of testing. All participants in both research studies were reimbursed for their time with a $100 WISH online gift card (Woolworths group) upon completion of the second assessment session. Both studies were approved by the University of the Sunshine Coast Human Research Ethics Committee (A211677).

2.4 | Materials

2.4.1 | Online questionnaire

Information on demographics, medical history, body composition, medications and drug use history were obtained through an online Qualtrics questionnaire to characterise the samples. Symptoms of depression, anxiety and stress were also assessed using the 21-item short-form Depression Anxiety and Stress Scale (DASS-21; [21]).

2.4.2 | Neuropsychological test battery

An estimate of Full Scale Intelligence Quotient was obtained using Wechsler's Test of Adult Reading (WTAR) during the baseline (no cannabis) session [22]. During both sessions, participants completed six neuropsychological tests in the following order: Trail Making Test (TMT) A and B [23], Motor Screening Task [24] (to ensure participants were familiar with using the iPad and comprehended instructions), Simple and Five Choice Reaction Time (RTI; [24]), Rapid Visual Processing (RVP; [24]) and the 24-item Victoria version Stroop Test ([25]; refer to Table 1 for descriptions of the tests and outcome measures). TMT A, TMT B and the Stroop tests were administered in a traditional pencil and paper format, while the Motor Screening Task, RTI and RVP were administered using an iPad with wireless headphones [26]. Parallel versions of TMT A, TMT B and the Stroop tests were administered during the post-cannabis session to control for

TABLE 1 Neuropsychological test battery and key functions assessed.

Measure	Domain	Description	Outcome variables
Paper and pencil tests			
Trail making test A	Processing speed, attention, visual scanning	Examinees are required to draw straight lines to connect numbers in ascending order. The time taken to finish this pattern is recorded.	TMT A time (s)
Trail making test B	Processing speed, divided attention, set-shifting/ mental flexibility, visuomotor speed	Examinees are required to draw straight lines to connect alternating numbers and letters in ascending order. The time taken to finish this pattern is recorded.	TMT B time (s) TMT ratio = (TMT B time - TMT A time)/TMT A time
24-item stroop test	Processing speed, sustained attention, inhibitory control	The 24-item Stroop Test consists of three parts: A, B and C. In part A, examinees are required to read out loud the colour of various dots, grouped in threes. Part B requires examinees to say aloud the colour of the ink of various unrelated words, while part C requires examinees to say aloud the colour of the ink of various colour words (e.g., red, blue).	Stroop A time (s) Stroop B time (s) Stroop C time (s) Stroop ratio = (Stroop C time - Stroop A time)/Stroop A time
CANTAB			
Motor screening task (MOT)	Comprehension, motor function	Coloured crosses are presented in different locations on the screen, which participants must tap on as quickly and accurately as possible. Outcome is the speed and accuracy of responses.	MOT = Mean response latency on correct trials (ms)
Simple choice reaction time	Processing speed, sustained attention	The participant must hold a button at the bottom of the screen, with a circle presented above. When the circle above flashes yellow, the participant must release the bottom button and tap the top circle as swiftly as possible. Outcome is the average reaction time, excluding time taken to move to the target.	RTISMRT = Mean response latency on correct trials (ms)
Five choice reaction time	Processing speed, divided attention	The participant must hold a button at the bottom of the screen, with five circles presented above. When one of the circles above flashes yellow, the participant must release the bottom button and tap on that circle as swiftly as possible. Outcome is the average reaction time, excluding time taken to move to the target.	RTIFMRT = Mean response latency to five targets on correct trials (ms)
Rapid visual processing (RVP)	Sustained attention	A sequence of digits between 2 and 9 are presented in a pseudo-random order at a rate of 100 digits/min. Participants must detect a target sequence of digits (e.g., 2-4-6, 3-5-7, 4-6-8) by selecting the button at the bottom of the screen as swiftly as possible. Outcomes are mean detection latency and false alarm sensitivity.	RVPML = Mean response latency on correct trials (ms) RVPA = measures the participants' capacity to detect the target, ranging from 0 to 1, with 1 representing good.

learning effects. Test selection was informed by a recent meta-analysis on THC and cognition [16] and the senior author's clinical experience (Mathew J Summers, Clinical Neuropsychologist). The Cambridge Neuropsychological Test Automated Battery (CANTAB) tests were selected on the basis that they assessed similar functions as those assessed in the traditional paper and pencil tests. Further, the CANTAB tests have previously been shown to display

strong sensitivity to subclinical cognitive changes associated with mild cognitive impairment (e.g., [27–29]). In order to maximise the consistency of any potential acute THC effects across the assessments, the battery was restricted to a core set of tests of cognitive function. The cognitive testing battery took approximately 20 min to complete.

2.5 | Procedures

Prior to their first assessment session, participants completed the online questionnaire. Upon arrival to the laboratory, each participant presented their prescription for verification, and their THC product was examined to ensure it was in original packaging and matched their prescription. An oral fluid screening tool (DrugCheck 3000, Dräger) was administered to detect any recent use of THC, amphetamines, methamphetamines, opiates, benzodiazepines and cocaine. If a positive result for THC was obtained, participants were asked to confirm that they had abstained from consuming cannabis-based products for the 11.5-h cut-off period. It is also important to note that THC can remain detectable for up to 3 days in oral fluid [15]. In the no cannabis session, the drug screening was followed by the administration of the WTAR. Participants then completed the neuropsychological battery. In the post-cannabis session, the drug screening was followed by THC self-administration.

2.6 | Study 1: Cannabis oil condition

Participants orally (on top of tongue) or sublingually (under tongue) ingested a single prescribed dose of their oil product (dropper doses were visually inspected by a member of the research team to ensure that they were in accordance with the participant's prescription). Once participants had consumed their medication, they viewed nature documentary episodes during the 90-min delay period. Upon expiry of the 90 min, participants completed the neuropsychological battery. Note participants were provided with food (e.g., sandwich, biscuits) and tea/coffee during both sessions, as required.

2.7 | Study 2: Cannabis flower condition

During the cannabis condition, the Volcano Medic Vaporiser (Storz and Bickel) was used to administer a dose of the participant's prescribed cannabis flower. Participants were provided with an overview of the vaping procedures and advised that they would have approximately 10 min to consume their cannabis product. Each participant measured out their dose as they normally would when preparing their medication at home, after which it was accurately weighed and recorded before being vaporised into a polythene valve balloon for consumption. The cannabis was vaporised at a temperature of 210°C unless otherwise requested by the participant (none lower than 173°C), to allow for the efficient aeresolisation of THC [30, 31]. Upon conclusion of the designated consumption timeframe (or if the participant indicated that they had completed their preferred dose), a 15-min wait period was observed to allow for the onset of peak effects of inhaled cannabis, as informed by McCartney et al.'s [16] meta-regression analysis. Following this, the cognitive test battery was administered.

2.8 | Statistical analysis

For each study (cannabis oil and cannabis flower), a series of 11 paired samples t tests were conducted to examine whether neuropsychological test performance changed from no cannabis to post-cannabis. Note the mean reaction time for CANTAB tests (as opposed to median reaction time) was analysed on the basis that mean reaction times have been widely used in the research literature reporting CANTAB tests (e.g., [27, 32–34]).

To control the familywise error rate, a Bonferroni-Holm correction for multiple comparisons was applied separately for the TMT tests, Stroop tasks and CANTAB tests, respectively [35]. Effect sizes were quantified using Cohen's d (with 0.2 representing a small magnitude effect, 0.5 a moderate effect and 0.8 indicating a large magnitude effect; [36]). Analyses were conducted via IBM SPSS Statistics (version 27). Since some variables breached the assumption of normality, bootstrapped (bias-corrected, using 1000 samples) confidence limits were reported for all analyses [37]. In Study 1, a total of three participants were identified as extreme outliers (IBM, 2021). Consequently, a sensitivity analysis was conducted without these participants. Excluding these outliers did not affect the results (TMT B: $p < 0.001$ and TMT ratio: $p < 0.001$) and thus results from the total sample are reported. In Study 2, one participant was identified as an extreme outlier (IBM, 2021) and, as such, was excluded due to affecting the results of the full sample, leaving a total sample of $N = 37$.

3 | RESULTS

3.1 | Participant characteristics

The samples included 41 (56.1% male) medicinal cannabis oil patients (Study 1), and 37 (83.8% male) medicinal

TABLE 2 Sample characteristics.

Characteristic	Cannabis oil (Study 1; $N = 41$)		Cannabis flower (Study 2; $N = 37$)	
	Mean (SD) or *n* (%)	Range	Mean (SD) or *n* (%)	Range
BMI, kg/m^2	27.85 (5.47)	18.60–44.10	27.85 (6.81)	19.18–48.23
Education, years	12.24 (2.15)	9–17	11.33 (2.24)	4–17
Estimated FSIQ[a]	107.95 (5.70)	96–119	106.95 (7.28)	88–117
DASS-21, greater than mild[b]				
Depression	16 (39.0%)		12 (32.4%)	
Anxiety	12 (29.3%)		12 (32.4%)	
Stress	10 (24.4%)		12 (32.4%)	
Health conditions, current or historical				
Diagnosed psychiatric disorder	19 (46.3%)		16 (43.2%)	
Respiratory condition	3 (7.3%)		0 (0%)	
Cancer	2 (4.9%)		2 (5.4%)	
Cardiovascular disease	2 (4.9%)		0	
Physical injury	12 (29.3%)		6 (16.2%)	
Type II diabetes	3 (7.3%)		0	
Other (e.g., low vitamin B12, multiple sclerosis)	4 (9.8%)		2 (5.4%)	
Current prescription medications				
Antidepressants	11 (26.8%)		5 (13.5%)	
Anxiolytics	6 (14.6%)		0	
Anti-convulsants	3 (7.3%)		2 (5.4%)	
Opioids	7 (17.1%)		2 (5.4%)	
Other (e.g., blood pressure, anti-inflammatory)	23 (56.1%)		9 (24.4%)	

Note: Study 1: Note five (12.2%) participants met the criteria for mild or greater symptoms across all three subscales, seven (17.1%) met them for two subscales, and nine (22%) met them for one subscale. Study 2: Note seven (19.4%) participants met the criteria for mild or greater symptoms across all three subscales, five (13.9%) met them for two subscales, and five (13.9%) met them for one subscale.

Abbreviations: BMI, body mass index; DASS-21, Depression Anxiety and Stress Scale 21; FSIQ, full-scale intelligence quotient.

[a]Calculated from Wechsler's Test of Adult Reading scores.

[b]Cut-off scores (mild or greater): depression = ≥5, Anxiety = ≥4, Stress = ≥8.

cannabis flower patients (Study 2). Full participant characteristic data for both samples are reported in Table 2. Note that one participant in the flower sample did not provide data for the DASS-21 scale. Independent samples *t* tests revealed no significant differences in age ($p = 0.389$) or estimated Full Scale Intelligence Quotient ($p = 0.518$) between the groups.

3.2 | Cannabis use

3.2.1 | Study 1

The THC content of oil products used by participants ranged from 0.3 to 50 mg/mL ($M = 18.99$ mg/mL). Plant origin strain varied from sativa dominant ($n = 10$, 24.4%), to indica dominant ($n = 7$, 17.1%), and hybrid ($n = 2$, 4.9%). However, 22 (53.7%) of the products were isolates in a carrier oil without any particular strain. A total of 16 (39%) participants reported that their typical consumption of their prescribed cannabis was below the recommended prescription, while 21 (51%) reported their typical consumption was consistent with their prescription. The remaining 4 (10%) participants stated their consumption exceeded this. Ten participants (24%) reported typically experiencing peak effects of their medication in under 30 min, with the remaining participants nominating 30–60 min ($n = 15$, 37%), 60–90 min ($n = 13$, 32%) or 90–120 min ($n = 3$, 7%). Data concerning medicinal and illicit cannabis use are reported in Table 3.

A total of 17.1% ($n = 7$) of participants reported using illicit drugs (excluding cannabis). Cannabis use in the past month ranged from 2 to 31 days. However, the majority of the sample (82.9%) reported using cannabis for 20 or more days (including prescribed or illicit). While 15 participants reported that they had been using medicinal cannabis for

TABLE 3 Participant cannabis use history.

Outcome	Cannabis oil (Study 1)		Cannabis flower (Study 2)	
	Mean ± SD or *n* (%)	Range	Mean ± SD or *n* (%)	Range
Treating conditions				
Chronic pain	28 (68.3%)		24 (64.8%)	
Mental health	20 (48.8%)		18 (48.6%)	
Sleep	15 (36.6%)		17 (45.9%)	
Cancer symptoms	1 (2.4%)		0	
Gastrointestinal	2 (4.9%)		4 (10.8%)	
Other (e.g., migraines)	4 (9.8%)		6 (16.2%)	
Current illicit cannabis use	14 (34.2%)		18 (48.6%)	
Prescribed another type of medicinal cannabis product	34 (82.9%)		29 (78.4%)	
Age of onset cannabis use (prescribed/illicit)	30.37 (18.06)	8–67	20.62 (9.80)	11–59
Estimated years of cannabis use (prescribed/illicit)	15.46 (16.12)	0–48	23.00 (13.55)	1–51
Months using medicinal cannabis	12.61 (20.23)	1–121	11.20 (12.60)	0–61
Medicinal cannabis typical daily use (occasions)	1.63 (0.80)	1–5	4.97 (5.45)	1–30
Cannabis use (prescribed/illegal) past month, days	25.88 (7.81)	2–31	26.16 (7.28)	1–31
Years using illicit cannabis[a]	21.00 (15.44)	1–48	23.25 (12.85)	5–50

[a]Data from 16 of the participants that reported illicit cannabis use in Study 1. Data from 18 of the participants reporting illicit cannabis use in Study 2.

TABLE 4 Self-reported illicit drug and alcohol use (current).

Substance	Cannabis oil (Study 1)		Cannabis flower (Study 2)	
	n (%) or *M* (SD)	Range	*n* (%) or *M* (SD)	Range
Cocaine	4 (9.8%)		3 (8.1%)	
MDMA	2 (4.9%)		4 (10.8%)	
Ketamine	0		1 (2.7%)	
Hallucinogens	2 (4.9%)		5 (13.5%)	
Current alcohol use				
Daily	9 (22.0%)		8 (21.6%)	
Weekly	21 (51.2%)		17 (46.0%)	
Standard drinks per week	6.34 (9.65)	0–30	13.49 (23.13)	0–110

Note: Study 1, $N = 41$; Study 2, $N = 37$.

3 months or less, 10 of these participants reported using illicit cannabis for 5 or more years ($M = 18.93$). Self-reported alcohol and illicit drug use for both studies are presented in Table 4.

3.2.2 | Study 2

The THC content of the medicinal cannabis used by participants ranged from 17% to 26% (as a function of milligrams of THC per gram of product; $M = 21.11\%$). Cannabis flower was normally vaped ($n = 20$, 54.1%) or smoked ($n = 12$, 32.4%), with five participants reporting 'other' as method of ingestion. Although current prescribing guidelines state vaporisation is the recommended ingestion method for cannabis flower, some patients may smoke irrespective of this. Illicit drug use (excluding cannabis) was also reported by 13.5% ($n = 5$) of participants. While reported cannabis use in the past month ranged from 1 to 31 days, the majority of the sample (86.5%) reported 20 or more days of use (prescribed or illicit). A total of 11 participants reported that they had been using medicinal cannabis for 3 months or less (with one reporting zero) but had been regularly using illegal cannabis for at least 5 years or more ($M = 24.27$ years).

3.3 | Oral fluid test results

3.3.1 | Study 1

It was found that 21 participants (51.2%) tested positive for substances during their baseline appointment. A further 22 participants tested positive at their intervention appointment (53.7%). Sixteen (39.0%) participants tested positive for substances in both conditions. It was confirmed verbally that those who tested positive for THC had not consumed any cannabis products (containing THC) on the day of testing. Note that this outcome for THC detection is consistent with previous research assessing oral fluid samples of frequent cannabis users, who tend to demonstrate greater detectable cannabinoid concentrations, even after abstinence [15, 38]. The numbers of participants that tested positive for THC and other substances at the beginning of each session for Study 1 are reported in Table 5.

3.3.2 | Study 2

A total of 30 participants (81.1%) provided a positive drug indication at their baseline appointment, and another 28 participants (75.7%) provided a positive indication at their intervention appointment. Twenty-three participants (62.2%) tested positive in both conditions. One participant advised that they had consumed an opiate (pain medication) 1 h before session commencement, although this was not indicated in the oral drug screening. The number of participants that tested positive to THC and other substances at the beginning of each session for Study 2 is reported in Table 5.

3.4 | Post-cannabis condition

3.4.1 | Study 1

During the post-cannabis session, Study 1 participants consumed a mean of 10.80 mg THC (SD = 11.95, range = 0.06–50, or mean of 0.12 mg/kg THC, SD = 0.12, range = 0.00–0.59) and a mean of 16.05 mg cannabidiol (SD = 54.58, range = 0–350). Thirty-eight (92.7%) participants consumed the oil product using a sublingual administration method, while three (7.3%) participants used an oral administration method. No adverse reactions to cannabis oil occurred during the post-cannabis session.

3.4.2 | Study 2

During their post-cannabis session, Study 2 participants weighed out a mean dose of 0.22 g of cannabis flower, consumed in a minimum of 0.5 and a maximum of four polythene balloons ($M = 2$). Vaporiser temperature ranged

TABLE 5 Positive oral fluid indications for Study 1 (oil) and Study 2 (flower).

Substance type	Baseline, *n* (%)	Intervention, *n* (%)	Positive in both conditions, *n* (%)
Study 1 (oil)			
THC	19 (46.3%)	20 (48.8%)	14 (34.1%)
Amphetamines	0	1 (2.4%)	0
Methamphetamines	0	1 (2.4%)	0
Opiates	2 (4.9%)	4 (9.8%)	2 (4.9%)
Benzodiazepines	1 (2.4%)	1 (2.4%)	1 (2.4%)
Cocaine	1 (2.4%)	1 (2.4%)	1 (2.4%)
Study 2 (flower)			
THC	25 (67.6%)	25 (67.6%)	22 (59.5%)
Amphetamines	0	1 (2.6%)	0
Methamphetamines	0	1 (2.6%)	0
Opiates	2 (5.4%)	3 (8.1%)	1 (2.7%)
Benzodiazepines	2 (5.4%)	1 (2.7%)	0
Cocaine	0	0	0

Note: Study 1, $N = 41$; Study 2, $N = 37$.
Abbreviation: THC, Delta-9-tetrahydrocannabinol.

from 173°C to 210°C ($M = 198$°C). It should be noted that when THC is vaporised there is a large degree of variance in both the amount of THC that is delivered via vapour, in addition to the amount that is absorbed through inhalation [30, 39]. Consequently, accurate measurement of the dose received by each participant cannot be entirely denoted due to the variance in temperature, inhalation technique and also the number of balloons completed from each dose. This variability was also a result of the prescribed dose, whereby some participants were prescribed larger quantities and a greater strength of cannabis than others. For example, some participants were prescribed a maximum amount per day (e.g., 2 g) whereas others required a specific dose at certain times (e.g., 0.10 g as required).

Based only on the strength and measured weight of cannabis flower used by participants in the present study, there was a mean dose of 48.49 mg THC (SD = 33.33, range 10.20–190 mg). This equated to an average of 0.58 mg/kg of THC (SD = 0.38, range 0.11–2 mg/kg) across participants, although, as mentioned previously, these data should be interpreted with caution as it does not account for balloons consumed and variables impacting THC absorption. No adverse reactions to the cannabis flower occurred during the post-cannabis session.

3.5 | The acute effects of cannabis oil and flower on cognitive performance measures

Table 6 presents means, standard deviations and statistics for all cognitive performance measures for both studies.

3.5.1 | Study 1

No significant changes in performance following THC consumption were observed for TMT A, the Stroop measures (A, B, C and ratio), or any of the CANTAB tests. However, a significant reduction in performance at post-cannabis was observed on TMT B and TMT ratio scores (representing a slowing on TMT B relative to A), with large and moderate to large magnitude effect sizes, respectively. All data and statistics are reported in Table 6.

Since some participants tested positive to other substances (other than THC, $n = 7$) on the day of testing (as reported in Table 5), which are known to independently affect cognition, a sensitivity analysis was conducted without these participants. This revealed that excluding such participants did not affect the results. Further analyses were conducted to determine whether the effects were specific to participants who tested negative ($n = 22$) versus positive ($n = 19$) to THC at baseline. These analyses revealed that TMT B performance remained significantly worse at post-cannabis in both subgroups (THC negative: $d = 1.3$, $p < 0.001$ and THC positive: $d = 0.71$, $p = 0.009$), indicating the administered dose affected performance regardless of whether THC was detected at baseline. TMT ratio scores were significantly worse post-cannabis in the THC-negative group ($d = 0.69$, $p = 0.007$; $p = 0.049$ in the THC-positive group).

3.5.2 | Study 2

Within-subjects t tests revealed that from baseline to post-cannabis, there were significant reductions in performance observed in TMT A, TMT B, TMT ratio and Stroop C scores, resulting in moderate and large magnitude effects [36]. No significant change in performance was found on the Simple RTI, 5-Choice RTI, RVP, Stroop A or B tasks.

A sensitivity analysis was conducted excluding those participants who provided a positive drug indication at either time point (other than THC; $n = 8$) as the substances indicated may impart an influence on cognitive performance (methamphetamine, amphetamine, opiates and benzodiazepines). Consistent with the findings above, TMT A and B performance was significantly reduced following cannabis consumption. However, no other significant differences in performance were observed.

Additional analyses were conducted to examine effects in those who provided a positive oral fluid indication for THC at baseline ($n = 25$) and those who did not ($n = 12$). Only TMT B performance remained significantly reduced in both sub-samples ($p < 0.001$ and $p = 0.002$, respectively; both with a large effect size, $d = 0.82$ and 1.07). No other measures reached significance in either sub-sample.

4 | DISCUSSION

Scant research has examined the effects of THC on cognitive function among medicinal cannabis populations, who are likely to display a tolerance to the psychoactive effects of THC through frequent and ongoing use [17]. Consequently, the present studies investigated the effects of orally ingested THC (Study 1) and vaporised cannabis flower (Study 2) on cognitive functions relevant for driving amongst medicinal cannabis patients with long-term, frequent usage patterns. Further, these studies aimed to identify specific neuropsychological tests able to detect potentially subtle cognitive effects of THC. It was observed that, on average, participants had used THC products (either recreationally or medicinally) for

TABLE 6 The effect of THC on cognitive performance measures.

	Cannabis oil (study 1)					Cannabis flower (study 2)				
	No cannabis	Post-cannabis	Bias-corrected bootstrap		Effect size	No cannabis	Post-cannabis	Bias-corrected bootstrap		Effect size
Measure	*M* (SD)	*M* (SD)	*p*	95% CI	*d*	*M* (SD)	*M* (SD)	*p*	95% CI	*d*
Pen and paper										
TMT A time	23.04 (6.54)	24.85 (8.69)	0.166	[−4.47, 0.51]	0.24	23.35 (7.27)	26.89 (7.73)	0.006[a]	[−5.81, −1.47]	0.55
TMT B time	54.96 (18.92)	71.15 (23.40)	<0.001[a]	[−21.13, −11.22]	0.99	63.57 (20.87)	86.15 (30.59)	<0.001[a]	[−30.87, −14.16]	0.91
TMT ratio	1.43 (0.62)	1.96 (0.87)	<0.001[a]	[−0.80, −0.26]	0.61	1.81 (0.92)	2.30 (1.11)	0.017[a]	[−0.89, −0.09]	0.40
Stroop A time	12.71 (2.44)	12.92 (2.48)	0.421	[−0.75, 0.31]	0.13	12.86 (2.46)	13.26 (2.82)	0.238	[−1.04, 0.32]	0.19
Stroop B time	13.99 (3.06)	14.60 (2.59)	0.115	[−1.29, 0.13]	0.26	14.23 (2.91)	14.86 (3.38)	0.127	[−1.36, 0.14]	0.27
Stroop C time	21.85 (5.26)	23.28 (7.55)	0.105	[−3.19, 0.23]	0.26	23.36 (7.00)	25.90 (8.04)	0.006[a]	[−4.27, −0.69]	0.48
Stroop ratio	0.75 (0.45)	0.81 (0.49)	0.355	[−0.18, 0.05]	0.15	0.83 (0.55)	0.98 (0.54)	0.055	[−0.28, −0.00]	0.30
CANTAB										
RTISMRT	328.99 (35.33)	326.05 (29.42)	0.461	[−4.06, 11.17]	0.12	340.15 (33.94)	332.28 (34.84)	0.197	[−1.97, 17.34]	0.23
RTIFMRT	368.71 (34.24)	368.51 (34.36)	0.952	[−5.93, 6.29]	0.01	386.18 (40.31)	379.45 (40.49)	0.247	[−2.48. 16.78]	0.21
RVPA	0.93 (0.04)	0.93 (0.04)	0.467	[−0.01, 0.02]	0.11	0.91 (0.06)	0.91 (0.04)	0.537	[−0.02, 0.01]	0.10
RVPML	513.31 (95.77)	519.94 (94.85)	0.555	[−25.72, 12.98]	0.10	503.38 (90.14)	530.54 (100.85)	0.103	[−58.08, 2.46]	0.28

Note: Study 1 $N = 41$; Study 2 $N = 37$. RVP data based on $N = 40$ for Study 1.

Abbreviations: CANTAB, Cambridge Neuropsychological Test Automated Battery; CI, confidence interval; RTIFMRT, Five Choice Reaction Time; RTISMRT, Simple Choice Reaction Time; RVP, Rapid Visual Information Processing; THC, Delta-9-tetrahydrocannabinol; TMT A, Trail Making Test A; TMT B, Trail Making Test B.

[a]Significant with Bonferroni-Holm correction.

approximately 15 years and consumed a mean THC dose of 10.80 mg (0.12 mg/kg) during the post-cannabis session in Study 1. In Study 2, participants had used THC products for approximately 23 years and consumed a mean THC dose of 48.49 mg. Across studies and analyses, cannabis consumption (both oil and flower) did not affect performance on the Stroop, TMT A or CANTAB tests (after excluding participants with a positive drug indication at the start of either session), supporting the potential role of tolerance in mitigating effects in medicinal cannabis patients. However, across samples and analyses, cannabis significantly affected TMT B performance (exhibiting large magnitude effects) regardless of whether or not participants with a positive drug indication were excluded, suggesting that this finding is robust. TMT ratio scores were also found to be affected in the cannabis oil group (Study 1).

McCartney et al.'s [16] recent meta-analysis revealed reductions in performance on measures of processing speed, motor function, sustained and divided attention, tracking and inhibitory control, as a result of acute cannabis consumption. In the present studies, the absence of a significant effect of THC on the Stroop A, B and C, Stroop ratio, TMT A, RTI and RVP indicates that THC did not measurably affect information processing speed, divided and sustained attention, or inhibitory control performance in these samples. However, THC consumption resulted in significant reductions in performance on the TMT B and TMT ratio measures (for oil only), indicating that THC exerts an acute negative impact on mental flexibility (the capacity for switching attentional focus) and/or visuomotor attention, despite the fact that most participants were long-term regular THC users. However, mental flexibility as assessed using the Stroop C and RVP tasks was not affected by acute THC consumption across analyses in either study. These findings collectively indicate that the mental flexibility component of the TMT B task may not be adversely affected, with the performance decrement on the TMT B task following acute THC exposure likely to be a result of inhibition of visuomotor speed on complex tasks [23].

Nonetheless, there are important factors to consider in interpreting the present findings. First, the absence of measurable change on multiple measures of attentional processing, reaction time, and simple information processing speed suggests that tolerance to THC may mediate the known acute effects of cannabis on neurocognitive function in medicinal cannabis patients [18–20]. These findings are consistent with recent research in medicinal populations [19, 40], although these studies focused on a greater delay (e.g., 30 min and 2.5–3 h post in Olla et al., [19]; 3 h post in Arkell et al., [40]) following administration via oral and vaporised routes. Although a considerable amount of variability was present in cannabis usage patterns and history in the present samples, participants reported having consumed cannabis (both medicinal and illicit) for an average of 15 years in Study 1, and 23 years in Study 2. Participants from both studies predominantly consumed their medication daily. In addition, a substantial proportion of participants (34.2% in Study 1, 48.6% in study 2) reported use of illicit (non-prescribed) cannabis, with varying usage patterns. Inspection of the reasons as to why participants used illicit cannabis included symptom relief, used prior to being prescribed medicinal cannabis, financial benefits (i.e., cheaper), relaxation, recreational use (e.g., when younger) or enjoyment. Together, these findings suggest that some participants may find their cannabis prescription to be insufficient in managing their medical conditions or may be experiencing cannabis dependence. Alternatively, some participants may feel that medicinal cannabis is too costly and thus not sustainable.

Second, despite the aforementioned findings, the effect on TMT B persisted irrespective of whether participants tested positive to other substances, or tested positive/negative to THC at baseline, as well as across samples. Given the magnitude of change from baseline and that the present samples were frequent and long-term users, these findings suggest that TMT B may be sensitive to THC consumption. However, it should also be acknowledged that participants did not markedly differ from age-based population norms at baseline (oil M Z-score $= 0.70$; SD $= 0.72$; flower M Z-score $= 0.31$; SD $= 0.86$) or post-cannabis (oil M Z-score $= -0.05$; SD $= 0.88$; flower M Z-score $= -0.81$; SD $= 1.43$). Certainly, further research is needed to determine the nature and duration of these effects, and whether such changes would translate into temporary functional changes to driving capacity. While previous research has suggested that THC consumption can affect driving performance measures such as lane positioning and reaction time (e.g., see review by McCartney et al., [16]), the association between cognitive function and changes in driving performance following cannabis consumption remains under question. This is an important avenue to explore, given that such knowledge has the potential to inform the development of assessment tools to identify cannabis impairment.

There were a number of study limitations. First, many participants within each sample (46% in Study 1; 68% in Study 2) tested positive for THC in oral fluid at the beginning of either session, despite being asked to abstain from cannabis use for 11.5 h prior. It is possible that participants did not abstain from taking their medication and hence residual THC from previous cannabis may have had an independent effect on neurocognitive performance. However, detectable levels of THC and its relevant metabolites can remain present in oral fluid for up to 3 days

after last cannabis use [15]. In addition, effects on TMT B performance persisted irrespective of whether participants tested positive or negative at baseline. Second, usage histories and THC doses, as well as health conditions, varied substantially across participants. As such, it is likely that THC differentially affected participants based on individual differences in dosage, degree of tolerance and underlying health conditions. For instance, some participants may have benefited from THC by relieving symptoms known to impair performance, whereas others may have experienced decrements to performance. Similarly, the potential influence of food and tea/coffee on performance cannot be discounted.

In addition, performance was only assessed acutely at 90 min post-consumption of oil or 15 min post-vaporisation of flower. Testing at multiple time points would be needed to identify the duration of decrements on TMT B performance. Also, due to time constraints, a more comprehensive battery of cognitive tests could not be used, so it is possible that tests other than the TMT B could be affected by THC consumption in long-term regular users. Future research could also compare performance between regular/medicinal users and new or occasional users, since prior work suggests that neurocognitive effects are less pronounced in highly tolerant users [18–20]. Finally, the sample presented with a range of health conditions known to independently affect neurocognitive function, which may have potentially moderated the effects of THC on cognitive performance [17]. However, one strength of the present studies was that they utilised within-subjects designs, allowing the effect on performance of any underlying health conditions (independent of the effect of THC) to be held constant across the two conditions. While repeated learning effects are possible with such designs, parallel test versions were used and the order in which participants completed the sessions was counterbalanced.

As the use of medicinal cannabis continues to expand globally, research investigating the acute effects of prescribed THC remains a high priority. The present study suggests that medicinal cannabis patients with long-term and frequent usage patterns can present with tolerance to the effects of cannabis flower and oil consumption in some areas of cognitive function (namely inhibitory control, divided and sustained attention). The robust performance detriments seen on TMT B in these groups, in conjunction with the other findings, may point to an effect on visuomotor attention that persists despite tolerance and highlights the potential sensitivity of this task to cannabis consumption. The question of whether the reduction to TMT B performance translates into functional reductions in driving capacity needs to be addressed in future work. Such knowledge will not only contribute to current scientific understanding of the effects of cannabis on cognition and driving but will also serve as a foundational step towards identifying behavioural measures of impairment.

AUTHOR CONTRIBUTIONS

Kayla B. Stefanidis: Conception and design of the project or output, contribution of knowledge, analysis and interpretation of research data, drafting significant parts of the research output, and critically revising research output so as to contribute to its interpretation. **Carla Schiemer:** Design of the project or output, analysis and interpretation of research data, and drafting significant parts of the research output. **Taren Mieran:** Design of the project or output, analysis of data, and drafting significant parts of the research output. **Andrew Hill:** Design of the project or output, contribution of knowledge, interpretation of research data, and critically revising research output so as to contribute to its interpretation. **Mark S. Horswill:** Design of the project or output, contribution of knowledge, interpretation of research data, and critically revising research output so as to contribute to its interpretation. **Mathew J. Summers:** Conception and design of the project or output, contribution of knowledge, interpretation of research data, and critically revising research output so as to contribute to its interpretation.

ACKNOWLEDGMENTS

This research was funded by the Motor Accident Insurance Commission. The funders did not have any role in the study design, data collection and analysis, decision to publish or preparation of the manuscript. Open access publishing facilitated by University of the Sunshine Coast, as part of the Wiley - University of the Sunshine Coast agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

The authors have no interests to declare.

DATA AVAILABILITY STATEMENT

The authors do not have permission to share data.

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How to cite this article: Stefanidis KB, Schiemer C, Mieran T, Hill A, Horswill MS, Summers MJ. Elucidating the acute effects of medically prescribed oral and vaporised delta-9-tetrahydrocannabinol on cognitive functions important for driving. Drug Alcohol Rev. 2025; 44(4):1010–23. https://doi.org/10.1111/dar.14060