ORIGINAL RESEARCH ARTICLE

A Semi-Naturalistic, Open-Label Trial Examining the Effect of Prescribed Medical Cannabis on Neurocognitive Performance

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Abstract

Background and objectives Medical cannabis use is increasing in Australia and other jurisdictions, yet little is known about the effects of medical cannabis on cognitive function. Findings from studies of non-medical ('recreational') cannabis may not be applicable to patients using prescribed medical cannabis to manage a health condition.

Methods In this semi-naturalistic, open-label trial, patients with various health conditions attended a single laboratory session in which they self-administered a standard dose of prescribed medical cannabis as per instructions on the pharmacy label. We assessed cognitive performance using the Cambridge Neuropsychological Test Automated Battery (CANTAB) and Druid application (app) prior to and following (CANTAB: + 3 h; Druid: + 3 and 5.5 h) medical cannabis self-administration. We also assessed subjective drug effects prior to and following (1, 2 and 4 h) medical cannabis self-administration using a range of 0–10 cm visual analogue scales ('stoned', 'sedated', 'relaxed', 'comfortable', 'anxious' and 'confident'). Data were analyzed using linear fixed-effect models.

Results Participants ($N = 40$; 22 females) were prescribed a range of products including orally administered oils ($n = 23$) and flower for vaporization ($n = 17$). Participants had a mean (standard deviation [SD]) age of 41.38 (12.66) years and had been using medical cannabis for a mean (SD) of 10.18 (8.73) months. Chronic non-cancer pain was the most common indication for medical cannabis use ($n = 20$), followed by sleep disorder ($n = 18$) and anxiety ($n = 11$). The mean (SD) delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) dose administered by participants was 9.61 (8.52) mg/9.15 (10.11) mg among those using an oil, and 37.00 (24.53) mg/0.38 (1.58) mg among those who vaporized flower, respectively. Participants' performance improved over time on the CANTAB Multitasking Test and Rapid Visual Information Processing test (both p-values <0.001). All other changes in cognitive performance measures over time were non-significant ($p > 0.05$). Vaporization of flower was associated with significantly stronger subjective feelings of 'stoned' and 'sedated' relative to oils (both $p < 0.001$).

Conclusions These findings suggest that prescribed medical cannabis may have minimal acute impact on cognitive function among patients with chronic health conditions, although larger and controlled trials are needed.

1 Introduction

Medical cannabis is now widely prescribed for a range of conditions in Australia, most commonly chronic pain, anxiety and sleep disorders [1]. Medical cannabis products are considered 'unregistered medicines' by Australia's

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Key Points

Medical cannabis, when used as prescribed, did not negatively impact cognitive function.

These results suggest that patients taking a stable dose of medical cannabis may become tolerant to the potentially impairing effects of delta-9-tetrahydrocannabinol (THC).

Results cannot be generalized to non-medical cannabis or non-prescribed medical cannabis.

Therapeutic Goods Administration, which means doctors must seek regulatory approval to prescribe them. While few approvals were sought in the first few years following legalization, applications have since increased considerably and now exceed 390,000 [2]. As the number of patients prescribed medical cannabis continues to grow, there is an obvious need to consider potential impacts on cognitive function, driving and other safety-sensitive tasks such as operating machinery.

Most research into the cognitive effects of cannabis has focused on non-medical cannabis [3], in large part due to the relative novelty of medical cannabis prescribing as well as restrictions on cannabinoid research imposed by international controls on cannabis access and use [4]. While non-medical and medical cannabis are both derived from the cannabis plant, the 'medical' designation generally implies the use of a cannabinoid product to treat or manage a health condition, while the 'non-medical' or 'recreational' designation generally implies the use of cannabis for its intoxicating effects which are attributable to delta-9-tetrahydrocannabinol (THC). Considering this distinction and noting that patients who are prescribed medical cannabis may have existing cognitive impairments due to the condition being treated or use of other medications [5, 6], prior research into the cognitive effects of non-medical cannabis may have only limited applicability to patients prescribed medical cannabis to treat a chronic health condition. Moreover, laboratory studies into the acute effects of cannabis on cognitive function have typically involved young, healthy volunteers, while the average age of a medical cannabis patient in Australia is approximately 45–55 years [6, 7]. Given age-related changes in cognitive function [8] and age-related differences in the effects of cannabis on cognitive function [9], this age differential further complicates the generalization of findings from non-medical cannabis studies to patient populations.

A recent systematic review identified 23 studies (total $N = 917$) that looked at the effect of medical cannabis on cognitive function by comparing test performance prior to and after receiving treatment [10]. There was considerable heterogeneity in duration of treatment (from 1 day to 12 months), medical cannabis product type, THC dose, and indication for treatment. Fifteen studies found no impact of medical cannabis on cognitive function; one found an improvement, and six found some degree of performance impairment. All four studies that delivered medical cannabis via smoking or vaporization demonstrated impairment, although these studies were characterized by acute administration of relatively high THC doses rather than long-term treatment schedules. Consistent with another recent review [11] and a separate report of improvements in cognitive function among patients receiving medical cannabis treatment over 12 months [12], it was concluded that cognitive function is largely unaffected in patients undergoing long-term, stable treatment with medical cannabis containing low-moderate doses of THC. The fact that impairment tends to increase with higher doses of THC is well established [13, 14], but determining where this threshold for impairment lies in relation to THC dose for medical cannabis, if it can be established at all, is complicated by a multitude of factors such as tolerance, product type, concomitant medication use and the underlying health condition being treated.

Understanding the extent to which medical cannabis impacts cognitive function and determining whether cognitive function is differentially affected by non-medical and medical cannabis is important for effective and evidence-based medical cannabis policy and the development of prescribing guidelines. With this in mind, we aimed to assess cognitive performance and subjective drug effects before and after self-administration of prescribed medical cannabis in a group of Australian patients with a range of health conditions.

2 Methods

2.1 Study Design and Procedures

In this semi-naturalistic, open-label laboratory study, participants attended a single session in which they self-administered a standard dose of their prescribed medical cannabis product. Participants were first required to complete an online eligibility questionnaire prior to attending the laboratory session, which included questions on demographics (age, sex, employment), drug and alcohol use, medical cannabis use history and perceived improvement (%) in health condition since commencing treatment with medical cannabis. Eligible participants then attended a medical screen that involved a detailed review of the patient's medical history, concomitant medications, and drug and alcohol use. Participants were asked to abstain from illicit drugs for a minimum of 7 days before the session, from alcohol for the 24 h prior, and from medical cannabis the morning of the session. Participants remained at the testing site until deemed safe to leave by the research nurse. Upon completion, participants received a handout outlining post-study restrictions, a taxi voucher to provide transport home from the testing site ($50) and monetary reimbursement for their time totalling $100.

2.2 Participants

Participants were patients prescribed any medical cannabis product to manage a refractory health condition. Inclusion criteria were (1) aged > 21 years; (2) in possession of an unrestricted driver's license; (3) prescribed a medicinal cannabis

product containing ≥ 1 mg THC per dose; and (4) able to attend a 7-h session without using medical cannabis more than once. Exclusion criteria were (1) unable to provide written informed consent; (2) pregnant or lactating; and (3) patient is unable to abstain from illicit drug use for 7 days prior to testing. Participants were recruited through flyers placed in pharmacies and dispensaries around Melbourne, Australia. A total of 60 participants were assessed for eligibility; four declined to participate and three were excluded because of an expired or non-THC prescription. A total of 53 participants were thus recruited, with a further 13 excluded because they were unable to attend the test session, resulting in a final sample of 40 (Table 1). All participants gave written informed consent prior to study enrolment, and all procedures were approved by the Swinburne University Human Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. The trial was listed on the Australia New Zealand Clinical Trials Registry (ANZCTRN12621001205820).

2.3 Experimental Session

Upon arrival at the clinical research unit, participants completed a baseline cognitive assessment that included a range of Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, England) tasks and the Druid (Impairment Science Inc., USA) tasks described below, as well as a subjective drug effect questionnaire. Participants were then instructed to self-administer a standard dose of their prescribed medical cannabis, and this was witnessed by the researcher who checked that the dose administered was consistent with the instructions on the pharmacy label. THC/cannabidiol (CBD) dose for flower was calculated using the THC/CBD percentage as stated on the product label, and the dose of plant material in milligrams (e.g., for 150 mg of flower containing 20% THC, THC dose would be calculated as 150×0.20), while THC/CBD dose for oil was calculated based on the milligrams/millilitres THC/CBD content of the product and the quantity consumed in millilitres.

The subjective drug effect questionnaire was repeated at 1, 2, and 4 h after dosing. CANTAB assessment was repeated at 3 h, while the Druid assessment was repeated at 3 and 5.5 h after dosing. The 3-h timepoint was intended to capture the overlapping windows of impairment associated with inhaled and orally administered cannabis. Participants also completed a range of other assessments and provided blood and oral fluid samples for quantification of THC; these results will be reported elsewhere.

2.4 Cognitive Assessments

The CANTAB test battery included the following six tests: Multitasking Test (MTT), Pattern Recognition Memory

Table 1 Participant demographics and characteristics

	Mean (SD) or N (%)
Age, years	41.38 (12.66)
Female	18 (45%)
BMI	27.6 (5.3)
Education	
Secondary	30 (25%)
Tertiary	78 (65%)
Postgraduate	12 (10%)
Employed	26 (65%)
Health indication[a]	
Chronic non-cancer pain	20 (50%)
Sleep disorder	18 (45%)
Gastrointestinal condition	3 (7.5%)
PTSD	4 (10%)
Anxiety	11 (27.5%)
Depression	4 (10%)
Cancer pain	1 (2.5%)
Neurological disorder	1 (2.5%)
Perceived improvement in condition since commencing MC treatment (0–100)	78.9 (16.2)
Alcohol use > 1× per week	9 (22.5%)
Mean THC dose per dose	21.9 (23.4)
For oils only	9.61 (8.52)
For flower only	37.00 (42.53)
Mean CBD dose per dose	5.29 (8.66)
For oils only	9.15 (10.11)
For flower only	0.38 (1.58)
Prescribed product formulation	
Oil	22 (55%)
Dried flower	17 (42.5%)
Oromucosal spray[b]	1 (2.5%)
Cannabinoid profile	
THC-dominant	23 (57.5%)
Balanced	15 (37.5%)
CBD-dominant	2 (5%)

BMI body mass index, *CBD* cannabidiol, *MC* medical cannabis, *PTSD* post-traumatic stress disorder, *SD* standard deviation, *THC* delta-9-tetrahydrocannabinol

[a]Participants could select more than one condition

[b]Single case of spray considered oil for statistical analyses due to a comparable absorption profile

(PRM), Reaction Time (RTI), Rapid Visual Information Processing (RVP), Spatial Span (SSP), and Spatial Working Memory (SWM). Together, these tests assess working memory, sustained attention, response time, impulsivity, pattern recognition memory, and executive function. Table 2 describes each of these tests and the associated key outcome variables. All tests were completed on an iPad (9th Generation, Apple Inc., Cupertino, CA, USA) and included a practice phase with performance feedback and automated

voice instructions. The battery of tests took approximately 35 min to complete.

Druid is an iPad-based cognitive and psychomotor test battery that assesses response time, response inhibition, time estimation, divided attention and balance. Recent studies indicate that the test battery is sensitive to acute cannabis effects in non-patient populations [15, 16]. It is made up of four tasks that can be completed in under 3 min. The application (app) collects and integrates numerous measurements to produce a performance score that ranges from 0 to 100, with lower scores indicating better performance. Participants were required to practice the test battery three times prior to the baseline assessment to establish an accurate baseline score and to minimize practice effects.

2.5 Subjective Drug Effects

The subjective drug effect questionnaire consisted of six unipolar visual analogue scales ranging from 0 to 10 cm (not at all–very much so). These included 'stoned', 'sedated', 'relaxed', 'comfortable', 'anxious', and 'confident'. All questionnaires were completed on an iPad.

2.6 Statistical Analyses

An a priori power calculation indicated that a minimum sample size of 36 would be required to detect a meaningful difference (Cohens $d = 0.5$) in simulator driving performance with 95% power (note, driving performance data reported elsewhere). Cognitive test performance and subjective drug effect data were analyzed in SPSS v28 (IBM Corporation, Armonk, NY, USA) using linear fixed-effects models with the restricted maximum likelihood method. Fixed factors included time (2 levels for CANTAB data; 3 levels for Druid data; 4 levels for subjective drug effects), product type (2 levels), and a time*product type interaction. A heterogenous first-order autoregressive covariance structure was selected following a comparison of goodness-of-fit values for unstructured and compound symmetry structures using Schwarz's Bayesian Criterion. Where a significant main effect or interaction effect was observed, post hoc paired t-tests with a Bonferroni adjustment for multiple comparisons were conducted (two comparisons for CANTAB measures; three comparisons for Druid data; four comparisons for subjective drug effect data). All tests were two-tailed, with statistical significance set at the 0.05 level.

3 Results

As shown in Table 1, participants ($N = 40$; 22 females) had a mean (SD; range) age of 41.38 (12.66; 23–80) years and were prescribed a mixture of orally administered oils

($n = 22$), oral sprays ($n = 1$) and flower for vaporization ($N = 17$). As only one participant used an oral spray, they were included in the oil group for all statistical analyses. THC-dominant products (23/40) contained, on average (SD), 32.66 mg THC and 0.12 (0.41) mg CBD. Balanced products (15/40) contained, on average, 9.19 (8.29) mg THC and 10.38 (10.16) mg CBD, while CBD-dominant products contained, on average, 1.13 (0.18) mg THC and 16.25 (5.30) mg CBD. Oils contained, on average, 9.61 (8.52) mg THC and 9.15 (10.11) mg CBD, while flower products contained, on average, 37.00 (24.53) mg THC and 0.38 (1.58) mg CBD. The amount of THC/CBD in flower was calculated based on the THC content of the product and the dose administered, and therefore reflects the maximum possible dose that will inevitably be higher than the actual administered dose.

Chronic non-cancer pain was the most common indication for medical cannabis use ($n = 20$, 50%), followed by sleep disorders ($n = 18$, 45%) and anxiety ($n = 11$, 27.5%). Most participants ($n = 37$, 92.5%) had been using medical cannabis for more than 30 days at the time of their registration into the trial, with a mean (SD) treatment duration of 10.18 (8.73) months. All patients reported daily use of medical cannabis. Patients self-reported a mean improvement in their condition of 78.59% (SD 16.18) since commencing treatment with medical cannabis.

3.1 Cognitive Performance

Table 3 shows mean scores for each cognitive outcome variable and respective linear mixed-model test results. For the sake of brevity, only statistically significant results are reported in the text. Mean differences and confidence intervals reported below are derived from the model estimates of fixed effects are therefore differ slightly from the mean values reported in Table 3.

3.1.1 Multitasking Test

There was a significant main effect of time ($p < 0.001$) on median reaction latency and multitasking cost, but no effect of product type or a time*product type interaction for either outcome. Reaction latency improved from T1 (baseline) to T2 (3 h) by 56.39 ms (95% confidence interval [CI] 31.07–81.91, $p < 0.001$), and multitasking cost decreased (i.e., improved) from T1 to T2 by 64.49 ms (95% CI 31.69–97.30, $p < 0.001$). For incongruency cost and total incorrect, the main effects of time and product type and the time*product type interaction were non-significant.

Table 2 Description of Cambridge Neuropsychological Test Automated Battery and key outcome variables

Test	Description	Key outcome variables
Multitasking Test (MTT)	MTT is a test of executive function that provides a measure of the ability to use multiple sources of potentially conflicting information to guide behaviour	(1) Incongruency cost: difference between the median latency of response on congruent versus incongruent trials. A higher incongruency cost indicates that the subject takes longer to process conflicting information (2) Reaction latency: the median latency of response (3) Multitasking cost: the difference between the median latency of response during assessed blocks in which both rules are used versus assessed blocks in which only a single rule is used. A positive score indicates a higher cost of managing multiple sources of information (4) Total incorrect: the number of trials for which the outcome was an incorrect response
Pattern Recognition Memory (PRM)	PRM is a measure of immediate and delayed visual recognition memory	(1) Efficiency score delayed: the mean correct latency delayed score divided by the percentage of correct for delayed (lower score = more efficient, higher score = less efficient) (2) Efficiency score immediate: the mean correct latency immediate score divided by the percentage of correct for immediate (lower score = more efficient, higher score = less efficient)
Reaction Time (RTI)	RTI provides assays of motor and mental response speeds	(1) Five-choice reaction time: the median duration it took for a subject to release the response button after the presentation of a target stimulus. Includes trials in which the stimulus could appear in any one of five locations (2) Total error score (five-choice): the total number of trials where the subject made any form of response error (3) Simple reaction time: the median duration it took for a subject to release the response button after the presentation of a target stimulus. Includes trials in which the stimulus could appear in one location only (4) Total error score (simple): the total number of trials where the subject made any form of response error
Rapid Visual Information Processing (RVP)	RVP is a sensitive tool for assessment of sustained attention	(1) A prime: signal detection measure of a subject's sensitivity to the target sequence. A higher score indicated better performance (2) Response latency: the median response latency on trials where the subject responded correctly (3) Probability of hit: the number of target sequences during assessment blocks that were correctly responded to within the time allowed, divided by the number of target sequences during assessment blocks
Spatial Span (SSP)	SSP is a test of visuospatial working memory	(1) Forward span length: the longest sequence of boxes successfully recalled by the subject (2) Total errors: the total number of times a subject incorrectly touched a box that was not the next one in the sequence

Table 2 (continued)

Test	Description	Key outcome variables
Spatial Working Memory (SWM)	SWM requires retention and manipulation of visuospatial information. This test has notable executive function demands, and measures strategy use as well as errors	(1) Between errors: the number of times the subject incorrectly revisits a box in which a token has previously been found. Calculated across all assessed four, six and eight token trials
		(2) Strategy (6–8 boxes): the number of times a subject begins a new search pattern from the same box they started with previously. Lower scores indicate higher strategy use

3.1.2 Pattern Recognition Memory

The main effects of time and product type on both outcome measures were non-significant. There was a significant time*product type interaction for the delayed efficiency score ($p < 0.05$), although post hoc tests comparing performance over time within each level of product type, and performance across levels of product type within each level of time, were not statistically significant after correcting for multiple comparisons.

3.1.3 Reaction Time

For all four outcome measures, the main effects of time and product type and the time*product type interaction were non-significant.

3.1.4 Rapid Visual Information Processing

There was a significant main effect of time ($p < 0.001$) and product type ($p < 0.05$) on A prime (signal detection measure), such that performance increased by 0.03 points (range of 0–1) from T1 to T2 (95% CI 0.02–0.04) and was better overall for patients prescribed flower relative to oils (+ 0.40 points, 95% CI 0.01–0.07). For probability of hit, there was a significant main effect of time ($p < 0.001$), product type ($p < 0.05$) and a significant time*product type interaction ($p < 0.05$). Probability of hit was significantly increased from T1 to T2 by 0.10 points (95% CI 0.06–0.15), and by 0.13 points among patients prescribed flower relative to oil over both levels of time (95% CI 0.02–0.23). Further pairwise comparisons showed that only patients prescribed flower improved significantly from T1 to T2 (+ 0.16, 95% CI 0.09–0.23). There was no effect of time, product type, or time*product type on response latency.

3.1.5 Spatial Span

The main effects of time and product type, and the time*product type interaction, were non-significant for both SSP outcome measures.

3.1.6 Spatial Working Memory

The main effects of time and product type, and the time*product type interaction, were non-significant for both SWM outcome measures.

3.1.7 Druid Application (App)

The main effects of time and product type, and the time*product type interaction, were non-significant for the composite performance score.

3.2 Subjective Drug Effects

Figure 1 shows participant-reported subjective drug effects over time. There was a significant main effect of time on 'stoned' ($p < 0.001$), 'sedated' ($p < 0.001$) and 'anxious' ($p < 0.001$); a significant main effect of product type on 'confident'; and a significant time*product type interaction for 'stoned' ($p < 0.001$) and 'sedated' ($p < 0.001$). Post hoc tests showed that participants who self-administered flower rated themselves as significantly more stoned relative to baseline at 1 h (+ 3.47 cm, 95% CI 2.09–4.85, $p < 0.001$), 2 h (+ 2.12 cm, 95% CI 0.72–3.52, $p < 0.001$) and 4 h (+ 1.12 cm, 95% CI 0.04–2.20, $p < 0.05$), while participants who self-administered oil rated themselves as significantly more stoned relative to baseline at 2 h (+ 2.05 cm, 95% CI 0.73–3.37, $p < 0.001$) and 4 h (+ 0.95 cm, 95% CI 0.02–1.88 $p < 0.05$), but not at 1 h. Participants who self-administered flower also rated themselves as significantly more sedated relative to baseline at 1 h (+ 2.59 cm, 95% CI 1.85–3.32, $p < 0.001$), 2 h (+ 1.77 cm, 95% CI 0.51 3.02, $p < 0.05$) and 4 h (+ 1.29 cm, 95% CI 0.14–2.45, $p < 0.05$), while those participants who self-administered oil did not rate themselves as significantly more sedated relative to baseline at any timepoint.

Relative to participants who self-administered oil, those who self-administered flower rated themselves as more stoned at 1 h (+ 2.69 cm, 95% CI 1.27–4.12, $p < 0.001$) and more sedated at 1 h (+ 1.87 cm, 95% CI 0.87–2.87,

Table 3 Mean scores and linear mixed-model results for all cognitive performance outcomes

Test	Key outcome variables	Mean (SD) T1	Mean (SD) T2	Mean (SD) T3	Time	Product type	Time*product type
Multitasking Test (MTT)	(1) Incongruency cost	68.21 (52.92)	70.44 (43.71)	–	$F_{(1, 38)} = 0.00, p = 0.99$	$F_{(1,38)} = 1.08, p = 0.31$	$F_{(1,38)} = 2.31, p = 0.14$
	(2) Reaction latency (ms)	663.70 (113.41)	611.64 (132.88)	–	$\mathbf{F_{(1,37)} = 20.28, p < 0.001}$	$F_{(1,38)} = 3.46, p = 0.07$	$F_{(1,37)} = 0.06, p = 0.81$
	(3) Multitasking cost	206.54 (112.74)	143.24 (97.40)	–	$\mathbf{F_{(1,38)} = 15.84, p < 0.001}$	$F_{(1,38)} = 0.63, p = 0.43$	$F_{(1,38)} = 0.00, p = 0.97$
	(4) Total incorrect	5 (6)	4 (3)	–	$F_{(1,38)} = 2.84, p = 0.10$	$F_{(1,38)} = 1.26, p = 0.27$	$F_{(1,38)} = 0.22, p = 0.64$
Pattern Recognition Memory (PRM)	(1) Efficiency score delayed	20.36 (15.24)	19.49 (6.04)	–	$F_{(1,37)} = 0.69, p = 0.41$	$F_{(1,37)} = 0.93, p = 0.34$	$\mathbf{F_{(1,37)} = 4.78, p < 0.05}$
	(2) Efficiency score immediate	18.28 (9.18)	16.64 (4.19)	–	$F_{(1,38)} = 2.02, p = 0.16$	$F_{(1,38)} = 0.03, p = 0.86$	$F_{(1,38)} = 0.13, p = 0.72$
Reaction Time (RTI)	(1) Five-choice reaction time (ms)	388.53 (34.56)	389.29 (41.59)	–	$F_{(1,37)} = 0.02, p = 0.88$	$F_{(1,39)} = 0.37, p = 0.55$	$F_{(1,37)} = 2.98, p = 0.09$
	(2) Total error score (five-choice)	0.38 (0.78)	0.41 (0.68)	–	$F_{(1,38)} = 0.20, p = 0.66$	$F_{(1,39)} = 0.10, p = 0.76$	$F_{(1,38)} = 1.86, p = 0.18$
	(3) Simple reaction time (ms)	346.37 (35.97)	342.55 (40.86)	–	$F_{(1,37)} = 1.51, p = 0.23$	$F_{(1,38)} = 1.20, p = 0.28$	$F_{(1,37)} = 0.31, p = 0.58$
	(4) Total error score (simple)	1.00 (1.49)	0.69 (0.98)	–	$F_{(1,38)} = 1.40, p = 0.25$	$F_{(1,39)} = 1.09, p = 0.30$	$F_{(1,38)} = 0.00, p = 0.99$
Rapid Visual Information Processing (RVP)	(1) A prime	0.90 (0.06)	0.93 (0.05)	–	$\mathbf{F_{(1,38)} = 26.13, p < 0.001}$	$\mathbf{F_{(1,38)} = 6.21, p < 0.05}$	$F_{(1, 28)} = 1.83, p = 0.18$
	(2) Response latency (ms)	466.85 (108.85)	452.95 (80.78)	–	$F_{(1,38)} = 1.98, p = 0.17$	$F_{(1,38)} = 2.75, p = 0.11$	$F_{(1,38)} = 1.00, p = 0.32$
	(3) Probability of hit	0.65 (0.19)	0.74 (0.18)	–	$\mathbf{F_{(1,38)} = 20.99, p < 0.001}$	$\mathbf{F_{(1,38)} = 6.01, p < 0.05}$	$\mathbf{F_{(1,38)} = 5.51, p < 0.05}$
Spatial Span (SSP)	(1) Forward span length	6 (1)	6 (1)	–	$F_{(1,38)} = 0.59, p = 0.45$	$\mathbf{F_{(1,38)} = 4.28, p < 0.05}$	$F_{(1,38)} = 0.90, p = 0.35$
	(2) Total errors	14.31 (6.11)	16.53 (8.34)	–	$F_{(1,37)} = 1.02, p = 0.32$	$F_{(1,37)} = 1.48, p = 0.23$	$\mathbf{F_{(1,37)} = 4.99, p < 0.05}$
Spatial Working Memory (SWM)	(1) Between errors	8 (9)	7 (9)	–	$F_{(1,37)} = 1.60, p = 0.22$	$F_{(1,38)} = 3.86, p = 0.06$	$F_{(1,37)} = 0.01, p = 0.91$
	(2) Strategy (6–8 boxes)	6 (3)	6 (3)	–	$F_{(1,38)} = 4.84, p = 0.03$	$F_{(1,38)} = 2.63, p = 0.11$	$F_{(1,38)} = 0.58, p = 0.45$
Druid	(1) Overall score	49.28 (10.56)	50.15 (10.89)	49.95 (9.59)	$F_{(2,64)} = 0.47, p = 0.63$	$F_{(1,37)} = 1.93, p = 0.17$	$F_{(2,64)} = 0.99, p = 0.38$

SD standard deviation, *T1* baseline, *T2* 3 h after medical cannabis self-administration, *T3* 5.5 h after medical cannabis self-administration (only the Druid task was completed at T3)

Data presented are results from linear mixed models where ''time', 'product type' and 'time*product type' are the independent variables included as fixed effects. Significant effects are indicated in bold

Fig. 1 Estimated marginal mean (SE) participant ratings of 'stoned', 'sedated', 'relaxed', 'comfortable', 'anxious', and 'confident' at baseline (−1 h) and 1, 2 and 4 h after self-administration of prescribed medical cannabis. All scales were unipolar and ranged from 0 to 10. The asterisk symbol (*) indicates a statistically significant difference from baseline at that timepoint, with the letter above in brackets denoting statistical significance for flower (f) or oil (o) only. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The hash symbol (#) indicates a statistically significant difference between product types (oil or flower) at that timepoint. #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$. *SE* standard error
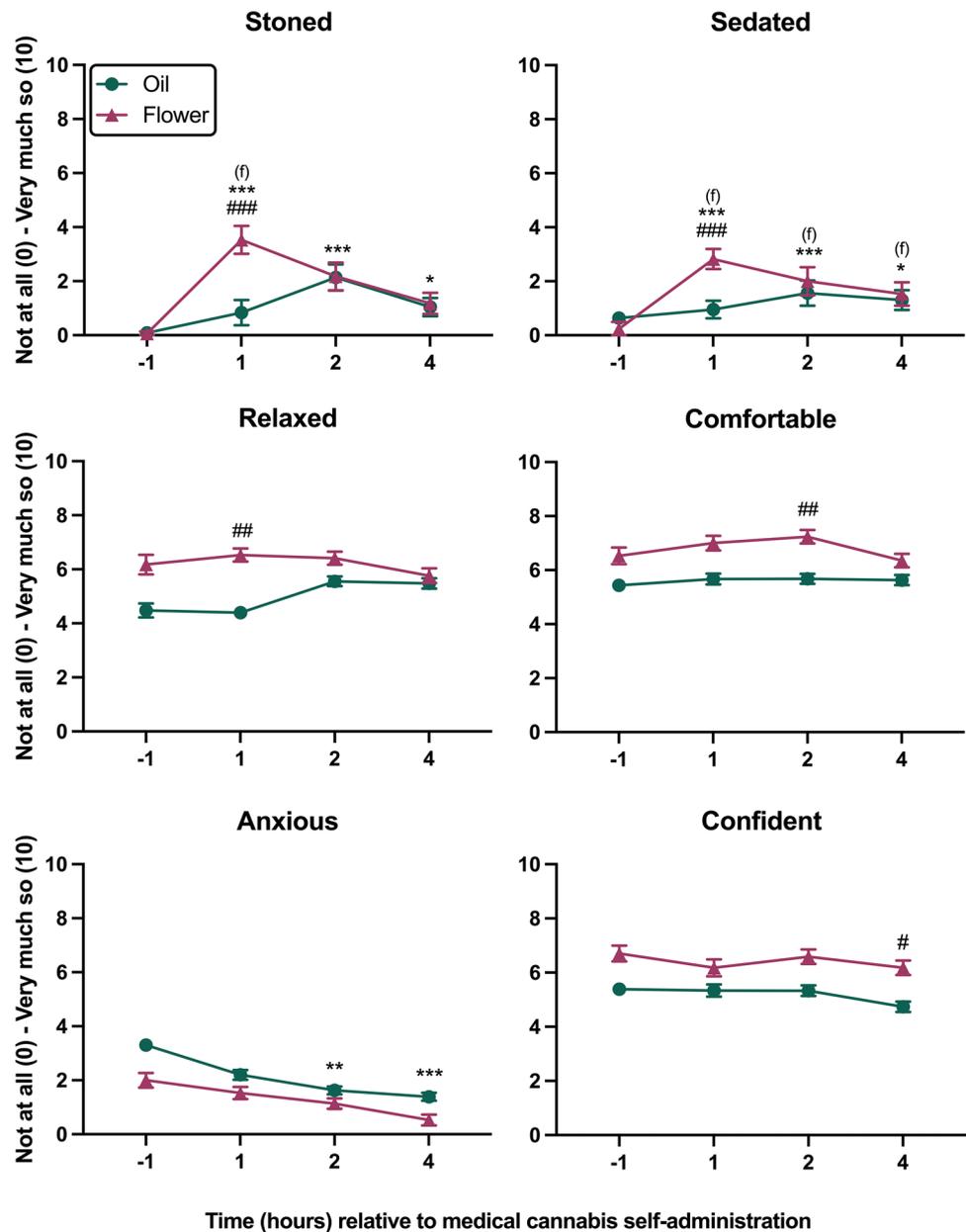
$p < 0.001$). There was a significant main effect of product type on 'relaxed' ($p < 0.05$) and 'comfortable' ($p < 0.05$), with participants who self-administered flower rating themselves as more relaxed at 1 h (+ 2.14 cm, 95% CI 0.85–3.42, $p < 0.01$) and more comfortable at 2 h (+ 1.56 cm, 95% CI 0.25–2.87, $p < 0.01$) relative to participants who self-administered oil. Ratings of 'anxious', on the other hand, were greatest at baseline and decreased significantly at 2 h (−1.27 cm, 95% CI − 2.25 to − 0.28, $p < 0.01$) and 4 h (− 1.69 cm, 95% CI − 2.77 to − 0.62, $p < 0.001$). Participants who self-administered flower rated themselves as more confident than those who self-administered oil, although this difference was only statistically significant at the 4-h timepoint (+ 1.44 cm, 95% CI

0.06–2.82, $p < 0.05$). Neither of the two patients using CBD-dominant products reported feeling 'stoned' at any timepoint.

4 Discussion

In this semi-naturalistic, open-label laboratory study, we investigated cognitive performance before and after self-administration of a prescribed medical cannabis product. We found no evidence for impaired cognitive function when comparing baseline with post-treatment scores on a comprehensive neuropsychological test battery, nor did we observe any change in performance on the Druid test battery over

time. The absence of evidence for cognitive impairment following medical cannabis self-administration was surprising, given prior and substantive evidence that non-medical ('recreational') cannabis use reliably impairs a range of cognitive functions [3]. At the same time, these findings are consistent with two systematic reviews published in the last year that suggest that medical cannabis, when used regularly and consistently for a chronic health condition, may have little if any impact on cognitive function [10, 11].

Wieghorst et al. [10] conducted a systematic review of 23 studies (total participant pool of $N = 917$) that administered any medical cannabis product to patients and compared cognitive performance under treatment and control (placebo or baseline) conditions. Participants were mostly female ($n = 448$) and the mean age ranged from 33 to 65 years. Treatment periods varied greatly from 1 day to 12 months. Fifteen studies found no impact of medical cannabis on cognitive function, while one reported an improvement and six reported impairments. Two of the studies that reported no cognitive impairment involved treatment with a CBD-only product that would not be expected to impact cognitive function [17, 18]. Of the six studies that reported impairment, four were characterized by administration of a single dose of cannabis via smoking or vaporization, and a requirement that patients avoid cannabis for 30 days prior to participating [19–22]. The fact that these patients were not taking a stable dose of medical cannabis might explain why we found no evidence for acute cognitive impairment when comparing baseline with post-treatment scores among patients who self-administered cannabis via vaporization.

We found little evidence in this study to suggest that magnitude of change in cognitive function differed with product type, apart from one measure (probability of a hit) on the RVP, where only patients who self-administered flower exhibited a significant improvement over time. Given the mean THC dose was higher for flower products (37.00 mg vs. 9.61 mg for oils), the observed improvement in performance, although minimal, is somewhat perplexing and might reflect a practice effect rather than true improvement following acute medical cannabis administration. It is also possible that any potential impairment had subsided by 3 h among patients who self-administered flower, noting that subjective drug effects were strongest at 1 h. Our rationale for having a second CANTAB assessment at 3 h and not sooner was based on two factors: (1) government data at the time indicated that most prescriptions were for orally administered products rather than flower; and (2) cognitive impairment following cannabis inhalation can still persist for up to 3–5 h despite the fact that self-reported intoxication tends to be strongest within the first 1–2 h [17, 23].

The recent systematic review by Motaghi et al. [11] examined studies that used an oromucosal spray containing an equal amount of THC and CBD, and compared cognitive performance under treatment and control (placebo or baseline) conditions. The mean age of patients ranged from 29 to 51 years, and again there was considerable heterogeneity in treatment duration, which ranged from 1 day to 12 months. The total number of sprays used by patients ranged from 4 to 16 per day, delivering approximately 10–40 mg THC and CBD, which is comparable with the range of doses used by patients in this study. Of the 10 studies that were included (total $N = 510$), seven included patients with multiple sclerosis. No evidence was found for cognitive impairment when comparing performance under treatment and control conditions; only one study reported impairment, and this was specific to a measure of long-term memory storage [24]. There has been speculation that CBD may attenuate THC effects [25, 26], which could explain the lack of cognitive impairment observed in the studies included in the review, but recent evidence suggests that this is unlikely and that coadministration of CBD may even increase blood THC concentrations [17, 27–29]. A wide range of cognitive tests were administered across the included studies, as was the case in the previous review [11] and in the study reported here, suggesting the lack of effects of medical cannabis on cognitive function is not specific to particular cognitive domains.

With increasing medical cannabis use in Australia and other international jurisdictions, there is considerable interest in the development of novel methods that might allow patients to assess their cognitive function in relation to their own baseline before performing safety-sensitive tasks such as driving [30]. The Druid app holds promise as it can be completed using a smartphone or tablet and takes only minutes to complete. Recent studies have indicated that it is indeed sensitive to cannabis intoxication in healthy volunteers [15, 16], but representative patient data are lacking. The changes in performance from baseline to +3 h (0.87 points) and +5.5 h (0.67) reported here are markedly smaller than the peak changes previously seen in healthy volunteers, with THC doses ranging from 5 mg (vaporized; +1.8 points) to 20 mg (vaporized; +9.0 points) to 25 mg (oral; +10.1 points) [15]. The fact that participants exhibited no impairment on either the Druid or the CANTAB tasks suggests concordance between these two test batteries. The Druid app may therefore be a useful tool for impairment screening, although further validation work is clearly needed. One notable caveat with the Druid app that has relevance for real-world use is the inclusion of a balance component that patients in the current study often found difficult due to age or condition-related balance issues, or due to exacerbation of pain.

While we found no evidence for cognitive impairment in this study, we did observe a change in subjective drug effects over time, with participants rating themselves as significantly more 'stoned' and 'sedated' and significantly less

'anxious' following medical cannabis self-administration. While significant, the overall magnitude of change in perceived intoxication (i.e., 'stoned') was considerably lower than the peak change seen in healthy volunteers administered 13.75 mg THC via vaporization [17], and closer to the peak change associated with a 13.75 mg dose of CBD (also vaporized), which is considered to be non-intoxicating [17]. There were however some differences in subjective drug effects depending on the product type. Inhalation of flower via vaporization was associated with feeling more stoned and sedated, likely due to the higher mean dose of THC in vaporized products relative to oils (37.00 mg vs. 9.61 mg) and a more rapid onset of effects relative to rapid absorption of THC through the lungs into the blood stream [31]. Interestingly, medical cannabis oils were not associated with a significant increase in sedation relative to baseline at any timepoint. By way of comparison, a 10 mg oral dose of THC (comparable with the mean THC dose of 9.61 mg here) elicited a significant 'drug effect' rating in healthy volunteers who had not used cannabis within the previous 3 months [13].

The absence of any ostensible cognitive impairment, despite reports of mild intoxication for up to 4 h, and particularly with vaporized products, might reflect acute symptom alleviation leading to an improvement in physical and/or psychological function, or potentially tolerance to the impairing effects of cannabis [3, 32]. Tolerance, which arises with repeated and long-term cannabis use, has been demonstrated in previous laboratory studies with non-medical cannabis [33–35] and has been comprehensively documented in recent reviews [36, 37]. In a neuroimaging study by Mason et al. [38], occasional cannabis users administered 300 μg/kg THC exhibited significant alterations in reward circuitry, including reduced functional connectivity and increased striatal glutamate, as well as impaired performance on a sustained attention task. Chronic cannabis users administered the same dose of THC did not exhibit these same neurometabolic alterations or performance decrements, despite reporting a significant increase in intoxication relative to placebo.

Considering this emerging evidence for pharmacodynamic tolerance to the effects of cannabis, stable dosing with THC (and gradual dose titration up until, and not beyond, the point that effective symptom relief is achieved) is likely critical for any potential mitigation of impairment. So long as medical cannabis is prescribed within a controlled, medical framework, this is something that can be effectively managed by the prescribing physician. Performing safety-sensitive tasks, such as driving, is therefore not advised until patients are taking a stable dose of THC, and should also be temporarily avoided following any increase in THC dose [39, 40]. Future studies might consider tracking cognitive performance over a longer period in patients commencing medical cannabis treatment, focusing on specific health

indications or other cannabinoid preparations, or recruiting patients from different age groups.

While this study benefits from a semi-naturalistic design that allowed us to quantify acute changes in the cognitive function of patients prescribed medical cannabis using a comprehensive neuropsychological test battery, the lack of a placebo control means we were unable to disentangle baseline performance from possible residual impairment resulting from medical cannabis use the evening prior. The use of a semi-naturalistic design gives this study high ecological validity and also introduced considerable variability in the type of medical cannabis products used, THC/CBD dose, route of administration, and health indication. We aimed to capture potential impairment resulting from either inhaled or oral medical cannabis by having an assessment at 3 h, but we recognize that impairment could have already subsided by this point in patients who were using flower. This means we cannot rule out the possibility of cognitive impairment 1–2 h after inhaling medical cannabis. It is also possible that participants improved on the CANTAB over time due to a practice effect, which may have masked potential performance decrements. Future studies might consider assessing cognitive function at different timepoints based on the type of product that patients are using and its expected peak effects, as well as assessment of baseline cognitive performance prior to initiation of medical cannabis treatment.

Accompanying blood and oral fluid THC data will be reported separately along with driving performance outcomes. The decision to present these data separately was based on the number of outcomes already being reported here, and the greater relevance of blood/oral fluid THC levels for driving laws. We also note that participants were not required to undergo urine or oral fluid screening for recent drug use prior to study initiation. This was because we expected some patients to be using prescribed medications (e.g., opioids and benzodiazepines) that can be detected in standard urine and oral fluid drug screens. Finally, we note that patients' use of medical cannabis in this study may not perfectly reflect their real-world use. For instance, patients may typically only use medical cannabis in the evening before sleeping. As patients had been using medical cannabis for more than 10 months on average, these findings cannot be generalized to patients who are just commencing treatment with medical cannabis or changing dose/product type. Given our small sample size and open-label naturalistic design, larger and controlled trials are needed to confirm these findings.

5 Conclusion

This study provides preliminary evidence to suggest that medical cannabis may have minimal acute impact on cognitive function when prescribed and used as directed, although

larger and controlled trials are needed to confirm this. It is important to note that these findings cannot be generalized to other forms of cannabis use (including medical cannabis products that are unprescribed, and non-medical cannabis) where there may be a lack of medical oversight, contraindications for treatment, or variability in THC dosage and product quality.

Declarations

Funding Open Access funding enabled and organized by CAUL and its Member Institutions. This research was partially funded by grants to ACH and LAD from the Rebecca Cooper Foundation and Australia's National Health and Medical Research Council, as well as a Research Training Program Stipend from Swinburne University to BM.

Conflicts of Interest Thomas R. Arkell reports receiving speaker fees from Althea, NUBU Pharmaceuticals, and the International College of Cannabinoid Medicine, as well as grants from the Barbara Dicker Foundation outside the submitted work. Brooke Manning reports no conflicts of interest. Luke A. Downey reports receiving grants from the National Health and Medical Research Council, grants from Cannvalate, and grants from the Barbara Dicker Foundation outside the submitted work. Amie C. Haley reports receiving grants from Cannvalate, the Rebecca L. Cooper Foundation for the Al and Val Rosenstrauss Fellowship (F2021894), the Barbara Dicker Foundation, and the Road Safety Innovation Fund outside the submitted work.

Availability of Data And Material Requests for access to study data can be submitted to the corresponding author.

Ethics Approval All procedures were approved by the Swinburne University Human Research Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Consent to Participate All participants provided written, informed consent prior to participating.

Consent for Publication Not applicable.

Data Availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Author Contributions Conceptualization: TRA, LAD, ACH. Data acquisition: TRA, ACH. Statistical analysis: TRA, BM. Drafting of the manuscript: TRA. Reviewing and editing: BM, LAD, ACH. All authors reviewed the manuscript, revised it critically for important intellectual content, have read and approved the final submitted manuscript, and agree to be accountable for this work.

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