Supplemental Online Content

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eMethods 1. Cognitive and Psychomotor Performance

In the Digit Symbol Substitution Task (DSST), participants were presented with a series of geometric patterns labelled from 1-9, each consisting of an array of filled and blank squares in a 3 x 3 grid. When a number appeared in the middle of the screen, participants were instructed to replicate the pattern corresponding to that array using the numeric keypad of a computer keyboard. Participants had 90 sec to replicate as many patterns as possible. Primary outcome measures included number of patterns attempted and accuracy (number of patterns correct / number of patterns attempted).

In the Divided Attention Task (DAT), participants were required to track a horizontally moving stimulus on the screen using their mouse while simultaneously responding to peripheral visual stimuli by clicking the left mouse button whenever a number in any corner of the screen matched a target number presented at the bottom of the screen. Outcome measures included mean distance of the cursor from the target (tracking error) and response time to peripheral stimuli.

In the Paced Serial Addition Task (PSAT), participants watched single digits appear on the screen and were instructed to sum each new digit with the preceding one. Participants responded by clicking on the correct answer from a list of numbers (1-10) presented on the screen. Outcome measures included response time on correct trials, total number of correct trials (/90) and % correct trials.

In the Tower of London (TOL), participants viewed side-by-side configurations of three coloured balls on three sticks and had to determine, as quickly as possible, the number of steps required (between 2 and 5) to move the balls from one configuration to the other. Participants responded by pushing the corresponding number-coded button on a separate response box. Outcome measures included number of correct decisions and response time.

In the Emotional Stroop Task (EST) participants were presented with 20 anxiety-related words and 20 anxiety-matched neutral words. All words were presented twice in a mixed-trail (anxiety related/neutral at random). The colour the words were presented were: blue, red, green, yellow. Outcome measures included changes in mean reaction time and number correct for the anxiety related words and neutral words.

eMethods 2. Plasma Cannabinoid Analysis

Chemicals and reagents

Acetonitrile, formic acid, methanol, dichloromethane, and methyl-*tert*-butyl ether were obtained from Fisher Scientific (Melbourne, VIC, Australia). Cannabinoid reference standards and deuterated internal standards were purchased from Cerilliant (Round Rock, TX, USA). All chemicals and solvents were at least American Chemical Society (ACS) or high-performance liquid chromatography grade, respectively.

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis

Cannabinoid analysis was performed as reported previously[1] with minor modification. 200 µL of plasma samples were aliquoted in triplicate and spiked with a mixture of cannabinoid internal standards (THC-d_3, CBD-d_3, 11-OH-THC-d_3, and THC-COOH-d_3) in methanol. Calibrator and quality control samples of known cannabinoid concentrations were prepared by addition of reference standards to cannabinoid-free plasma which were treated identically to participant samples. 600 µL ice cold acetonitrile was added to all samples to precipitate protein, and the samples were centrifuged at 6000 x *g* for 10 min at 4 °C. The resultant supernatant was decanted into 96 well plates and dried under nitrogen.

The samples were reconstituted in 90 µL acetonitrile and 300 µL 0.1% formic acid and water and extracted using supported liquid extraction. The sample solutions were absorbed on Biotage Isolute SLE+ 400 µL capacity 96 well plates (Rydalmere, NSW, Australia), and the analytes were eluted with 700 µL dicholoromethane and 900 µL methyl-*tert*-butyl ether into a clean 96 well plate. The eluate was immediately evaporated to dryness under a gentle stream of nitrogen and reconstituted in 100 µL of 40:60 0.1% formic acid and methanol for immediate analysis via LC-MS/MS.

[1] Kevin RC, Allsop DJ, Lintzeris N, Dunlop AJ, Booth J, McGregor IS. Urinary cannabinoid levels during nabiximols (Sativex®)-medicated inpatient cannabis withdrawal. Forensic Toxicol. 2017;35(1):33-44.

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Cannabinoid quantification was performed using a Shimadzu Nexera LC-30AD ultra-high-performance liquid chromatograph (Shimadzu Corp., Kyoto, Japan) coupled to a Shimadzu LCMS-8040 triple quadrupole mass spectrometer. 20 µL injections of each sample, kept in an 8 °C autosampler, were chromatographically separated using an Agilent Zorbax XDB-C18 reverse-phased analytical column (50 x 2.1 mm i.d., particle size 3.5 µm; CA, USA). This was performed via gradient elution with 0.1% formic acid in water and methanol at a flow rate of 0.6 mL/min. The mass spectrometer was operated in positive electrospray ionization mode with multiple reaction monitoring to identify and quantify analytes against 7-point standard curves.

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eTable 1. Results of Linear Mixed-Effects Models With Data From Study Completers Only (N=22)

	condition		time		condition*time	
Subjective drug effects	F	*P*	F	*P*	F	*P*
Strength of drug effect	F(3,7.57) = 50.26	<.001	F(5,388.06) = 131.24	<.001	F(15,357.74) = 17.68	<.001
Liking of drug effect	F(3,110.37) = 5.31	0.002	F(5,367.58) = 12.03	<.001	F(15,345.27) = 1.26	0.22
Stoned	F(3,130.86) = 34.63	<.001	F(5,410.26) = 106.05	<.001	F(15,394.78) = 15.89	<.001
Sedated	F(3,92.47) = 17.06	<.001	F(5,385.46) = 37.00	<.001	F(15,353.72) = 4.02	<.001
Relaxed	F(3,130.65) = 3.87	0.01	F(5,340.80) = 2.34	0.04	F(15,329.14) = .87	0.60
Anxious	F(3,135.28) = 19.27	<.001	F(5,356.19) = 7.14	<.001	F(15,342.66) = 2.53	0.001
Confident to drive	F(3,115.17) = 22.63	<.001	F(5,362.23) = 23.28	<.001	F(342.88) = 3.72	<.001
State Anxiety Inventory						
Total score	F(3,49.99) = 15.19	<.001	-	-	-	-
Driving measures						
SDLP (cm)	F(3,143.02) = 14.30	<.001	F(1,143.07) = .55	0.46	F(3,143.02) = 3.01	0.03
Mean speed (km/h)	F(3,65.35) = 0.60	0.62	F(1,95.21) = 4.21	0.04	F(3,124.16) = 1.41	0.24
Standard deviation of speed (km/h)	F(3, 79.47) = 0.44	0.72	F(1,67.56) = 6.73	0.01	F(3,122.06) = 2.13	0.10
Perceived driving quality						
Driving quality	F(3,80.80) = 4.93	0.003	F(1,70.02) = .44	0.51	F(3,122.97) = .88	0.46
Driving impairment	F(3,73.74) = 15.10	<.001	F(1,87.66) = 8.03	0.006	F(3,127.48) = 1.85	0.14
Cognitive measures						
Digit Symbol Substitution Task						
No. attempted	F(3,78.33) = 1.88	0.14	F(1,86.04) = 27.17	<.001	F(3,129.73) = 3.12	0.03
No. correct	F(3,80.46) = 4.01	0.01	F(1,81.22) = 21.59	<.001	F(3,128.05) = 3.96	0.01
% correct	F(3,78.19) = 3.93	0.01	F(1,68.95) = 1.06	0.31	F(3,125.11) = 1.69	0.17

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	condition		time		condition*time	
Divided Attention Task						
Tracking error (pixels)	F(3,69.94) = 3.04	0.04	F(1,144.86) = .03	0.86	F(3,133.56) = .38	0.77
Response time (ms)	F(3,84.14) = 4.83	0.004	F(1,73.10) = .23	0.63	F(3,125.70) = 1.98	0.12
Paced Serial Addition Task						
Response time (ms)	F(3,83.80) = 6.28	0.001	F(1,72.16) = 29.95	<.001	F(3,126.06) = 4.19	0.007
Number correct	F(3,73.70) = 7.56	<.001	F(1,77.45) = 20.60	<.001	F(3,128.80) = 2.43	0.07
% correct	F(3,69.05) = 5.68	0.002	F(1,84.89) = 23.07	<.001	F(3,131.38) = 2.38	0.07
Emotional Stroop Task						
Number correct	F(3,62.52) = 0.30	0.83	-		-	
Response time	F(3,47.86) = 1.21	0.32	-		-	
Tower of London						
Number correct	F(3,41.00) = 2.10	0.115	-	-	-	-
Response time	F(3,42.95) = 3.47	0.02	-	-	-	-
Plasma cannabinoids						
THC	F(3,144.34) = 40.16	<.001	F(5,307.74) = 100.41	<.001	F(15,303.39) 29.55	<.001
11-OH-THC	F(3,93.68) = 21.59	<.001	F(5,337.95) = 52.31	<.001	F(15,316.71) = 12.00	<.001
11-COOH-THC	F(3,83.07) = 14.34	<.001	F(5,355.00) 40.33	<.001	F(15,331.35) = 9.78	<.001
CBD	F(3,127.63) = 86.68	<.001	F(5,317.10) = 140.52	<.001	F(15,308.12) = 49.82	<.001
Cardiovascular measures						
BP (systolic)	F(3,140.57) = .42	0.74	F(5,329.97) = 1.33	0.25	F(15,321.71) = 2.47	0.002
BP (diastolic)	F(3,135.38) = 2.03	0.11	F(5,329.16) = 4.29	0.001	F(15,319.82) = 1.09	0.36
HR	F(3,125.07) = 22.21	<.001	F(5,346.53) = 62.02	<.001	F(15,331.25) = 17.27	<.001

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eTable 2. Results of Linear Mixed-Effects Models With Data From All Participants (N=26)

	condition		time		condition*time	
Subjective drug effects	F	*P*	F	*P*	F	*P*
Strength of drug effect	F(3,110.92) = 59.35	<.001	F(5,420.04) = 148.17	<.001	F(15,389.63) = 20.71	<.001
Liking of drug effect	F(3,118.85) = 5.29	0.002	F(5,398.48) = 15.26	<.001	F(15,371.81) = 1.27	0.22
Stoned	F(3,145.13) = 42.01	<.001	F(5,444.06) = 118.94	<.001	F(15,429.15) = 19.37	<.001
Sedated	F(3,102.50) = 18.01	<.001	F(5,416.00) = 38.24	<.001	F(15,382.76) = 4.22	<.001
Relaxed	F(3,146.53) = 3.72	0.01	F(5,362.90) = 1.75	0.12	F(15,352.22) = 0.76	0.72
Anxious	F(3,150.78) = 18.66	<.001	F(5,381.66) = 7.01	<.001	F(15,368.15) = 3.01	<.001
Confident to drive	F(3,125.67) = 22.84	<.001	F(5,391.15) = 24.07	<.001	F(15,369.31) = 4.40	<.001
State Anxiety Inventory						
Total score	F(3,49.97) = 15.55	<.001	-	-	-	-
Driving performance						
SDLP (cm)	F(2,92.21) = 12.16	<.001	F(1,76.44) = 0.483	0.49	F(3,135.62) = .031	0.03
Mean speed (km/h)	F(3,71.24) = 0.69	0.56	F(1,105.19) = 4.51	0.04	F(3,135.08) = 1.48	0.22
Standard deviation of speed (km/h)	F(3,87.77) = 0.52	0.67	F(1,76.53) = 8.18	0.01	F(3,135.00) = 2.03	0.11
Perceived driving quality						
Driving quality	F(93.28) = 5.04	0.003	F(1,76.69) = .17	0.68	F(3,135,40) = .95	0.42
Driving impairment	F(3,86.33) = 16.50	<.001	F(1,90.92) = 5.97	0.02	F(3,136.82) = 2.07	0.11
Cognitive measures						
Digit Symbol Substitution Task						
No. attempted	F(3,86.72) = 1.38	0.26	F(1,94.42) = 27.53	<.001	F(3,140.99) = 3.38 *	0.02
No. correct	F(3,89.32) = 2.94	0.04	F(1,89.59) = 20.23	<.001	F(3,139.63) = 4.56	0.004
% correct	F(3,87.04) = 3.04	0.03	F(1,77.91) = 0.61	0.44	F(3,139.64) = 2.44	0.07

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	condition		**time**		**condition*time**	
Divided Attention Task						
Tracking error (pixels)	F(3,83.68) = 3.57	0.02	F(1,157.34) = 0.00	>.99	F(3,146.56) = 0.26	0.85
Response time (ms)	F(3,92.64) = 5.09	0.003	F(1,80.20) = 0.45	0.51	F(3,138.79) = 2.51	0.06
Paced Serial Addition Task						
Response time (ms)	F(3,90.47) = 6.08	0.001	F(1,81.54) = 34.55	<.001	F(3,139.68) = 4.07	0.008
Number correct	F(3,82.60) = 7.07	<.001	F(1,87.79) = 25.04	<.001	F(3,141.08) = 2.26	0.08
% correct	F(3,79.28) = 5.33	0.002	F(1,95.23) = 27.62	<.001	F(3,143.04) = 2.18	0.09
Emotional Stroop Task						
Number correct	F(3,67.16) = 0.59	0.62	-		-	
Response time	F(3,44.34) = 0.31	0.82	-		-	
Tower of London						
Number correct	F(3,47.96) = 3.28	0.03	-		-	
Response time (s)	F(3,47.465) = 3.90	0.02	-		-	
Plasma cannabinoids						
THC	F(3,163.62) = 47.92	<.001	F(5,338.80) = 119.29	<.001	F(15,334.10) = 35.60	<.001
11-OH-THC	F(3,107.37) = 25.04	<.001	F(5,371.57) = 59.95	<.001	F(15,349.43) = 14.21	<.001
11-COOH-THC	F(3,93.08) = 16.58	<.001	F(5,388.88) = 43.91	<.001	F(363.31) = 11.05	<.001
CBD	F(3,145.16) = 98.82	<.001	F(5,347.60) = 159.33	<.001	F(15,338.20) = 57.11	<.001
Cardiovascular measures						
Systolic BP	F(3,155.520) = .32	0.81	F(5,360.50) = 1.29	.27	F(15,351.59) = 2.70	.001
Diastolic BP	F(3,152.40) = 1.96	0.12	F(5,359.71) = 4.81	<.001	F(15,350.01) = 1.14	0.32
HR	F(3,135.89) = 5.27	<.001	F(5,379.08) = 71.23	<.001	F(15,361.99) = 19.97	<.001

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eTable 3. Results of Bonferroni Post Hoc Tests for Subjective Drug Effect Measures and State Anxiety Inventory Scores

	CBD - PLA				THC - PLA				THC/CBD - PLA				THC/CBD - THC			
Time (min)	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI
Subjective Drug Effects																
Strength of drug effect																
0	**1.33**	**0.03**	**0.10**	**2.56**	**6.76**	**<.001**	**5.48**	**8.03**	**5.09**	**<.001**	**3.80**	**6.38**	**-1.67**	**0.004**	**-2.97**	**-0.37**
25	0.35	>.99	-0.89	1.59	**6.08**	**<.001**	**4.80**	**7.35**	**4.51**	**<.001**	**3.22**	**5.80**	**-1.57**	**0.01**	**-2.87**	**-0.27**
130	0.40	>.99	-0.84	1.63	**4.19**	**<.001**	**2.91**	**5.46**	**3.73**	**<.001**	**2.43**	**5.02**	-0.46	>.99	-1.76	0.84
200	0.32	>.99	-0.91	1.56	**2.17**	**<.001**	**0.89**	**3.44**	**2.08**	**<.001**	**0.79**	**3.37**	-0.08	>.99	-1.38	1.22
240	-0.11	>.99	-1.34	1.12	**1.49**	**0.01**	**0.22**	2.77	**1.38**	**0.03**	**0.09**	**2.67**	-0.11	>.99	-1.41	1.19
Liking of drug effect																
0	0.15	>.99	-1.11	1.41	0.51	>.99	-0.78	1.80	1.12	0.14	-0.19	2.42	0.61	>.99	-0.71	1.93
25	-0.41	>.99	-1.68	0.85	0.87	0.45	-0.42	2.16	0.99	0.27	-0.32	2.29	0.12	>.99	-1.20	1.44
130	-0.23	>.99	-1.49	1.03	**1.50**	**0.01**	**0.21**	**2.79**	0.62	>.99	-0.68	1.93	-0.88	0.47	-2.20	0.44
200	0.57	>.99	-0.69	1.82	0.59	>.99	-0.70	1.88	0.83	0.54	-0.47	2.14	0.25	>.99	-1.08	1.57
240	0.06	>.99	-1.19	1.32	0.87	0.45	-0.42	2.17	0.59	>.99	-0.73	1.90	-0.29	>.99	-1.63	1.06
Stoned																
0	1.21	0.10	-0.13	2.55	**6.54**	**<.001**	**5.15**	**7.93**	**5.24**	**<.001**	**3.83**	**6.65**	-1.30	0.08	-2.70	0.10
25	0.45	>.99	-0.89	1.79	**5.83**	**<.001**	**4.44**	**7.22**	**4.95**	**<.001**	**3.54**	**6.36**	-0.88	0.58	-2.29	0.52
130	0.06	>.99	-1.28	1.39	**3.98**	**<.001**	**2.59**	**5.37**	**3.48**	**<.001**	**2.07**	**4.89**	-0.50	>.99	-1.90	0.91
200	0.46	>.99	-0.87	1.79	**2.08**	**0.001**	**0.68**	**3.47**	**2.09**	**0.001**	**0.68**	**3.50**	0.02	>.99	-1.39	1.42
240	0.03	>.99	-1.30	1.35	1.24	0.11	-0.15	2.63	**1.47**	**0.03**	**0.07**	**2.88**	0.23	>.99	-1.17	1.64
Sedated																
0	0.64	>.99	-0.89	2.17	**3.58**	**<.001**	**1.99**	**5.16**	**2.70**	**<.001**	**1.10**	**4.30**	-0.87	0.90	-2.48	0.73
25	0.11	>.99	-1.42	1.65	**2.96**	**<.001**	**1.37**	**4.54**	**3.07**	**<.001**	**1.47**	**4.68**	0.11	>.99	-1.50	1.72
130	-0.05	>.99	-1.58	1.48	**2.02**	**0.005**	**0.44**	**3.60**	**2.87**	**<.001**	**1.27**	**4.48**	0.85	0.97	-0.76	2.46
200	0.22	>.99	-1.31	1.75	**2.23**	**0.001**	**0.65**	**3.81**	**2.06**	**0.004**	**0.46**	**3.67**	-0.17	>.99	-1.78	1.44
240	0.09	>.99	-1.44	1.61	**2.16**	**0.002**	**0.58**	**3.74**	**2.33**	**0.001**	**0.73**	**3.93**	0.16	>.99	-1.45	1.78

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	CBD - PLA				THC - PLA				THC/CBD - PLA				THC/CBD - THC			
Time (min)	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI
Relaxed																
0	-0.42	>.99	-1.52	0.67	**-1.29**	**0.01**	**-2.40**	**-0.18**	-0.26	>.99	-1.39	0.87	1.03	0.11	-0.12	2.18
25	-0.16	>.99	-1.27	0.94	**-1.25**	**0.02**	**-2.36**	**-0.13**	-0.40	>.99	-1.54	0.74	0.85	0.32	-0.31	2.01
130	-0.09	>.99	-1.19	1.00	-0.54	>.99	-1.65	0.58	-0.38	>.99	-1.51	0.75	0.16	>.99	-0.99	1.31
200	0.37	>.99	-0.73	1.46	0.04	>.99	-1.07	1.16	0.02	>.99	-1.11	1.15	-0.02	>.99	-1.17	1.12
240	-0.08	>.99	-1.17	1.01	-0.48	>.99	-1.59	0.63	-0.12	>.99	-1.25	1.00	0.36	>.99	-0.79	1.50
Anxious																
0	0.57	0.92	-0.49	1.64	**2.75**	**<.001**	**1.66**	**3.83**	0.87	0.22	-0.23	1.97	**-1.88**	**<.001**	**-2.99**	**-0.76**
25	0.24	>.99	-0.84	1.31	**2.61**	**<.001**	**1.53**	**3.70**	**1.47**	**0.00**	**0.37**	**2.57**	**-1.14**	**0.04**	**-2.26**	**-0.02**
130	-0.09	>.99	-1.15	0.98	**1.17**	**0.03**	**0.08**	**2.25**	0.86	0.23	-0.24	1.96	-0.31	>.99	-1.42	0.81
200	0.15	>.99	-0.92	1.21	**1.30**	**0.01**	**0.21**	**2.38**	0.79	0.34	-0.30	1.89	-0.50	>.99	-1.62	0.62
240	0.31	>.99	-0.75	1.37	0.19	>.99	-0.89	1.28	0.28	>.99	-0.82	1.38	0.08	>.99	-1.04	1.20
Confident to drive																
0	-1.00	0.25	-2.29	0.30	**-4.30**	**<.001**	**-5.61**	**-2.98**	**-2.48**	**<.001**	**-3.81**	**-1.14**	**1.82**	**0.002**	**0.47**	**3.17**
25	-0.73	0.80	-2.03	0.56	**-3.65**	**<.001**	**-4.96**	**-2.33**	**-2.08**	**<.001**	**-3.41**	**-0.75**	**1.57**	**0.01**	**0.22**	**2.92**
130	-0.33	>.99	-1.62	0.95	**-2.18**	**<.001**	**-3.49**	**-0.86**	**-1.74**	**0.003**	**-3.07**	**-0.41**	0.43	>.99	-0.92	1.78
200	-0.08	>.99	-1.36	1.21	-1.13	0.14	-2.45	0.18	-0.71	0.94	-2.04	0.62	0.42	>.99	-0.93	1.77
240	0.11	>.99	-1.18	1.39	-0.53	>.99	-1.84	0.78	-1.12	0.16	-2.45	0.21	-0.59	>.99	-1.94	0.76
State Anxiety Inventory																
Total score																
20	2.35	>.99	-2.55	7.24	**13.18**	**<.001**	**7.42**	**18.95**	**6.65**	**0.03**	**0.45**	**12.86**	**-6.53**	**<.01**	**-11.82**	**-1.23**

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eTable 4. Results of Bonferroni Post Hoc Tests for Driving Measures

	CBD - PLA				THC - PLA				THC/CBD - PLA				THC/CBD - THC			
Time (min)	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI
Driving performance																
SDLP																
40-100	-0.05	>.99	-1.49	1.39	**2.33**	**<.001**	**0.80**	**3.86**	**2.83**	**<.001**	**1.28**	**4.39**	0.50	>.99	-1.10	2.10
240-300	-0.34	>.99	-1.77	1.10	0.51	>.99	-1.01	2.02	1.22	0.20	-0.29	2.74	0.71	>.99	-0.83	2.25
Mean speed (km/h)																
40-100	0.24	>.99	-1.01	1.49	0.71	>.99	-0.72	2.14	-0.32	>.99	-1.79	1.15	-1.03	0.27	-2.40	0.34
240-300	0.07	>.99	-1.16	1.31	-0.43	>.99	-1.85	0.98	-0.44	>.99	-1.88	0.99	-0.01	>.99	-1.33	1.31
Standard deviation of speed (km/h)																
40-100	-0.13	>.99	-0.54	0.28	-0.38	0.12	-0.82	0.05	-0.24	0.85	-0.69	0.20	0.14	>.99	-0.32	0.59
240-300	0.11	>.99	-0.30	0.52	0.14	>.99	-0.29	0.57	0.03	>.99	-0.40	0.46	-0.11	>.99	-0.54	0.33
Perceived driving quality																
Driving quality																
100	-0.69	>.99	-2.27	0.90	**-1.95**	**0.01**	**-3.64**	**-0.26**	**-2.14**	**0.006**	**-3.83**	**-0.44**	-0.18	>.99	-1.92	1.56
300	-0.11	>.99	-1.69	1.47	-0.64	>.99	-2.31	1.03	-1.19	0.35	-2.87	0.48	-0.55	>.99	-2.25	1.15
Driving impairment																
100	1.24	0.32	-0.46	2.93	**4.15**	**<.001**	**2.29**	**6.02**	**4.09**	**<.001**	**2.20**	**5.98**	-0.06	>.99	-1.92	1.80
300	0.56	>.99	-1.14	2.25	**2.27**	**0.008**	**0.41**	**4.12**	**2.70**	**0.001**	**0.83**	**4.57**	0.43	>.99	-1.39	2.25

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eTable 5. Results of Post Hoc Tests for Cognitive/Psychomotor Task Performance Measures

	CBD - PLA				THC - PLA				THC/CBD - PLA				THC/CBD - THC			
Time (min)	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI
Digit Symbol Substitution Task																
No. attempted																
5	-2.45	0.13	-5.28	0.39	**-3.52**	**0.01**	**-6.51**	**-0.53**	-2.66	0.13	-5.71	0.39	0.86	>.99	-2.12	3.83
205	1.23	>.99	-1.57	4.03	-0.03	>.99	-3.03	2.97	0.71	>.99	-2.39	3.80	0.74	>.99	-2.28	3.76
No. correct																
5	-3.31	0.06	-6.72	0.11	**-5.46**	**<.001**	**-9.03**	**-1.89**	**-4.43**	**0.01**	**-8.06**	**-0.80**	1.03	>.99	-2.56	4.61
205	1.69	>.99	-1.69	5.06	-0.44	>.99	-4.02	3.14	0.56	>.99	-3.12	4.25	1.01	>.99	-2.63	4.65
% correct																
5	-1.82	0.69	-4.89	1.25	**-3.93**	**0.01**	**-7.09**	**-0.78**	**-3.64**	**0.02**	**-6.84**	**-0.44**	0.30	>.99	-2.93	3.53
205	1.34	>.99	-1.69	4.38	-0.51	>.99	-3.67	2.65	0.04	>.99	-3.20	3.29	0.55	>.99	-2.72	3.83
Divided Attention Task																
Tracking error (pixels)																
5	1.55	>.99	-2.63	5.73	4.88	0.08	-0.29	10.05	4.42	0.23	-1.28	10.11	-0.46	>.99	-4.86	3.94
205	0.23	>.99	-3.93	4.39	4.96	0.07	-0.26	10.17	4.28	0.28	-1.47	10.04	-0.67	>.99	-5.17	3.82
Response time (ms)																
5	119.78	0.48	-62.04	301.59	**289.20**	**<.001**	**100.05**	**478.35**	**257.61**	**<.001**	**65.65**	**449.57**	-31.59	>.99	-224.67	161.49
205	-50.44	>.99	-232.09	131.20	50.35	>.99	-139.08	239.77	72.01	>.99	-122.67	266.69	21.66	>.99	-174.20	217.52
Paced Serial Addition Task																
Response time (ms)																
5	-3.61	>.99	-63.64	56.43	**92.00**	**<.001**	**29.51**	**154.50**	**88.75**	**<.001**	**25.30**	**152.20**	-3.25	>.99	-66.97	60.46
205	-2.79	>.99	-62.76	57.17	19.22	>.99	-43.38	81.82	12.16	>.99	-52.20	76.52	-7.06	>.99	-71.70	57.58
Number correct																
5	-0.42	>.99	-7.13	6.28	**-10.97**	**<.001**	**-18.07**	**-3.86**	**-8.561**	**0.01**	**-15.79**	**-1.33**	2.41	>.99	-4.71	9.52
205	-2.45	>.99	-9.14	4.25	-6.24	0.12	-13.36	0.89	-3.67	>.99	-10.99	3.66	2.57	>.99	-4.66	9.80

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	CBD - PLA				THC - PLA				THC/CBD - PLA				THC/CBD - THC			
Time (min)	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI
% correct																
5	0.01	>.99	-7.57	7.59	**-11.45**	**<.001**	**-19.62**	**-3.28**	-8.20	0.06	-16.54	0.14	3.25	>.99	-4.79	11.28
205	-1.50	>.99	-9.06	6.07	-5.65	0.40	-13.85	2.54	-2.77	>.99	-11.22	5.68	2.88	>.99	-5.29	11.05
Tower of London																
Number correct																
135	1.26	>.99	-1.46	3.98	-1.60	0.93	-4.63	1.44	-1.70	0.86	-4.86	1.45	-0.11	>.99	-3.01	2.80
Response time (s)																
135	-0.01	>.99	-1.11	1.10	**-1.337**	**0.05**	**-2.65**	**-0.02**	-1.03	0.32	-2.45	0.40	0.31	>.99	-0.87	1.49

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eTable 6. Results of Post Hoc Tests for Plasma Cannabinoid Concentrations

	CBD - PLA				THC - PLA				THC/CBD - PLA				THC/CBD - THC			
Time (min)	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI
THC																
0	1.57	>.99	-1.48	4.62	**22.71**	**<.001**	**19.66**	**25.76**	**20.79**	**<.001**	**17.50**	**24.07**	-1.93	0.71	-5.18	1.33
25	0.53	>.99	-2.55	3.61	**7.20**	**<.001**	**4.05**	**10.35**	**4.91**	**0.00**	**1.62**	**8.19**	-2.29	0.42	-5.64	1.06
130	0.22	>.99	-2.86	3.30	2.05	0.52	-1.11	5.20	1.63	>.99	-1.61	4.87	-0.42	>.99	-3.73	2.89
200	0.10	>.99	-2.98	3.18	0.84	>.99	-2.35	4.03	0.73	>.99	-2.60	4.07	-0.11	>.99	-3.55	3.33
320	0.16	>.99	-3.10	3.41	0.44	>.99	-2.94	3.81	0.30	>.99	-3.17	3.78	-0.13	>.99	-3.61	3.35
11-OH-THC																
0	0.74	0.10	-0.08	1.55	**3.21**	**<.001**	**2.39**	**4.03**	**3.46**	**<.001**	**2.58**	**4.34**	0.25	>.99	-0.62	1.11
25	0.43	0.97	-0.39	1.25	**2.74**	**<.001**	**1.90**	**3.58**	**2.27**	**<.001**	**1.39**	**3.15**	-0.47	0.95	-1.35	0.41
130	0.17	>.99	-0.65	0.99	**1.34**	**<.001**	**0.49**	**2.18**	**1.42**	**<.001**	**0.55**	**2.29**	0.08	>.99	-0.80	0.96
200	0.18	>.99	-0.64	1.00	0.77	0.11	-0.09	1.62	0.64	0.35	-0.25	1.52	-0.13	>.99	-1.03	0.77
320	0.14	1.00	-0.70	0.99	0.46	>.99	-0.42	1.34	0.45	>.99	-0.46	1.36	-0.01	>.99	-0.92	0.91
11-COOH-THC																
0	1.57	>.99	-1.54	4.67	**8.90**	**<.001**	**5.69**	**12.12**	**8.14**	**<.001**	**4.71**	**11.58**	-0.76	>.99	-4.04	2.52
25	1.56	1.00	-1.56	4.68	**9.82**	**<.001**	**6.54**	**13.10**	**8.56**	**<.001**	**5.11**	**12.01**	-1.26	>.99	-4.61	2.09
130	1.31	>.99	-1.81	4.43	**5.94**	**<.001**	**2.64**	**9.25**	**6.17**	**<.001**	**2.74**	**9.60**	0.23	>.99	-3.13	3.58
200	0.94	>.99	-2.16	4.05	**4.66**	**0.00**	**1.33**	**7.99**	**4.65**	**0.00**	**1.17**	**8.13**	-0.01	>.99	-3.44	3.42
320	0.97	>.99	-2.18	4.12	**3.71**	**0.02**	**0.31**	**7.11**	2.80	0.22	-0.75	6.35	-0.91	>.99	-4.38	2.56
CBD																
0	15.76	>.99	13.96	17.57	-0.03	>.99	-1.83	1.77	**14.51**	**<.001**	**12.57**	**16.45**	**14.54**	**<.001**	**12.62**	**16.47**
25	7.32	>.99	5.50	9.14	-0.01	>.99	-1.87	1.85	**5.21**	**<.001**	**3.27**	**7.15**	**5.22**	**<.001**	**3.25**	**7.20**
130	2.75	>.99	0.93	4.57	-0.02	>.99	-1.88	1.85	**2.18**	**0.02**	**0.26**	**4.10**	**2.20**	**0.02**	**0.24**	**4.15**
200	1.24	0.43	-0.58	3.06	0.00	>.99	-1.89	1.89	0.95	>.99	-1.02	2.92	0.95	>.99	-1.07	2.98
320	0.43	>.99	-1.49	2.34	-0.02	>.99	-2.00	1.97	0.35	>.99	-1.70	2.39	0.36	>.99	-1.69	2.41

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eTable 7. Results of Post Hoc Tests for Cardiovascular Measures

	CBD - PLA				THC - PLA				THC/CBD - PLA				THC/CBD - THC			
Time (min)	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI	Mean Difference	*P*	Lower 95% CI	Upper 95% CI
Blood pressure (systolic)																
0	-1.27	>.99	-7.46	4.92	3.03	>.99	-3.54	9.60	1.09	>.99	-5.59	7.77	-1.94	>.99	-8.95	5.07
25	-3.30	0.95	-9.50	2.90	6.20	0.06	-0.22	12.61	1.33	>.99	-5.26	7.93	-4.87	0.35	-11.64	1.91
130	-0.44	>.99	-6.69	5.81	-0.18	>.99	-6.58	6.23	-0.73	>.99	-7.38	5.93	-0.55	>.99	-7.26	6.16
200	-1.54	>.99	-7.68	4.61	-0.84	>.99	-7.25	5.57	-2.59	>.99	-9.37	4.20	-1.75	>.99	-8.71	5.21
320	1.88	>.99	-4.26	8.02	-2.13	>.99	-8.54	4.28	0.73	>.99	-5.96	7.42	2.86	>.99	-4.01	9.73
Heart rate																
0	4.27	0.41	-1.94	10.47	**35.11**	**<.001**	**28.69**	**41.53**	**24.83**	**<.001**	**18.22**	**31.44**	**-10.28**	**<.001**	**-17.05**	**-3.51**
25	3.51	0.81	-2.71	9.72	**16.43**	**<.001**	**10.06**	**22.79**	**13.18**	**<.001**	**6.56**	**19.79**	-3.25	>.99	-9.97	3.47
130	2.20	>.99	-4.01	8.40	**6.51**	**0.04**	**0.14**	**12.87**	2.84	>.99	-3.78	9.45	-3.67	0.89	-10.39	3.05
200	1.68	>.99	-4.48	7.84	5.21	0.19	-1.21	11.64	3.22	>.99	-3.41	9.85	-1.99	>.99	-8.78	4.80
320	2.76	>.99	-3.39	8.91	2.59	>.99	-3.83	9.01	4.30	0.54	-2.41	11.02	1.72	>.99	-5.16	8.59

Note: Diastolic blood pressure not shown as the main effect of condition and the condition*time interaction were non-significant.

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eTable 8. Symmetry Analysis of Proportions Impaired and Improved Drivers in Each Treatment Condition at 2 BAC Thresholds of Impairment

	Criterion BAC=0.02%				**Criterion BAC=0.05%**		
Treatment	Time (min)	*ΔSDLP >1.12 cm n(%) impaired*	*ΔSDLP <-1,12 cm n(%) improved*	McNemar P	*ΔSDLP >2.40 cm n(%) impaired*	*ΔSDLP <-2.40 cm n(%) improved*	McNemar P
CBD	40-100	9(40)	11(44)	0.86	4(16)	3(12)	>.99
	240-300	4(16)	6(24)	0.75	2(8)	4(16)	0.68
THC	40-100	**13(62)**	**2(9)**	**<.01**	**10(48)**	**2(9)**	**0.04**
	240-300	8(36)	7(32)	>.99	6(27)	2(9)	0.29
THC/CBD	40-100	**15(75)**	**1(5)**	**<.01**	**12(60)**	**0(0)**	**<.001**
	240-300	11(50)	3(14)	0.07	7(32)	1(4)	0.07

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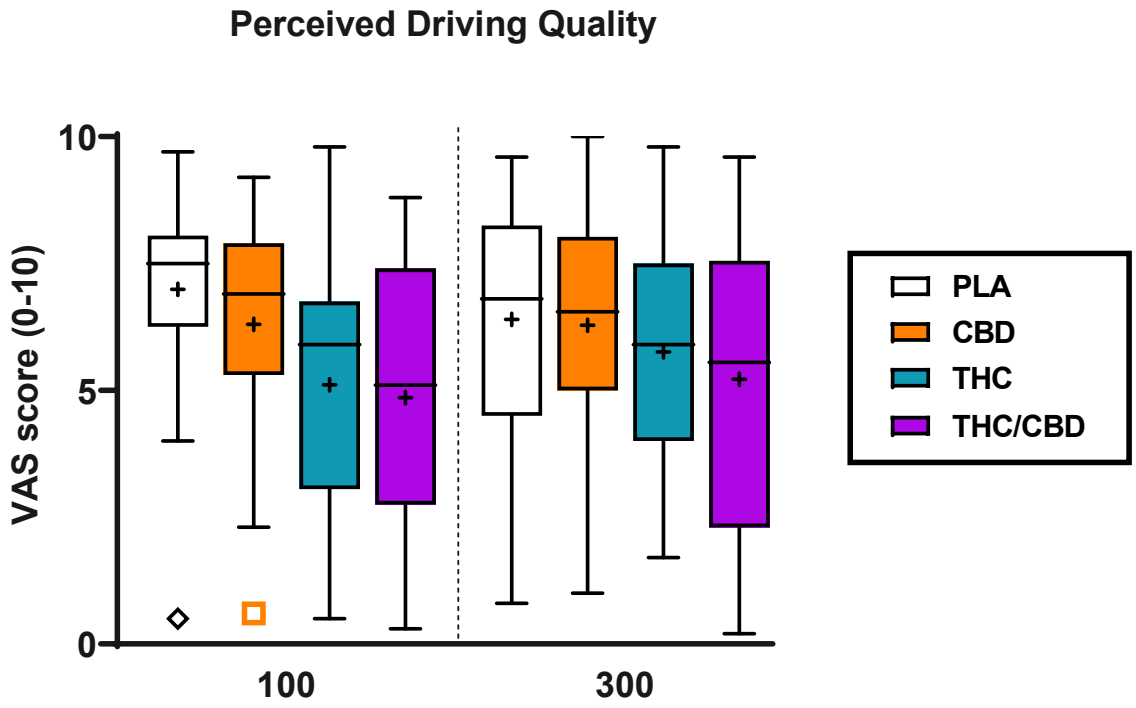
eFigure 1. Perceived Driving Quality



eFigure 1. A boxplot showing scores on the VAS (0-10 cm) item "How Would You Rate the Quality of Your Driving Just Now?" (Very Poor – Very Good) as assessed at the end of each on-road driving test. The edges of the boxes represent the 25th and 75th quartile values. The horizontal line shows the median and the '+' shows the mean. If there are no outliers (Q1 − 1.5 × (Q3 − Q1) and Q3 + 1.5 × (Q3 − Q1)), the whiskers show minimum and maximum values. If there are outliers (shown as coloured symbols), the whiskers show the lowest and highest values that are not outliers.

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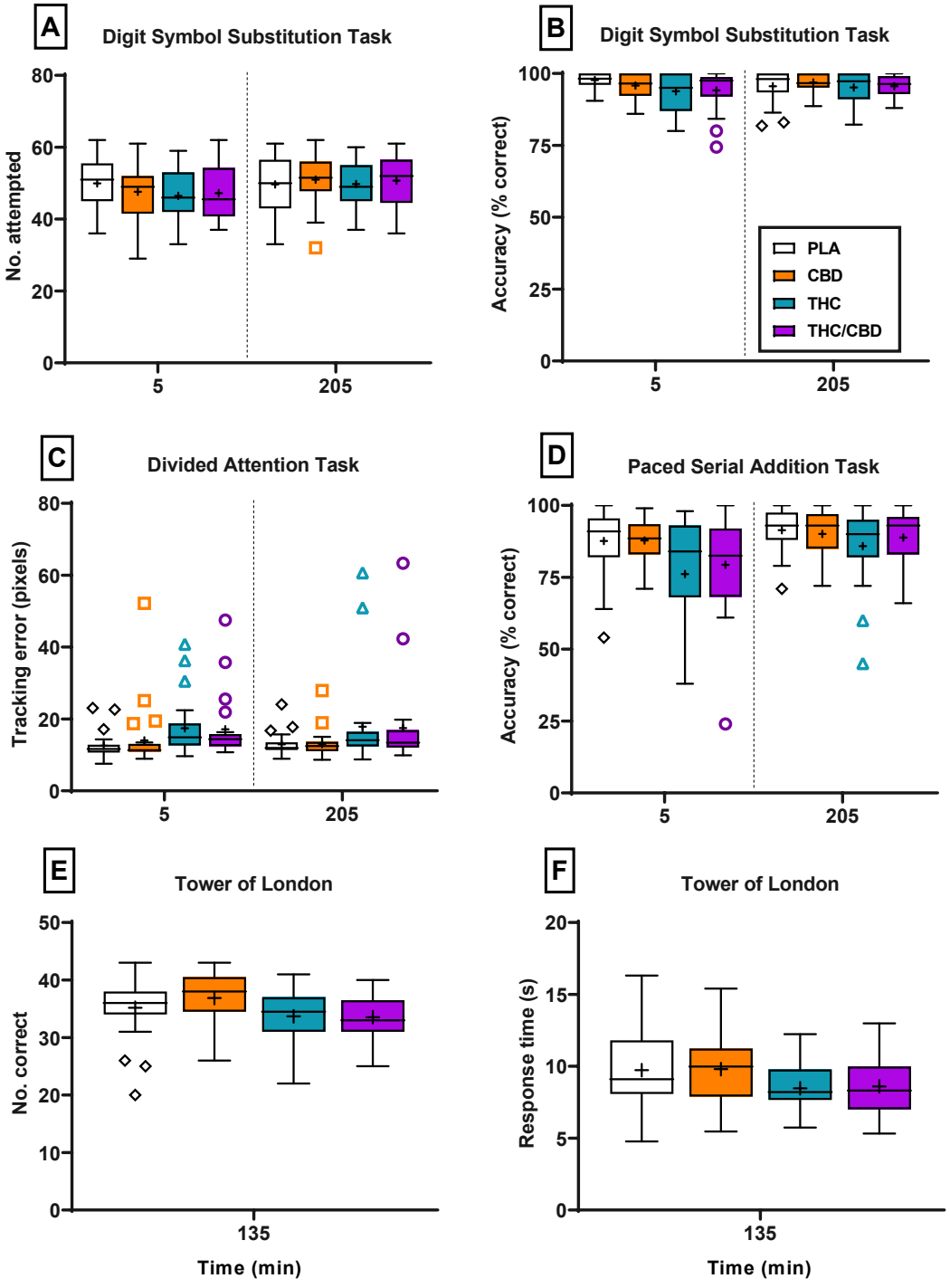
eFigure 2. Additional Outcome Measures for the Digit Symbol Substitution Task (A-B), Divided Attention Task (C), Paced Serial Addition Task (D), and Tower of London (E-F)



eFigure 2. Boxplots showing additional outcome measures on the Digit Symbol Substitution Task (DSST), Divided Attention Task (DAT), Paced Serial Addition Task (PSAT) and the Tower of London (TOL). The edges of the boxes represent the 25th and 75th quartile values. The horizontal line shows the median and the '+' shows the mean. If there are no outliers (Q1 − 1.5 × (Q3 − Q1) and Q3 + 1.5 × (Q3 − Q1)), the whiskers show minimum and maximum values. If there are outliers (shown as coloured symbols), the whiskers show the lowest and highest values that are not outliers. Time as shown on the x-axis indicates time elapsed since vaporization.

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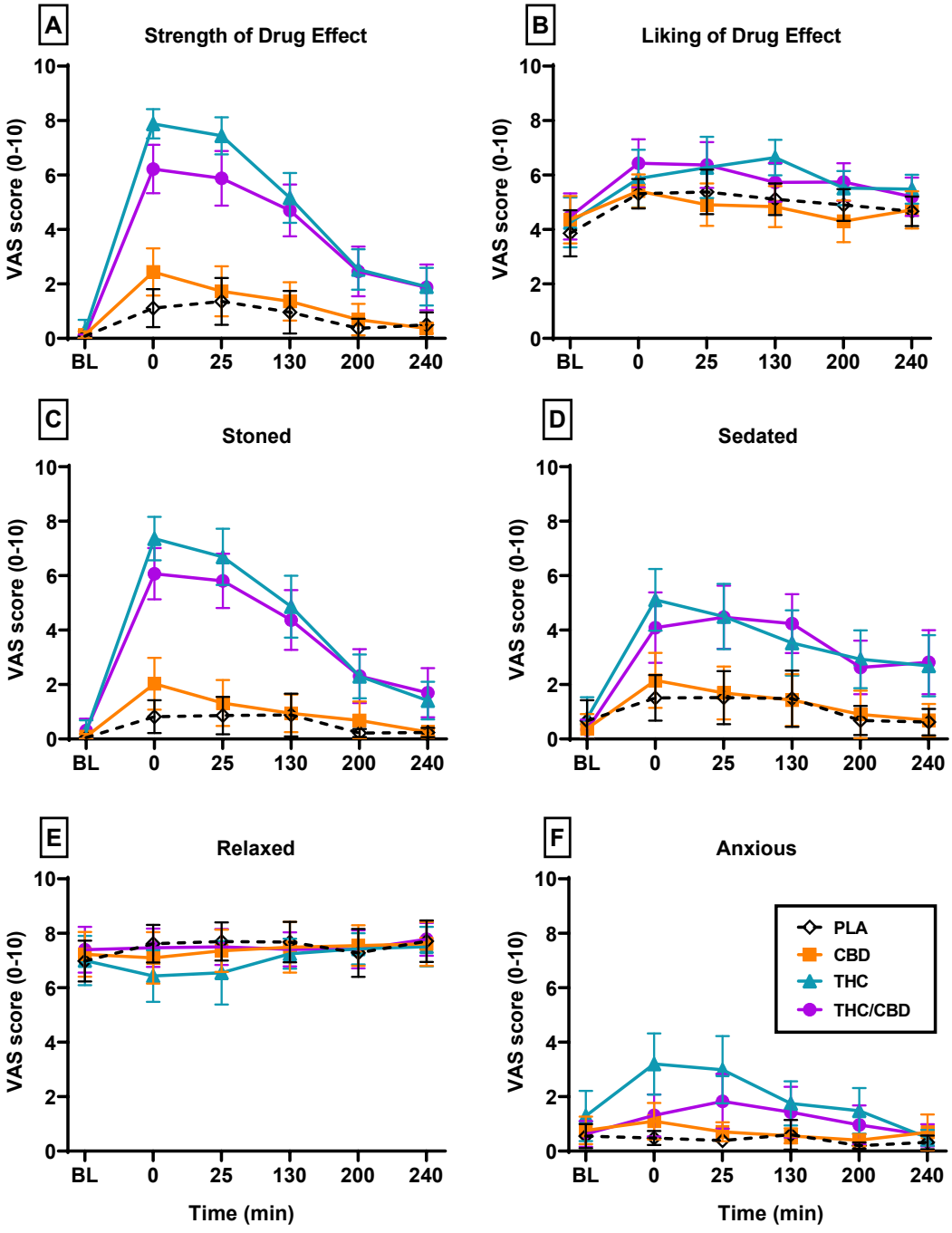
eFigure 3. Mean Ratings of Visual Analog Scale (VAS) Items “Strength of Drug Effect” (A), “Liking of Drug Effect” (B), “Stoned” (C), “Sedated” (D), “Relaxed” (E), and “Anxious” (F)



eFigure 3. Scores were assessed using 10 cm visual analog scales (VAS) as follows: Strength of Drug Effect (No Effect – Very Strong), (Liking of Drug Effect (Dislike Very Much – Like Very Much); Stoned (Not Stoned – Very Stoned), Sedated (Not Sedated – Very Sedated), Relaxed (Not Relaxed – Very Relaxed); Anxious (Not Anxious – Very Anxious). Error bars show 95% CIs. Time as shown on the x-axis indicates time elapsed since vaporization. BL = baseline.

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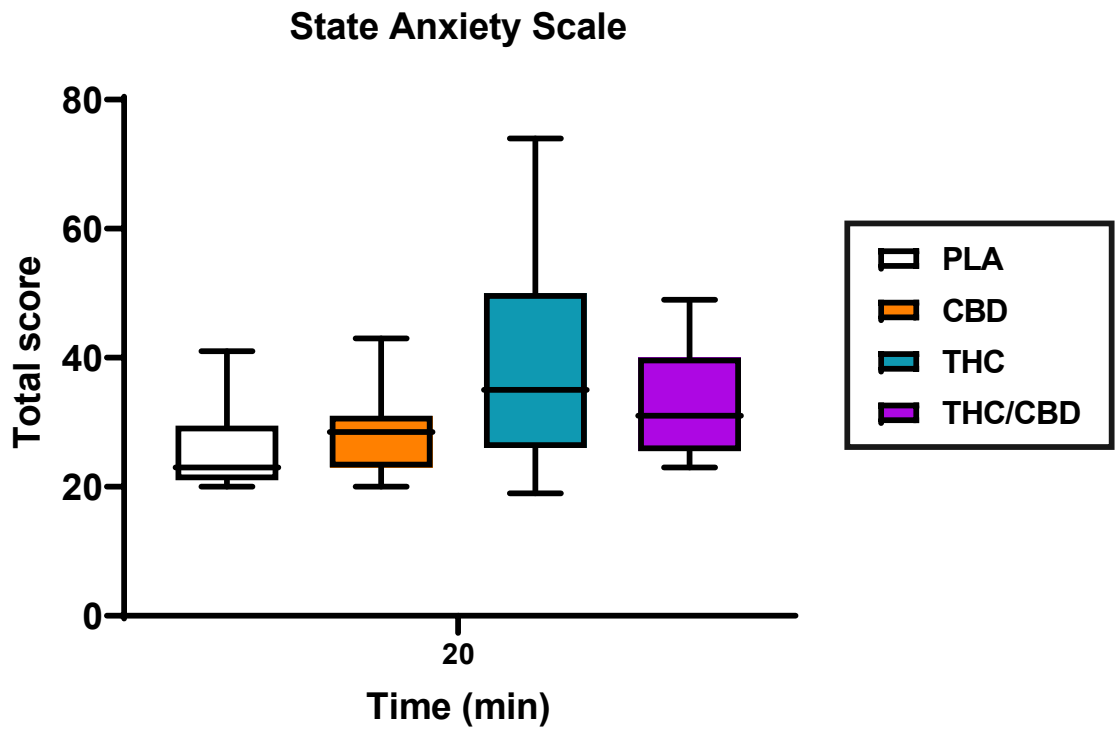
eFigure 4. State Anxiety Inventory (STAI-S) Scores



eFigure 4. A boxplot showing scores on the 'State' subscale of the State Trait Anxiety Inventory. The edges of the boxes represent the 25th and 75th quartile values. The horizontal line shows the median and the '+' shows the mean. If there are no outliers (Q1 − 1.5 × (Q3 − Q1) and Q3 + 1.5 × (Q3 − Q1)), the whiskers show minimum and maximum values. If there are outliers (shown as coloured symbols), the whiskers show the lowest and highest values that are not outliers. Time as shown on the x-axis indicates time elapsed since vaporization

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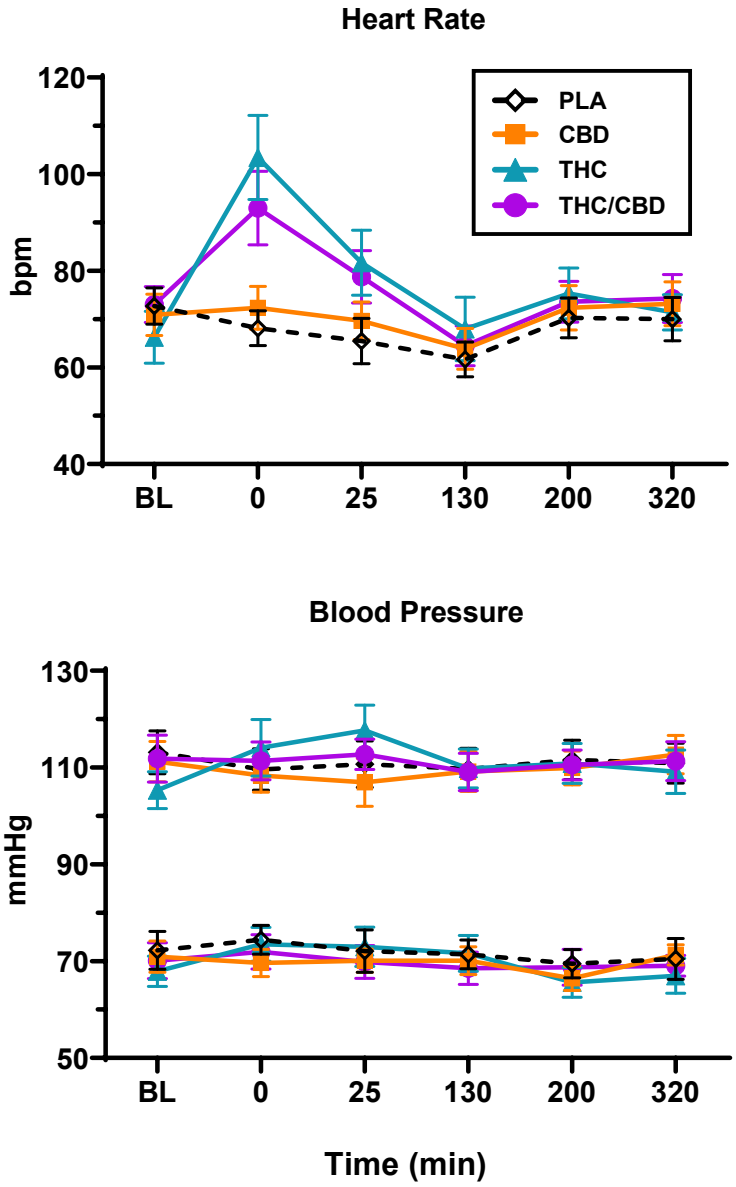
eFigure 5. Cardiovascular Measures



eFigure 5. Mean (95% CI) heart rate and blood pressure readings over time. The upper lines in the bottom graph show systolic blood pressure while the lower lines show diastolic blood pressure. Time as shown on the x-axis indicates time elapsed since vaporization. BL = baseline.

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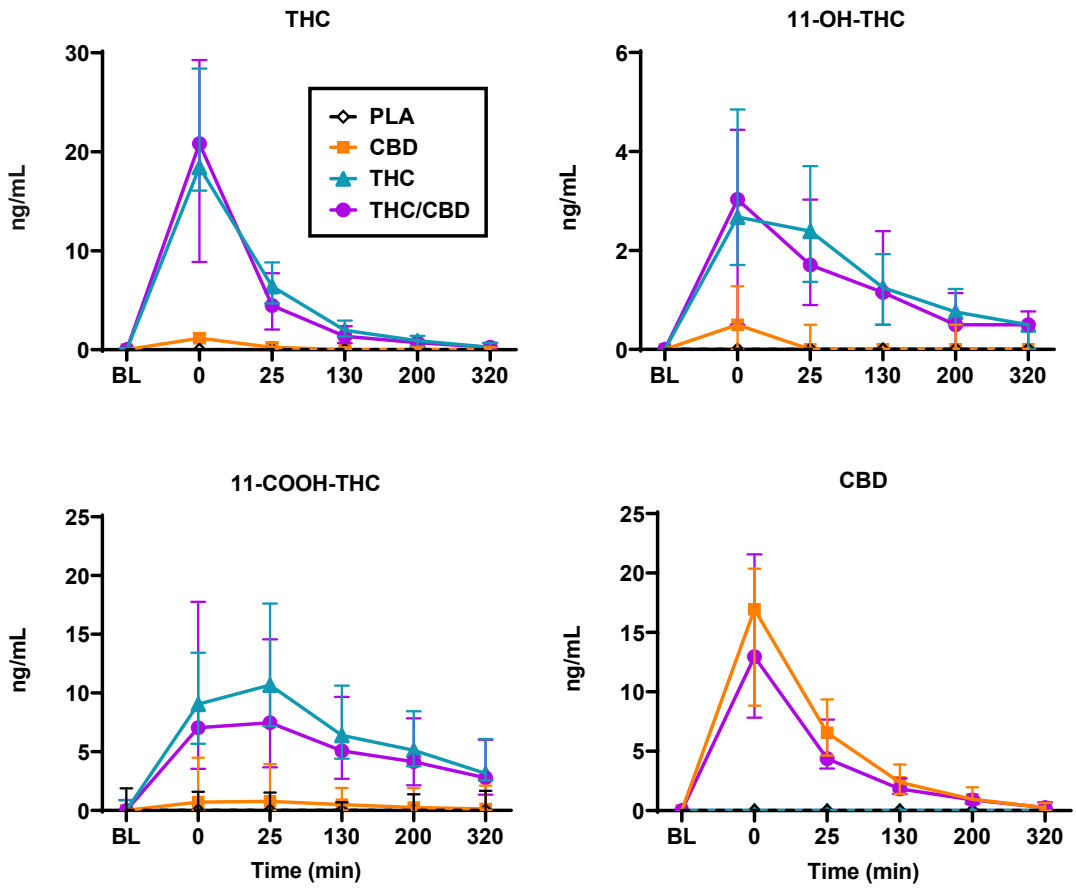
eFigure 6. Median Concentrations of THC, 11-OH-THC, 11-COOH-THC, and CBD Concentrations (ng/mL) in Plasma Over Time



eFigure 6. Error bars show IQR. Time as shown on the x-axis indicates time since vaporization. BL = baseline.

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