European Neuropsychopharmacology 82 (2024) 35–43

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

A randomised, placebo-controlled, double blind, crossover trial on the effect of a 20:1 cannabidiol: Δ9-tetrahydrocannabinol medical cannabis product on neurocognition, attention, and mood

Brooke Manning [a], Amie C. Hayley [a,b,c,*], Sarah Catchlove [a], Con Stough [a], Luke A. Downey [a,c]

[a] Centre for Human Psychopharmacology, Swinburne University of Technology, Hawthorn, Australia
[b] International Council for Alcohol, Drugs, and Traffic Safety (ICADTS), Rotterdam, the Netherland
[c] Institute for Breathing and Sleep (IBAS), Austin Health, Melbourne Australia

ARTICLE INFO

Keywords:
Δ9-tetrahydrocannabinol
Cannabidiol
CANTAB
Visuospatial memory
Attention

ABSTRACT

As cannabinoid-based medications gain popularity in the treatment of refractory medical conditions, it is crucial to examine the neurocognitive effects of commonly prescribed products to ensure associated safety profiles. The present study aims to investigate the acute effects of a standard 1 mL sublingual dose of CannEpil®, a medicinal cannabis oil containing 100 mg cannabidiol (CBD) and 5 mg Δ9-tetrahydrocannabinol (THC) on neurocognition, attention, and mood. A randomised, double-blind, placebo-controlled, within-subjects design assessed 31 healthy participants (16 female, 15 male), aged between 21 and 58 years, over a two-week experimental protocol. Neurocognitive performance outcomes were assessed using the Cambridge Neuropsychological Test Automated Battery, with the Profile of Mood States questionnaire, and the Bond-Lader Visual Analogue Scale used to assess subjective state and mood. CannEpil increased Total Errors in Spatial Span and Correct Latency (median) in Pattern Recognition Memory, while also increasing Efficiency Score (lower score indicates greater efficiency) relative to placebo (all $p < .05$). Subjective Contentedness ($p < .01$) and Amicability ($p < .05$) were also increased at around 2.5 h post dosing, relative to placebo. Drowsiness or sedative effect was reported by 23 % of participants between three to six hours post CannEpil administration. Plasma concentrations of CBD, THC, and their metabolites were not significantly correlated with any observed alterations in neurocognition, subjective state, or adverse event occurrence. An acute dose of CannEpil impairs select aspects of visuospatial working memory and delayed pattern recognition, while largely preserving mood states among healthy individuals. Intermittent reports of drowsiness and sedation underscore the inter-individual variability of medicinal cannabis effects on subjective state. (ANZCTR; ACTRN12619000932167; https://www.anzctr.org.au)

1. Introduction

The increasing global application of medical cannabis products for therapeutic purposes has brought cannabinoids like cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) to the forefront in managing chronic pain, neurological disorders, and psychiatric diseases (Allan et al., 2018; Banerjee et al., 2021). Though numerous studies associate acute cannabis use, especially THC exposure, with cognitive disruptions in information processing (Kelleher et al., 2004; Solowij et al., 2002), working memory (Lamers et al., 2006; Solowij and Battisti, 2008), and attention (Hunault et al., 2009), these findings are primarily linked to recreational usage patterns. Recent research, however, presents a nuanced understanding of these effects, especially regarding the interaction between THC and CBD. Consistently, recent studies indicate that THC significantly impairs cognitive functions such as memory, executive function, and psychomotor abilities, particularly in tasks requiring attention, verbal learning, and memory (Englund et al., 2023; Bossong et al., 2013; Spindle et al., 2018). In contrast, the role of CBD in mitigating THC's effects remains ambiguous. While some suggest CBD may lessen THC's anxiety or psychosis-like effects (Freeman et al., 2019), studies like Englund et al. (2023) report no significant modulation. Thus, the interaction between THC and CBD and their collective impact on cognition is complex and not fully understood.

The neuropsychological effects of recreational cannabis use on cognitive functioning have been extensively studied, with both acute and ongoing cannabis consumption contributing to deficits in working

* Corresponding author: Centre for Human Psychopharmacology, Swinburne University of Technology, Hawthorn, VIC, 3122, Australia.
E-mail address: ahayley@swin.edu.au (A.C. Hayley).

https://doi.org/10.1016/j.euroneuro.2024.02.002
Received 8 October 2023; Received in revised form 30 January 2024; Accepted 2 February 2024
Available online 14 March 2024

memory capabilities and measures of attention (Desrosiers et al., 2015; Solowij, 1998; Solowij and Pesa, 2010). THC's dose-dependent effect on response time in tasks assessing visuospatial selective attention, divided attention, and sustained attention (Hunault et al., 2009) is noteworthy, as these are crucial in the effective functioning of perceptual processes (Sanders and Astheimer, 2008; Walker and Trick, 2018). Reduced processing speed and vigilance following cannabis use may be partly attributed to the sedative effects associated with THC and higher CBD doses (Babson et al., 2017), suggesting drowsiness as a factor in cannabis-related cognitive deficits (Hunault et al., 2009). The impact of cannabis administration methods further adds complexity to this landscape. Spindle et al. (2018) demonstrated that vaporised cannabis produces stronger effects and higher peak THC concentrations than oral consumption, emphasising the influence of consumption mode on cognitive effects. Additionally, studies such as Eadie et al. (2021) and Olla et al. (2019) indicate less severe cognitive impairments in medical cannabis users, highlighting the differences between recreational and medical usage. Importantly, the persistence and recovery of cognitive functions, particularly in verbal memory and attention, may extend beyond acute intoxication in long-term users (Broyd et al., 2016).

Cannabis also induces notable changes in subjective alertness and mood (Bıçaksız and Özkan, 2016; Crippa et al., 2003). Its generalised depressant effect on the central nervous system, promoting drowsiness following an initial period of excitement after an acute dose (Paton and Pertwee, 1973), can negatively impact cognitive functioning. This is partly due to disruptions in prefrontal cortex processes essential for decision-making (Goldstein and Volkow, 2011) and alterations in the endocannabinoid system, which regulates memory, attention, and mood (Szkudlarek et al., 2018). Mood changes can influence an individual's ability to attend to and process information, and may consequently increase distractibility, impair attentional control, and heighten the likelihood of cognitive task errors (Dolcos et al., 2020; Pessoa, 2009).

Given these complexities, exploring the acute neurocognitive and subjective effects at therapeutic dosages and formulations used in medicinal cannabis products is imperative (Blessing et al., 2015; Wieghorst et al., 2022). Additional research is crucial, given the diverse relationship between neurocognition and cannabis-related impairment, which varies according to usage patterns, dose, administration route, and prior cannabis experience (Ramaekers et al., 2008, 2009). This exploration is vital for informing the safe and effective use of medical cannabis products across various therapeutic indications. The present study aims to examine the effect of a standard 1 mL sublingual dose of CannEpil® (a 20:1 CBD to THC medicinal cannabis oil) on functional neurocognition, alertness, and mood, with an additional focus on investigating any correlations between observed changes and plasma concentrations of key cannabinoids (CBD, THC, 11-OH-THC, or THC—COOH).

2. Experimental procedures

2.1. Participants

This randomised, within-subjects, double-blind, placebo-controlled, crossover trial comprised a final sample of 31 healthy adults (16 males, 15 females) who were aged between 21 and 58 years old (M = 38.13, SD ± 10.78) and weighed between 50 and 98 kg (M = 73.10, SD ± 12.42). Participants were recruited via convenience sampling methods utilising print advertisements and an email campaign sent out to prior participants who had indicated their interest in future studies. A CONSORT diagram displaying recruitment flow is presented in Fig. 1.

All participants were fluent in written and spoken English, had a full and unregulated driver's license, and reported being a regular driver (> 4000 km/year). One-week prior to study commencement, participants underwent a screening visit to complete the Beck Depression Inventory II and Beck Anxiety Inventory (Beck et al., 1961, 1988) for mental health assessment and to discuss their medical and drug history with a nurse. Participants were excluded if they scored within the clinically significant range during mental health screening, had a history of substance misuse or dependence, currently used prescription medication, had a significant medical condition, were currently pregnancy or breastfeeding, or had participated in another investigational study within the last month. All participants had previous experience with cannabinoid products, reporting at least one instance of usage without adverse effects in their lifetime. Eligibility criteria did not specify minimum or maximum cannabis exposure limits but required a two-week abstinence period before study commencement. Participants were required to abstain from illicit drug use for two-weeks prior to study commencement and throughout its duration, with compliance verified using a DrugWipe 6S test, prior to the initiation of testing procedures on each study day.

The study protocol was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12619000932167). This project was approved by Swinburne University of Technology Human Research Ethics committee (2019/20220392–9708) and was

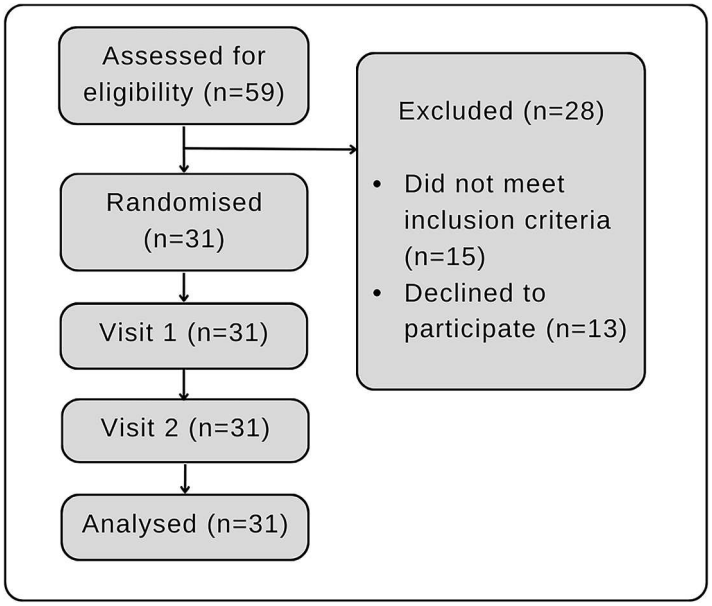

Fig. 1. CONSORT diagram depicting participant recruitment flow.

conducted in accordance with Good Clinical Practice guidelines and the ethical standards of the Declaration of Helsinki.

2.2. Procedure

An overview of the study schedule, conducted across two counterbalanced testing sessions, is presented in Fig. 2. Prior to testing sessions, participants self-reported abstinence from alcohol for 24 h, caffeine for 12 h and had a light breakfast that was replicated across both sessions. In the case that a participant self-reported consuming either alcohol or caffeine within these time periods, their testing visit was rescheduled. Immediately after arriving on testing days, participants were screened for the presence of THC, benzodiazepines, cocaine, amphetamines, and opiates using a Securetec 6S DrugWipe to ensure drug abstinence. Female participants also provided a urine sample to test for pregnancy. Upon departure from testing sessions, participants received reimbursement for their time, a transportation voucher, and were escorted to their mode of transport (taxi/Uber). Participants were also provided with an information sheet to advise of the possibility for the study drug to remain detectable in their system for up to 48-hours and of restrictions from operating a vehicle or heavy machinery.

2.2.1. Investigational product

The investigational product CannEpil and matched placebo were provided by MCG Pharmaceuticals and were packaged individually with identical labelling, appearance, and taste. CannEpil and placebo treatments were centrally randomised and counterbalanced by the study sponsor (Cannvalate) with un-blinding information secured by a neutral third party (Clinical Trials Coordinator). CannEpil is a phytocannabinoid-based product containing a ratio of 20:1 CBD to THC delivered in an oil carrier which has been indicated for the treatment of epilepsy and as a sleep aid for conditions such as insomnia. The product contains no other cannabinoids other than CBD and THC. In this study, a given dose of 1 ml of palatable bearer oil containing either CannEpil (100 mg of CBD and 5 mg of THC) or placebo, was administered sublingually via an oral syringe. Peak effect was expected at approximately 120 min, with acute effects evident from 60 min following ingestion and possibly lasting for 4–6 h (Badowski, 2017). Two experimental sessions were scheduled with a minimum one-week interval washout period between them to mitigate potential carryover effects, with a 100 mg CBD dosage calculated to persist in plasma for an average duration of approximately five days (McCartney et al., 2022).

2.3. Measures

2.3.1. Cambridge neuropsychological test automated battery (CANTAB)

The CANTAB is a cloud-based program that combines a series of tests to assess cognition and cognitive performance, which are sensitive to drug effects and cognitive impairments and have been extensively validated (Robbins, 1994; Smith et al., 2013). Each test included in the CANTAB is standardised with automated voice over instructions. To mitigate potential practice effects and minimise learning curves, each task is preceded by a self-guided practice session that continues until the participant reaches proficiency. Domains of interest, each represented by a computerized cognitive task, were selected based on their relevance to key cognitive domains essential to driving performance. Tasks are systematically completed in sequence across six domains of interest: Multitasking (MTT), Spatial Working Memory (SWM), Rapid Visual Information Processing (RVP), Reaction Time (RTI), Pattern Recognition Memory (PRM), and Spatial Span (SSP). Completion of all tasks requires approximately 35- to 50-minutes, with the same task version used for all sessions. Full task descriptions and previous validations are provided at [https://www.cambridgecognition.com/cantab/cognitive-tests/].

2.3.2. Profile of mood states (POMS)

Mood state was assessed using the POMS (McNair et al., 1981) following the CANTAB at 85-minutes post dosing. The POMS is a self-report questionnaire consisting of 65 adjectives describing feeling and mood which are answered on a five-point Likert-type scale ranging from 0 = "not at all" to 4 = "extremely", and is designed to measure six dimensions of mood, including tension, depression, anger, vigour, fatigue, and confusion. Two out of 65 items were reverse scored, including 'relaxed' within the tension dimension and 'efficient' within the confusion dimension. Likert scores for items within each dimension were summed to create a dimension score, with higher scores indicative of greater affect in the respective dimension (i.e., a higher score in vigour is indicative of greater vigour). A Total Mood Disturbance (TMD) score was then calculated from adding the dimension scores from tension, depression, anger, fatigue, and confusion and then subtracting the vigour dimension score, resulting in a value between −40 and 224. TMD may be interpreted as a global index of distress with lower scores indicative of a more stable mood profile (Searight and Montone, 2020).

2.3.3. Bond–Lader visual analogue scale (BL-VAS)

Subjective alertness and self-evaluation of mood was assessed using the BL-VAS (Bond and Lader, 1974) prior to (80-minutes post dosing) and following the CANTAB (135-minutes post dosing). Outcome measures were examined on a question-by-question basis with subjective symptoms comprising 16 dimensions of mood separated across three affective dimensions of alertness, calmness, and contentedness. Items within the alertness dimension included alert-drowsy, attentive-dreamy, lethargic-energetic, muzzy-clearheaded, coordinated-clumsy, mentally slow-quick witted, strong-feeble, interested-bored, and incompetent-proficient. Items within the contentedness dimension included contented-discontented, troubled-tranquil, happy-sad, antagonistic-amicable, and withdrawn-gregarious. Items within the calmness

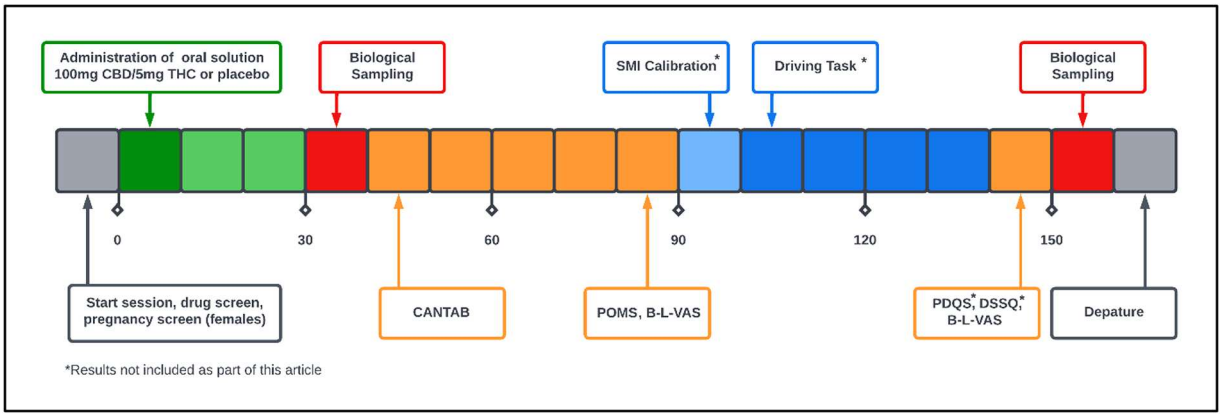

Fig. 2. Overview of study procedures on each testing day.

dimension included calm-excited and tense-relaxed. Several items were reverse scored across all dimensions, including alert-drowsy, attentive-dreamy, coordinated-clumsy, strong-feeble, interested-bored, calm--excited, contented-discontented, and happy-sad. Participants moved an on-screen slider to the desired position on a scale (0–100) when asked to describe to what extent the given state is appropriate to them at that moment in time. Item scores from each dimension of the BL VAS were averaged to create a factor score for alertness, calmness, and contentedness. Factor scores ranged between 0 and 100, with higher scores indicating increased alertness, contentedness, or calmness and lower scores indicating increased drowsiness, discontentedness, or tension respectively.

2.3.4. Adverse event reporting

Participants were instructed to report any adverse events (AE) either in person, via email, or through a phone call. Additionally, participants were queried about the occurrence of any adverse events, their severity, and duration, prior to the start of their second visit, as well as during a follow-up phone call or email following the study's completion. AE severity was categorised as follows: "mild" if easily tolerated with minimal discomfort and no interference with daily activities; "moderate" if causing enough discomfort to interfere with daily activities; and "severe" if incapacitating or prohibiting daily activities. The relationship between the AE and the study treatment or procedures was evaluated in follow-up interviews, considering both the investigator's and the participant's perspectives on whether the AE was directly related to the study protocol or the investigational product.

2.3.5. Plasma sampling

Plasma samples were collected twice during each testing session, both prior to (30-minutes post dosing) and following the CANTAB (~2.5 h post dosing). A registered research nurse collected approximately 15 mL of blood into an EDTA vacutainer via a single venous blood draw. Venous whole blood samples were centrifuged at 3000 rpm for 10-minutes, prior to the surfaced plasma being transferred into separate specimen vials. Collected plasma samples were stored at −80° until a courier transported them to the Victorian Institute of Forensic Medicine (VIFM) for biochemical analysis of CBD, THC, 11-OH-THC, and THC—COOH concentrations. Plasma concentration values are detailed in a separate manuscript (Manning et al., 2023).

2.4. Statistical analyses

To assess differences in CANTAB outcomes and POMS scores between CannEpil and placebo conditions, paired-samples *t*-tests were performed. Linear fixed-effects models with Restricted Maximum Likelihood Estimation evaluated BL-VAS item and factor scores, incorporating Condition and Time as repeated factors and fixed effects. Separate models were constructed for each outcome and interaction, with the likelihood ratio statistic confirming Compound Symmetry as the optimal covariance structure. Post-hoc paired *t*-tests with planned Bonferroni adjustments for multiple comparisons, controlled for Type I error and further examined Condition and Time variations. Linear regressions assessed correlations between plasma concentrations of CBD, THC, 11-OH-THC, or THC—COOH at each individual time point and observed alterations in cognitive and affective outcomes. Binomial logistic regressions assessed the relationship between CBD or THC concentrations and AE reports of drowsiness. While plasma regression results are reported within the current paper, plasma data are reported separately along with oral fluid and driving performance outcomes (Manning et al., 2023). This decision was influenced by the number of outcomes included in this report and the particular importance of plasma/oral fluid THC levels in relation to driving regulations.

Covariates including sex, cannabis use history, and driving experience were examined prior to the planned analysis. However, these covariates did not provide additional explanatory value to the results and were therefore omitted from the final model. Prior to analyses, data was evaluated for completeness and analysis of standard residuals was performed to identify potential outliers. Outliers were identified for CANTAB outcomes including MTT Total Incorrect, RVP Target sequence detection score, SSP Forward total errors, PRM Correct Latency Immediate (median), and PRM Efficiency score immediate and delayed. Sensitivity analyses were conducted with and without these outliers included in the dataset, with results not altered enough for different conclusions to be drawn (i.e., no change in significance). All identified outliers were considered to be genuinely unusual (i.e., not due to error) and thus were retained for analyses (Aguinis et al., 2013). All randomised participants fully completed the trial resulting in zero attrition. Statistical analyses were performed using SPSS (version 26), with all analytical procedures being two-tailed, and statistical significance defined as $p < .05$.

3. Results

3.1. Participant characteristics

Participant demographics and characteristics for the total sample ($N = 31$) are presented in Table 1.

3.2. CANTAB

Descriptive statistics and paired samples *t*-test results for CANTAB outcomes are presented in Table 2. Differences in CANTAB outcomes between CannEpil and placebo across time are displayed in Fig. 3.

Paired-samples *t*-tests revealed that SSP forward total errors significantly increased ($t_{(30)} = 2.514$, $p < .05$) following CannEpil administration relative to placebo. Paired samples *t*-tests additionally revealed significant differences among several outcomes in the PRM domain during delayed tasks, including increased Correct median latency ($t_{(30)} = 2.309$, $p < .05$) and increased Efficiency score (lower score = more efficient; $t_{(30)} = 2.589$, $p < .05$) in the CannEpil condition relative to placebo. Linear regressions established that plasma concentrations of CBD, THC, and metabolites did not significantly correlate with any observed alterations in CANTAB outcomes, nor were any other significant differences noted for CANTAB outcomes between CannEpil and placebo (all > 0.05).

3.3. POMS

Descriptive statistics of POMS dimension and TMD scores between CannEpil and placebo are presented in Table 2. There were no significant differences between CannEpil and placebo in any of the sub-scales (all $p > .05$).

Table 1
Participant demographics and cannabis use history ($N = 31$).

Sex (male/female)	15/16
Age (years)	38.13 (10.78)
Weight (kg)	73.16 (12.21)
Body mass index (kg/m^2)	26.10 (4.19)
Ethnicity (%)	Caucasian (65), Asian (26), Unspecified (9)
English as first language (%)	84
Tertiary educated (%)	90.3
≤ Weekly cannabis use in prior 12 months (%)	9.7
≤ Fortnightly cannabis use in prior 12 months (%)	22.6
≤ Monthly cannabis use in prior 12 months (%)	16.1
No cannabis use in prior 12 months (%)	51.6

Note: Data are shown as means (SD), frequency, or percentage of total sample.

Table 2
Descriptive statistics and results for CANTAB (N = 31) and POMS (N = 30) outcomes between CannEpil and placebo.

Measure	Outcome	CannEpil	Placebo	*t*-value	*p*-value
CANTAB MTT	Incongruency cost	69.92 (42.52)	68.60 (53.88)	.158	ns
	Reaction latency (med)	562.63 (104.75)	569.74 (104.23)	−0.584	ns
	Multitasking cost (med)	177.58 (92.63)	165.61 (102.15)	.566	ns
	Total incorrect	4.03 (4.96)	4.87 (6.44)	−0.870	ns
CANTAB SWM	Between errors	6.52 (8.85)	6.71 (8.56)	−0.121	ns
	Strategy score	5.65 (3.22)	5.65 (3.39)	.000	ns
CANTAB RVP	Target sequence detection score	.932 (0.041)	.925 (0.055)	.859	ns
	Response latency (med)	419.24 (56.74)	436.29 (79.58)	−1.791	ns
CANTAB RTI	Five-choice movement time (med)	234.37 (52.86)	236.37 (62.26)	−0.290	ns
	Five-choice reaction time (med)	365.31 (34.19)	360.26 (35.64)	1.357	ns
CANTAB SSP	Forward span length	6.94 (1.21)	6.77 (1.20)	.634	ns
	Forward total errors	**16.52 (6.16)**	**13.06 (4.98)**	**2.514**	**.018**
CANTAB PRM	Correct latency immediate (med)	1565.08 (507.03)	1504.87 (414.30)	.724	ns
	Correct latency immediate (SD)	657.10 (452.67)	534.63 (390.66)	1.224	ns
	Efficiency score immediate	19.68 (7.77)	17.94 (6.21)	1.649	ns
	Correct latency delayed (med)	**1676.66 (433.90)**	**1537.16 (312.62)**	**2.309**	**.028**
	Correct latency delayed (SD)	**607.72 (235.34)**	**522.59 (240.88)**	**2.218**	**.034**
	Efficiency score delayed	**22.23 (7.71)**	**19.96 (6.36)**	**2.589**	**.015**
POMS	Tension	2.03 (5.28)	1.57 (4.20)	.572	ns
	Depression	4.30 (5.24)	4.10 (6.49)	.255	ns
	Anger	4.47 (4.95)	4.67 (6.80)	−0.198	ns
	Vigour	18.33 (4.64)	17.43 (5.37)	−1.074	ns
	Fatigue	5.70 (5.60)	6.57 (5.18)	−1.254	ns
	Confusion	1.27 (2.80)	1.63 (3.58)	−0.537	ns
	TMD	−0.57 (20.41)	1.10 (23.78)	−0.470	ns

Note: Values shown are mean (standard deviation). Bolded values indicate significant differences based on paired *t*-test for group comparisons.
MTT = Multitasking Test, SWM = Spatial Working Memory, RVP = Rapid Visual Information Processing, RTI = Reaction Time, SSP = Spatial Span, PRM = Pattern Recognition Memory, POMS = Profile of Mood States, TMD = Total Mood Disturbance, med = median, SD = standard deviation, ns = not significant.

3.4. BL-VAS

Descriptive statistics for individual BL-VAS items and factor scores between treatment conditions and across time are presented in Table 3. Significant differences in BL-VAS item and factor scores between CannEpil and placebo across time are displayed in Fig. 4.

Within the alertness factor, the item Coordinated-clumsy was observed to have a significant main effect of both Condition ($F_{(1,89)}$ = 5.22, $p < .05$) and Time ($F_{(1,89)} = 4.31$, $p < .05$), but not its Interaction. Post-hoc comparisons revealed those in the CannEpil condition reported increased 'Clumsiness' relative to placebo; however, this was only observed at time point one ($F_{(1,89)} = 4.44$, $p < .05$). No other significant Condition, Time, or Interaction effects were noted for BL-VAS alertness items or the overall factor score.

Within the contentedness factor, a significant Condition by Time interaction was noted for the item Antagonistic-amicable ($F_{(1,89)} = 4.01$, $p < .05$). Subsequent post-hoc analysis indicated a significant increase in 'Amicableness' in the CannEpil condition compared to placebo at time point two ($F_{(1,89)} = 4.265$, $p < .05$). Additionally, 'Amicableness' significantly increased over time in the CannEpil condition ($F_{(1,89)}$ = 4.39, $p < .05$). A trend towards a main effect of Condition was noted for the BL-VAS item Contented-discontented ($F_{(1,89)} = 3.37$, $p = .070$), with planned post-hoc analysis showing a significant decrease in 'Discontentedness' in the CannEpil condition compared to placebo at time point two ($F_{(1,89)} = 4.97$, $p < .05$). Furthermore, a significant Condition by Time interaction was observed for the BL-VAS factor score Contentedness ($F_{(1,90)} = 5.07$, $p < .05$). Post-hoc analysis revealed a significant increase in reported Contentedness in the CannEpil condition compared to placebo at time point two ($F_{(1,90)} = 7.07$, $p < .01$), and a significant decrease in Contentedness over time in the placebo condition ($F_{(1,90)}$ = 3.99, $p < .05$). Linear regressions confirmed no significant correlation between plasma concentrations of CBD, THC, and metabolites with any observed alterations in Contentedness.

In the case of BL-VAS calmness items and overall factor score, the main effects of Condition, Time, and its Interaction were non-significant.

3.5. Adverse events

While a significant alteration in alertness was not captured in the self-reported subjective BL VAS results at the time of testing, several participants contacted a researcher after they had left the testing session noting increased drowsiness or sedation, which were reported as adverse events (AEs). Specifically, of the 31 participants, seven (approximately 22.6 %) reported AEs. The distribution of these AEs in terms of severity was varied: one event was mild (14.3 % of AEs), three were moderate (42.9 %), and three were severe (42.9 %). Notably, all of these AEs (100 %) were reported following the CannEpil condition, with no incidents documented after the placebo. All AEs were resolved without any participants seeking to withdraw from the study due to the experience of drowsiness or a sedative effect. Moreover, all reported AEs were confirmed to occur directly after active treatment sessions. Binomial logistic regressions established that plasma concentrations of CBD and THC were not significantly correlated with the occurrences of reported subjective sedation as an AE.

4. Discussion

This randomised, within-subjects, double-blind, placebo-controlled, crossover trial examined the effects of acute, sublingual administration of a 20:1 CBD:THC medication (CannEpil®) on healthy adults. CannEpil was observed to impair selective aspects of visuospatial working memory and pattern recognition. However, subjective affect and mood state remained largely unchanged, except for noted increases in contentedness and sedation. Intriguingly, plasma levels of CBD, THC, 11-OH-THC, or THC—COOH did not correlate with observed neurocognitive or subjective changes, suggesting a complex interaction that is not directly related to systemic concentrations of these compounds.

More specifically, CannEpil consumption was linked to a heightened frequency of errors in the spatial span task, indicative of a reduced capacity to memorise and retrieve spatial information. These findings align with existing research that outlines the negative impact of cannabis on visual working memory tasks. Specifically, Selamoglu et al. (2021) observed that cannabis-dependent individuals made more errors compared to controls, while Harvey et al. (2007) documented deficits in the ability of chronic cannabis users to integrate complex information. The underlying mechanism for these cognitive and working memory

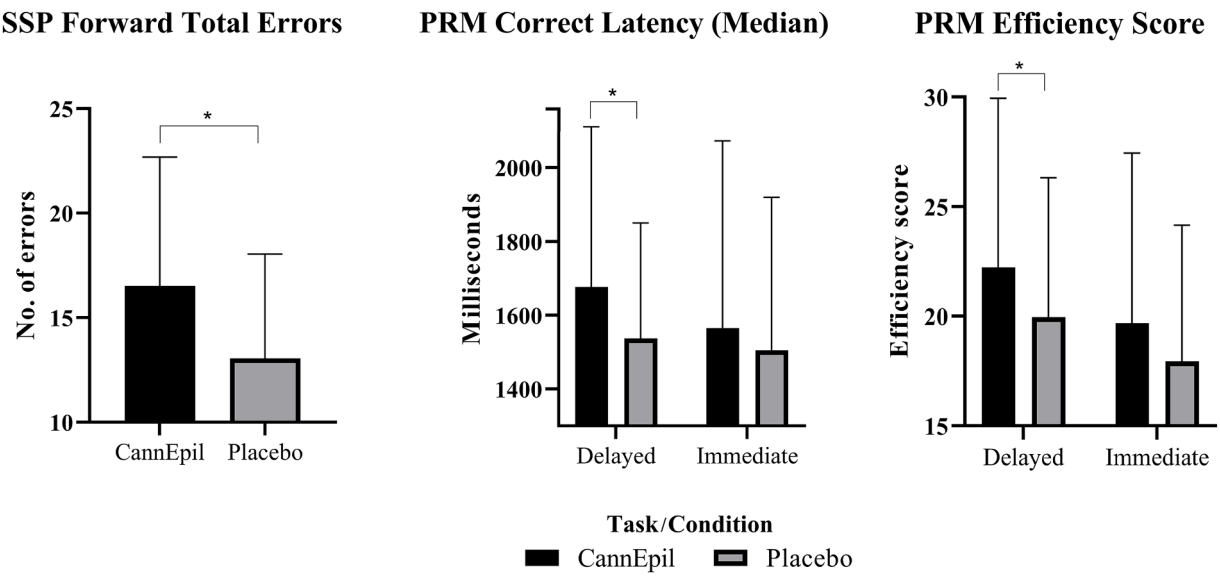

Fig. 3. CANTAB outcomes of SSP Forward Total Errors, PRM Correct Median Latency and Efficiency Score differences between CannEpil and placebo.

Table 3
Descriptive statistics for BL-VAS outcomes between CannEpil and placebo and across time.

Measure	Outcome	CannEpil T1 ($N = 31$)	Placebo T1 ($N = 31$)	CannEpil T2 ($N = 31$)	Placebo T2 ($N = 30$)
BL-VAS Alertness	Alert-drowsy [a]	40.13 (26.53)	37.39 (24.38)	47.58 (29.50)	40.50 (27.28)
	Attentive-dreamy [a]	37.16 (26.05)	34.84 (24.56)	42.65 (27.79)	34.90 (22.59)
	Coordinated-clumsy [a]	**25.58 (21.45)***,2	**17.77 (17.35)***,2	29.26 (25.88)	24.83 (20.26)
	Incompetent-proficient	75.87 (18.62)	76.23 (16.77)	70.45 (22.27)	73.87 (17.28)
	Interested-bored [a]	25.87 (22.44)	33.52 (28.61)	32.77 (24.94)	37.37 (31.16)
	Lethargic-energetic	52.23 (26.07)	57.74 (22.40)	45.84 (25.25)	51.70 (21.27)
	Mentally slow-quick witted	61.35 (21.79)	63.81 (25.09)	54.48 (24.54)	62.00 (21.58)
	Muzzy-clearheaded	63.35 (24.90)	65.81 (24.79)	57.74 (26.11)	61.80 (25.88)
	Strong-feeble [a]	26.35 (21.52)	25.39 (18.89)	27.68 (22.24)	27.37 (20.29)
	Alertness factor score	66.42 (19.16)	68.26 (17.94)	60.87 (20.96)	64.97 (18.20)
BL-VAS Calmness	Calm-excited [a]	21.48 (22.02)	20.00 (19.09)	21.81 (24.88)	21.07 (16.39)
	Tense-relaxed	73.87 (22.60)	74.81 (21.32)	78.35 (20.14)	70.97 (19.87)
	Calmness factor score	76.19 (18.70)	77.40 (16.92)	78.27 (20.37)	74.15 (16.00)
BL-VAS Contentedness	Antagonistic-amicable*,1	**76.84 (20.34)***,3	79.26 (14.67)	**83.52 (16.46)***,2,3	**76.77 (21.45)***,2
	Contented-discontented [a]	16.35 (15.09)	17.23 (15.75)	**12.87 (13.04)***	**18.17 (14.71)***
	Happy-sad [a]	19.61 (16.78)	17.29 (14.13)	15.06 (16.96)	17.13 (13.78)
	Troubled-tranquil	78.00 (19.76)	78.13 (17.83)	79.06 (20.63)	72.93 (21.35)
	Withdrawn-gregarious	66.52 (21.71)	68.52 (17.83)	64.29 (22.80)	63.10 (18.07)
	Contentedness factor score*,1	77.08 (15.51)	**78.28 (12.05)***,3	**79.79 (14.35)****,2	**73.72 (16.80)****,2,3

Note: Values shown are mean (standard deviation). BL-VAS = Bond-Lader Visual Analogue Scale.
[a] Items were reverse scored when calculating factor score.
[1] Condition*Time Interaction.
[2] Post-hoc Condition.
[3] Post-hoc Time.
* p-value < 0.05.
** p-value < 0.01.

impairments may involve the activation of cannabinoid type 1 (CB1) receptors (Smith et al., 2010). Such activation disrupts the normal functioning of hippocampal circuits, which are integral to cognitive functioning (Robledo-Menendez et al., 2021). Consequently, tasks that rely on these neural systems may require increased cognitive effort, leading to diminished performance as task demands escalate (Solowij et al., 2002).

Post-administration of CannEpil, there was an observed decline in overall efficiency and an increase in latency, specifically in the time required to provide correct responses in delayed visual recognition memory tasks. Noteworthily, this effect was not evident in tasks involving immediate visual recognition memory. This pattern suggests a potential impairment in the encoding, storage, and retrieval of visual information after a delay. Our observations are consistent with previous research (McHale and Hunt, 2008; Schoeler et al., 2015), which report deficits in delayed but not immediate recall of visual stimuli associated with cannabis use. Furthermore, these findings are congruent with Ramaekers et al. (2021) documentation of domain-specific impairments in short-term episodic and working memory following acute cannabis intoxication.

The findings from our study become particularly salient in light of Solmi et al. (2023), which highlights the diverse and sometimes paradoxical impacts of cannabinoids across various conditions and demographic groups. While our study observed acute visual memory deficits in healthy individuals, other research has not consistently replicated these effects in medical cannabis patient groups (Arkell et al., 2023; Schoeler et al., 2015). This discrepancy further emphasises that cannabinoid-based medicines possess significant therapeutic potential, yet their impacts are complex, potentially leading to distinct vulnerabilities in cognitive function, especially in individuals who are either

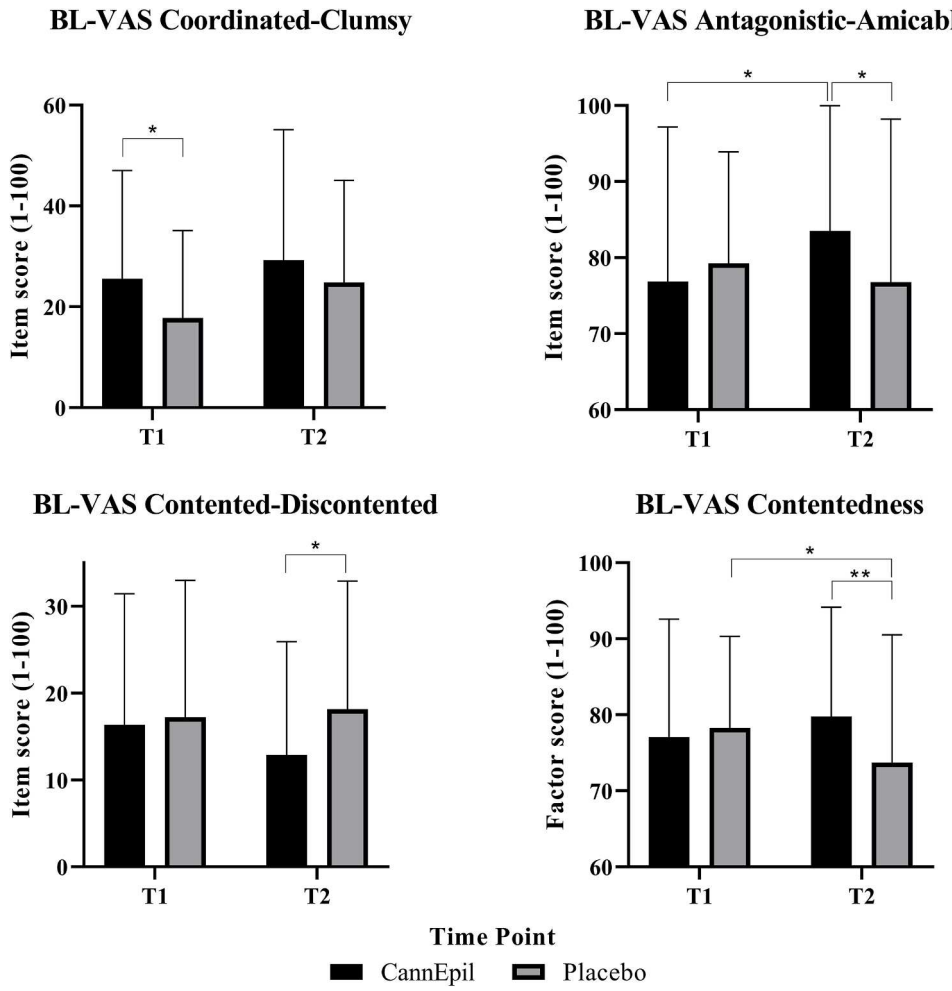

Fig. 4. Differences in BL-VAS items Coordinated-Clumsy, Antagonistic-Amicable, Contented-Discontented and factor score Contentedness between CannEpil and placebo across time.

cannabis naïve or newly prescribed.

Subjective affect and mood disturbance scores following CannEpil administration remained largely unchanged, though there were noted increases in self-reported contentedness and sedation. High CBD dosages in medicinal cannabis formulations have been shown to effectively treat anxiety and enhance mood in individuals with affective disorders (Narayan et al., 2022). However, among healthy individuals at therapeutic doses, alterations in subjective state or mood are less pronounced (Arndt and de Wit, 2017). This discrepancy suggests that mood alterations are more likely to be significant with ongoing cannabinoid treatments aimed at enhancing overall enduring affect, rather than in acute clinical dosing scenarios. The widely held belief that cannabis use leads to enhanced positive subjective affect (Zvolensky et al., 2007) may also influence users' expectations of emotional improvement post-cannabis consumption. Thus, the increased reports of subjective contentedness and amicability in this study could be attributed to an enhanced sensitivity and readiness to perceive such affective changes.

CannEpil administration did not significantly alter subjective attention; however, 23 % of the total sample reported (AE report) delayed onset of drowsiness, which typically occurred three to six hours after administration. Many cannabinoid formulations are now being indicated for use as a sleep aid, in part due to their ability to boost the production of melatonin and suppress wake-promoting functions (Lissoni et al., 1986); however, their efficacy and direct mode of action is yet to be clearly established (Narayan et al., 2024). Differences in sedative effect have become increasingly evident in individuals who are naïve users of cannabis, rather than those who use it habitually (Nicholson et al., 2004) and is more pronounced among healthy individuals (Narayan et al., 2022). In the present study, the delayed onset of drowsiness may additionally be attributed to the controlled laboratory environment and elevated cognitive and attentional demands of the tasks performed. It is possible that these factors resulted in a scenario where sedation became more pronounced once participants left the testing site, due to a rebound or compounding effect. Nonetheless, further attention is needed to investigate the potential sedative effects of medicinal cannabis products in various scenarios; particularly with some cannabis preparations being prescribed as sleep aids.

Our findings also compliment those of Arkell et al. (2020), who observed that THC/CBD equivalent cannabis did not significantly mitigate impairment in cognitive tasks. Considering insights from Englund et al. (2023), who found that increased CBD did not significantly modulate the acute adverse effects of THC, it is conceivable that the unique pharmacodynamics of the 20:1 CBD:THC ratio in CannEpil may lead to a more pronounced modulation of cognitive processes in healthy adults, while having a comparatively smaller effect on structures and processes responsible for emotional and subjective experiences. This nuanced pharmacodynamic profile positions CannEpil as a relatively safer option within the framework of 'cannabis risky use' (Balcells-Oliveró and Oliveras, 2023). The lack of significant mood disturbances observed in our study, coupled with limited cognitive impairment, suggest a lower risk profile associated with CannEpil, particularly compared to other cannabis products with higher THC content. While the sedative effects of CannEpil seem to be less immediately impairing compared to those observed in products with higher

THC dosages (Narayan et al., 2022), the delayed nature of these sedative effects warrants attention, nonetheless. Responsible medical supervision, paired with patient education about its sedative properties, is essential in reducing the likelihood of unintended consequences and ensuring its safe use.

The present study's findings should be considered in view of several methodological limitations. This study examined a sample of healthy volunteers who were predominantly non-frequent users of cannabis. This approach does not clearly represent patients using medical cannabis products on regular medication schedules for extended periods. Such populations might have developed tolerance to the impairing effects of CBD and THC, which our study does not address (Arkell et al., 2020; Celius et al., 2018; Hartman and Huestis, 2013). Our study was also constrained by a small sample size, preventing the inclusion of sex as a distinct analytical parameter without compromising robustness, although we sought to counter this by carefully balancing gender within our sample. Additionally, the absence of baseline neurocognitive and mood assessments prior to drug administration poses challenges for the interpretive validity of our findings. Without these initial measurements, it is challenging to accurately evaluate changes within subjects across different conditions and to discern how these variations contribute to the observed effects.

It is important to note that the controlled environment of the trial may not accurately mirror the real-world conditions of cannabis usage. External factors including environmental context and variances in individuals' expectations, likely significantly impact cannabis effects, underscoring the importance of exercising caution when applying our findings to broader, real-world contexts. Lastly, the brief duration of testing visits precluded a thorough assessment of AE reports, as participants only reported drowsiness after leaving the testing site. Given the onset of peak and residual effects associated with oral/sublingual cannabis products have been observed to be significantly longer than other routes of administration (McCartney et al., 2021; Vandrey et al., 2017), an extended assessment period beyond 3-hours is warranted to capture any prolonged subjective or performance effects following the use of the CannEpil treatment that may impact patient safety.

Future research would benefit from the examination of subjective and behavioural effects over an extended period to provide greater insight into any protracted effects on levels of sedation reported by some individuals. Future research is also urged to be inclusive of both medical cannabis consuming patient populations and healthy adults to facilitate our understanding of how variations in medicinal cannabis formulations and differences in titration may contribute to impairments in task performance, and to what extent impairment may arise across widely varied use indications.

The administration of an acute dose of CannEpil to healthy adults was observed to produce marked deficits in selective aspects of visuospatial working memory and pattern recognition, reflected by increased errors and latency, reduced task efficiency, and delayed recall of visual information. While CannEpil produced only limited subjective improvements to positive affect, no changes to mood disturbance were observed. Although subjective attention was unaffected, delayed onset of drowsiness and sedation was reported, highlighting the need for further investigation into the potential sedative effects of medicinal cannabis products across varying scenarios and cannabis user groups.

CRediT authorship contribution statement

Brooke Manning: Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Amie C. Hayley:** Funding acquisition, Conceptualization, Methodology, Formal analysis, Visualization, Writing – review & editing. **Sarah Catchlove:** Funding acquisition, Conceptualization, Methodology, Writing – review & editing. **Con Stough:** . **Luke A. Downey:** Funding acquisition, Conceptualization, Methodology, Formal analysis, Visualization, Writing – review & editing.

Declaration of competing interest

AH is supported by a Rebecca L Cooper Al and Val Rosenstrauss Fellowship (GNT: F2021894). BM, SC, CS, BS, and LD have no conflicts of interest to declare.

Role of the funding source

Cannvalate (Australia), Toorak, Australia.

References

Aguinis, H., Gottfredson, R.K., Joo, H., 2013. Best-practice recommendations for defining, identifying, and handling outliers. Organ. Res. Methods 16 (2), 270–301. https://doi.org/10.1177/1094428112470848.

Allan, G.M., Finley, C.R., Ton, J., Perry, D., Ramji, J., Crawford, K., Lindblad, A.J., Korownyk, C., Kolber, M.R., 2018. Systematic review of systematic reviews for medical cannabinoids. Can. Fam. Phys. 64 (2), e78–e94.

Arkell, T.R., Manning, B., Downey, L.A., Hayley, A.C., 2023. A semi-naturalistic, open-label trial examining the effect of prescribed medical cannabis on neurocognitive performance. CNS Drugs 37, 981–992. https://doi.org/10.1007/s40263-023-01046-z.

Arkell, T.R., Vinckenbosch, F., Kevin, R.C., Theunissen, E.L., McGregor, I.S., Ramaekers, J.G., 2020. Effect of cannabidiol and Δ9-tetrahydrocannabinol on driving performance: a randomised clinical trial. JAMA 324 (21), 2177–2186. https://doi.org/10.1001/jama.2020.21218.

Arndt, D.L., de Wit, H., 2017. Cannabidiol does not dampen responses to emotional stimuli in healthy adults. Cannabis Cannabinoid Res. 2 (1), 105–113. https://doi.org/10.1089/can.2017.0014.

Babson, K.A., Sottile, J., Morabito, D., 2017. Cannabis, cannabinoids, and sleep: a review of the literature. Curr. Psychiatry Rep. 19, 23. https://doi.org/10.1007/s11920-017-0775-9.

Badowski, M.E., 2017. A review of oral cannabinoids and medical marijuana for the treatment of chemotherapy-induced nausea and vomiting: a focus on pharmacokinetic variability and pharmacodynamics. Cancer Chemother. Pharmacol. 80, 441–449. https://doi.org/10.1007/s00280-017-3387-5.

Balcells-Oliveró, M., Oliveras, C., 2023. Defining cannabis risky use: building the plane while you fly it. Eur. Neuropsychopharmacol. 69, 84–86. https://doi.org/10.1016/j.euroneuro.2023.02.003.

Banerjee, R., Erridge, S., Salazar, O., Mangal, N., Couch, D., Pacchetti, B., Sodergren, M. H., 2021. Real world evidence in medical cannabis research. Ther. Innov. Regul. Sci. 56, 8–14. https://doi.org/10.1007/s43441-021-00346-0.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. J. Consult. Clin. Psychol. 56 (6), 893. https://doi.org/10.1037//0022-006x.56.6.893.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4 (6), 561–571. https://doi.org/10.1001/archpsyc.1961.01710120031004.

Bıçaksız, P., Özkan, T., 2016. Impulsivity and driver behaviors, offences, and accident involvement: a systematic review. Transp. Res. Part F: Traffic Psychol. Behav. 38, 194–223. https://doi.org/10.1016/j.trf.2015.06.001.

Blessing, E.M., Steenkamp, M.M., Manzanares, J., Marmar, C.R., 2015. Cannabidiol as a potential treatment for anxiety disorders. Neurotherapeutics 12 (4), 825–836. https://doi.org/10.1007/s13311-015-0387-1.

Bond, A., Lader, M., 1974. The use of analogue scales in rating subjective feelings. Br. J. Med. Psychol. 47, 211–218. https://doi.org/10.1111/j.2044-8341.1974.tb02285.x.

Bossong, M.G., Jansma, J.M., van Hell, H.H., Jager, G., Kahn, R.S., Ramsey, N.F., 2013. Default mode network in the effects of Δ9-tetrahydrocannabinol (THC) on human executive function. PLoS ONE 8 (7), e70074. https://doi.org/10.1371/journal.pone.0070074.

Broyd, S.J., van Hell, H.H., Beale, C., Yucel, M., Solowij, N., 2016. Acute and chronic effects of cannabinoids on human cognition: a systematic review. Biol. Psychiatry 79 (7), 557–567. https://doi.org/10.1016/j.biopsych.2015.12.002.

Celius, E.G., Vila, C, 2018. The influence of THC:CBD oromucosal spray on driving ability in patients with multiple sclerosis-related spasticity. Brain Behav. 8 (5), e00962. https://doi.org/10.1002/brb3.962.

Crippa, J., Zuardi, A.W., Garrido, G.E.J., Wichert-Ana, L., Guarnieri, R., Ferrari, L., Azevedo-Marques, P.M., Hallak, J.E.C., McGuire, P.K., Busatto, G.F., 2003. Effects of cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology 29, 417–426. https://doi.org/10.1038/sj.npp.1300340.

Desrosiers, N.A., Ramaekers, J.G., Chauchard, E., Gorelick, D.A., Huestis, M.A., 2015. Smoked cannabis' psychomotor and neurocognitive effects in occasional and frequent smokers. J. Anal. Toxicol. 39 (4), 251–261. https://doi.org/10.1093/jat/bkv012.

Dolcos, F., Katsumi, Y., Moore, M., Berggren, N., de Gelder, B., Derakshan, N., Hamm, A. O., Koster, E.H.W., Ladouceur, C.D., Okon-Singer, H., Pegna, A.J., Richter, T., Schweizer, S., Van den Stock, J., Ventura-Bort, C., Weymar, M., Dolcos, S., 2020. Neural correlates of emotion-attention interactions: from perception, learning, and memory to social cognition, individual differences, and training interventions. Neurosci. Biobehav. Rev. 108, 559–601. https://doi.org/10.1016/j.neubiorev.2019.08.017.

Eadie, L., Lo, L.A., Christiansen, A., Brucacher, J.R., Barr, A.M., Panenka, W.J., MacCallum, C.A., 2021. Duration of neurocognitive impairment with medical cannabis use: a scoping review. Front. Psychiatry 12. https://doi.org/10.3389/fpsyt.2021.638962.

Englund, A., Oliver, D., Chesney, E., Chester, L., Wilson, J., Sovi, S., De Micheli, A., Hodsoll, J., Fusar-Poli, P., Strang, J., Murray, R.M., Freeman, T.P., McGuire, P., 2023. Does cannabidiol make cannabis safer? A randomised, double-blind, cross-over trial of cannabis with four different CBD:THC ratios. Neuropsychopharmacology 48, 869–876. https://doi.org/10.1038/s41386-022-01478-z.

Freeman, A.M., Petrilli, K., Lees, R., Hindocha, C., Mokrysz, C., Curran, V.H., Saunders, R., Freeman, T.P., 2019. How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. Neurosci. Biobehav. Rev. 107, 696–712. https://doi.org/10.1016/j.neubiorev.2019.09.036.

Goldstein, R., Volkow, N., 2011. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat. Rev. Neurosci. 12, 652–669. https://doi.org/10.1038/nrn3119.

Hartman, R.L., Huestis, M.A., 2013. Cannabis effects of driving skills. Clin. Chem. 59 (3), 478–492. https://doi.org/10.1373/clinchem.2012.194381.

Harvey, M.A., Sellman, J.D., Porter, R.J., Frampton, C.M., 2007. The relationship between non-acute adolescent cannabis use and cognition. Drug Alcohol Rev. 26, 309–319. https://doi.org/10.1080/09595230701247772.

Hunault, C.C., Mensinga, T.T., Böcker, K.B.E., Schipper, C.M.A., Kruidenier, M., Leenders, M.E.C., de Vries, I., Meulenbelt, J., 2009. Cognitive and psychomotor effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg delta-9-tetrahydrocannabinol (THC). Psychopharmacology (Berl.) 204, 85–94. https://doi.org/10.1007/s00213-008-1440-0.

Kelleher, L.M., Stough, C., Sergejew, A.A., Rolfe, T., 2004. The effects of cannabis on information-processing speed. Addict. Behav. 29 (6), 1213–1219. https://doi.org/10.1016/j.addbeh.2004.03.039.

Lamers, C.T.J., Bechara, A., Rizzo, M., Ramaekers, J.G., 2006. Cognitive function and mood in MDMA/THC users, THC users, and non-drug using controls. J. Psychopharmacol. 20 (2), 302–311. https://doi.org/10.1177/0269881106059495.

Lissoni, P., Resentini, M., Mauri, R., Esposti, D., Esposti, G., Rossi, D., Legname, G., Fraschini, F., 1986. Effects of tetrahydrocannabinol on melatonin secretion in man. Hormone Metabol. Res. 18 (1), 77–78. https://doi.org/10.1055/s-2007-1012235.

Manning, B., Hayley, A.C., Catchlove, S., Shiferaw, B., Stough, C., Downey, L.A., 2023. Effect of CannEpil® on simulated driving performance and co-monitoring of ocular activity: a randomised controlled trial. J. Psychopharmacol. 37 (5), 472–483. https://doi.org/10.1177/02698811231170360.

McCartney, D., Kevin, R.C., Suraev, A.S., Sahinovic, A., Doohan, P.T., Bedoya-Perez, M. A., Grunstein, R.R., Hoyos, C.M., McGregor, I.S., 2022. How long does a single oral dose of cannabidiol persist in plasma? Findings from three clinical trials. Drug Test Anal. 15, 334–344. https://doi.org/10.1002/dta.3419.

McCartney, D., Arkell, T.R., Irwin, C., McGregor, I.S., 2021. Determining the magnitude and duration of acute Δ9-tetrahydrocannabinol (Δ9-THC)-induced driving and cognitive impairment: a systematic and meta-analytic review. Neurosci. Biobehav. Rev. 126, 175–193. https://doi.org/10.1016/j.neubiorev.2021.01.003.

McHale, S., Hunt, N., 2008. Executive function deficits in short-term abstinent cannabis users. Hum. Psychopharmacol.: Clin. Exp. 23 (5), 409–415. https://doi.org/10.1002/hup.941.

McNair, D.M., Lorr, M., Droppleman, L.F., 1981. Profile of Mood States. Educational and Industrial Testing Service, San Diego.

Narayan, A.J., Downey, L.A., Manning, B., Hayley, A.C., 2022. Cannabinoid treatments for anxiety: a systematic review and consideration of the impact of sleep disturbance. Neurosci. Biobehav. Rev. 143, 104941 https://doi.org/10.1016/j.neubiorev.2022.104941.

Narayan, A.J., Downey, L.A., Rose, S., Di Natale, L., Hayley, A.C., 2024. Cannabidiol for moderate-severe insomnia: a randomized controlled pilot trial of 150 mg of nightly dosing. J. Clin. Sleep Med. https://doi.org/10.5664/jcsm.10998.

Nicholson, A.N., Turner, C., Stone, B., Robson, P., 2004. Effect of Δ-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. J. Clin. Psychopharmacol. 24 (3), 305–313. https://doi.org/10.1097/01.jcp.0000125688.05091.8f.

Olla, P., Rykulski, N., Hurtubise, J.L., Bartol, S., Foote, R., Cutler, L., Abeare, K., McVinnie, N., Sabelli, A.G., Hastings, M., Erdodi, L.A., 2019. Short-term effects of cannabis consumption on cognitive performance in medical cannabis patients. Appl. Neuropsychopl.: Adult 28 (6), 647–657. https://doi.org/10.1080/23279095.2019.1681424.

Paton, W.D.M., Pertwee, R.G., 1973. The actions of cannabis in man. In: Mechoulam, R (Ed.), Marijuana: Chemistry, Pharmacology, Metabolism and Clinical Effects. Academic Press, New York.

Pessoa, L., 2009. How do emotion and motivation direct executive control? Trends Cognit. Sci. 13 (4), 160–166. https://doi.org/10.1016/j.tics.2009.01.006.

Ramaekers, J.G., Berghaus, G., van Laar, M.W., Drummer, O.H., 2009. Dose related risk of motor vehicle crashes after cannabis use: an update. In: Verster, J.C., Pandi-Perumal, S.R., Ramaekers, J.G., de Gier, J.J. (Eds.), Drugs, Driving, and Traffic Safety. Birkhauser Basel. https://doi.org/10.1007/978-3-7643-9923-8_29.

Ramaekers, J.G., Kauert, G., Theunissen, F.L., Toennes, S.W., Moeller, M.R., 2008. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. J. Psychopharmacol. 23 (3), 266–277. https://doi.org/10.1177/0269881108092393.

Ramaekers, J.G., Mason, N.L., Kloft, L., Theunissen, E.L., 2021. The why behind the high: determinants of neurocognition during acute cannabis exposure. Nat. Rev. Neurosci. 22, 439–454. https://doi.org/10.1038/s41583-021-00466-4.

Robbins, T.W., 1994. Cambridge Neuropsychological Test Automated Battery (CANTAB): utility and validation. In: IEE Colloquium on Computer-Aided Tests of Drug Effectiveness. London, UK.

Robledo-Menendez, A., Vella, M., Grandes, P., Soria-Gomez, E., 2021. Cannabinoid control of hippocampal functions: the *where* matters. FEBS J. 289 (8), 2162–2175. https://doi.org/10.1111/febs.15907.

Sanders, L.D., Astheimer, L.B., 2008. Temporally selective attention modulated early perceptual processing: event-related potential evidence. Percept. Psychophys. 70, 732–742. https://doi.org/10.3758/PP.70.4.732.

Schoeler, T., Kambeitz, J., Behlke, I., Murray, R., Bhattacharyya, S., 2015. The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis. Psychol. Med. 46 (1), 177–188. https://doi.org/10.1017/S0033291715001646.

Searight, H.R., Montone, K., 2020. Profile of Mood States. In: Zeigler-Hill, V., Shackelford, T.K. (Eds.), Encyclopedia of Personality and Individual Differences. Springer, Cham. https://doi.org/10.1007/978-3-319-24612-3_63.

Selamoglu, A., Langley, C., Crean, R., Savulich, G., Cormack, F., Sahakain, B.J., Mason, B., 2021. Neuropsychological performance in young adults with cannabis use disorder. J. Psychopharmacol. 35 (11), 1349–1355. https://doi.org/10.1177/02698811211050548.

Smith, A.M., Longo, C.A., Fried, P.A., Hogan, M.J., Cameron, I., 2010. Effects of marijuana on visuospatial working memory: an fMRI study in young adults. Psychopharmacology (Berl.) 210, 429–438. https://doi.org/10.1007/s00213-010-1841-8.

Smith, P.J., Need, A.C., Cirulli, E.T., Chiba-Falek, O., Attix, D.K., 2013. A comparison of the Cambridge Automated Neuropsychological Test Battery (CANTAB) with "traditional" neuropsychological testing instruments. J. Clin. Exp. Neuropsychol. 35 (3), 319–328. https://doi.org/10.1080/13803395.2013.771618.

Solmi, M., De Toffol, M., Kim, J.Y., Choi, M.J., Stubbs, B., Thompson, T., Firth, J., Miola, A., Croatto, G., Baggio, F., Michelon, S., Ballan, L., Gerdle, B., Monaco, F., Simonato, P., Scocco, P., Ricca, V., Castellini, G., Fornaro, M., Murru, A., Vieta, E., Fusar-Poli, P., Barbui, C., Ioannidis, J.P.A., Carvalho, A.F., Radua, J., Correll, C.U., Cortese, S., Murray, R.M., Castle, D., Shin, J.I., Dragioti, E., 2023. Balancing risks and benefits of cannabis use: umbrella review of meta-analyses of randomised controlled trials and observational studies. BMJ 382, e072348. https://doi.org/10.1136/bmj-2022-072348.

Solowij, N., Battisti, R., 2008. The chronic effects of cannabis on memory in humans: a review. Curr. Drug Abuse Rev. 1 (1), 81–98. https://doi.org/10.2174/1874473710801010081.

Solowij, N., Pesa, N., 2010. Cognitive abnormalities and cannabis use. Braz. J. Psychiatry 32 (1), 31–40. https://doi.org/10.1590/S1516-44462010000500006.

Solowij, N., Stephens, R.S., Roffman, R.A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B., Vendetti, J., Marijuana Treatment Project Research Group, 2002. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA 287 (9), 1123–1131. https://doi.org/10.1001/jama.287.9.1123.

Solowij, N., 1998. Cannabis and Cognitive Functioning. Cambridge University Press. https://doi.org/10.1017/CBO9780511526824.

Spindle, T.R., Cone, E.J., Schlienz, N.J., Mitchell, J.M., Bigelow, G.E., Flegel, R., Hayes, E., Vandrey, R., 2018. Acute effects of smoked and vaporized cannabis in healthy adults who infrequently use cannabis: a crossover trial. JAMA Network Open 1 (7), e184841. https://doi.org/10.1001/jamanetworkopen.2018.4841.

Szkudlarek, H.J., Desai, S.J., Renard, J., Pereira, B., Norris, C., Jobson, C.E.L., Rajakumar, N., Allman, B.L., Laviolette, S.R., 2018. Δ-9-tetrahydrocannabinol and cannabidiol produce dissociable effects on prefrontal cortical executive function and regulation of affective behaviors. Neuropsychopharmacology 44, 817–825. https://doi.org/10.1038/s41386-018-0282-7.

Vandrey, R., Herrmann, E.S., Mitchell, J.M., Bigelow, G.E., Flegel, R., LoDico, C., & Cone, E.J. (2017) Pharmacokinetic profile of oral cannabis in humans: blood and oral fluid disposition and relation to pharmacodynamic outcomes. *J. Anal. Toxicol.,* 41(2), 83–99. https://doi.org/10.1093/jat/bkx012.

Walker, H.E.K., Trick, L.M., 2018. Mind-wandering while driving: the impact of fatigue, task length, and sustained attention abilities. Transp. Res. Part F: Psychol.Behav. 59 (Part A), 81–97. https://doi.org/10.1016/j.trf.2018.08.009.

Wieghorst, A., Roessler, K.K., Hendricks, O., Andersen, T.E., 2022. The effect of medical cannabis on cognitive functions: a systematic review. Syst. Rev. 11 (1), 210. https://doi.org/10.1186/s13643-022-02073-5.

Zvolensky, M.J., Vujanovic, A.A., Bernstein, A., Bonn-Miller, M.O., Marshall, E.C., Leyro, T.M., 2007. Marijuana use motives: a confirmatory test and evaluation among young adult marijuana users. Addict. Behav. 32 (12), 3122–3130. https://doi.org/10.1016/j.addbeh.2007.06.010.