Appendix 1 to Silveira MM, Adams WK, Morena M, et al. Δ9-Tetrahydrocannabinol decreases willingness to exert cognitive effort in male rats. *J Psychiatry Neurosci* 2016.

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Supplementary Materials and Methods

Subjects

Subjects were 32 male, Long-Evans rats (Charles River Laboratories, St Constant, QC, Canada) weighing 275-300g at the start of the experiment. Two weeks following arrival, rats were food-restricted to 14g of rat chow per day and maintained at 85% of their free-feeding weight. Water was available *ad libitum.* All subjects were pair-housed in a climate-controlled colony room under a 12h reverse light-dark cycle (21° C; lights off at 8am). Behavioral testing took place 5 days per week. Housing and testing conditions were in accordance with the Canadian Council of Animal Care, and experimental protocols were approved by the UBC Animal Care Committee.

Behavioural Apparatus

Testing took place in 16 standard five-hole operant chambers, each of which was enclosed in a ventilated, sound-attenuating chamber (Med Associates Inc, Vermont). Chambers were fitted with an array composed of five equidistantly spaced response hole apertures. A stimulus light was located at the back of each hole, and nose-poke responses into these apertures were detected by vertical infrared beams. On the opposite wall, a retractable lever was installed on either side of a food magazine, and sucrose pellets (45 mg; Bioserv, New Jersey) were delivered to the magazine via an external pellet dispenser. The food magazine was also fitted with a tray light and infrared sensors to detect food collection. A house light illuminated the chamber. The operant

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chambers were operated by software written in Med-PC by CAW, running on an IBM-compatible computer.

The Rat Cognitive Effort Task (rCET) Training and Testing

Habituation to the operant chambers took place over two daily sessions, during which the chambers were turned on and sucrose pellets were placed in the response holes and food magazine. As per five-choice serial reaction time task (5-CSRTT) training, rats were trained to nose-poke an illuminated response hole within 5s to earn a reward. In subsequent sessions, subjects were trained to respond on two retractable levers at a fixed ratio 1 schedule for reward. Animals were then exposed to a forced-choice variant of the rCET (~70 sessions), wherein only a single lever extended per trial, before progressing to the standard free-choice program.

The design of the rCET has been described previously (Cocker et al., 2012) and a schematic of the task is provided (Supplementary Figure 1). Briefly, animals were tested 5 days per week in 30-minute sessions of no fixed trial limit. Prior to the onset of training, levers were permanently designated to initiate either low-effort/low reward (LR) or high-effort/high reward (HR) trials, and these designations were counterbalanced across subjects. Subjects began each trial by nose-poking in the illuminated food tray, thereby extending the levers. Pressing a lever would set the trial as LR or HR, at which point the levers would retract and a 5 s inter-trial interval (ITI) would be initiated. Following this ITI, one of the five stimulus lights would be briefly illuminated, with

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stimulus durations of 1.0 s for LR trials and 0.2 s for HR trials. Animals then had 5 s to nosepoke within the previously illuminated response hole (correct response) for reward. Subjects were rewarded with one sugar pellet for a correct LR trial and two sugar pellets for a correct HR trial, at which point the tray light would re-illuminate to signal the opportunity to start the next trial.

Trials went unrewarded for a number of reasons: if animals failed to make a lever response within 10 s (a choice omission); if animals nosepoked during the ITI (a premature response, a long-used behavioural measure of motor impulsivity; Robbins, 2002); if animals nosepoked in any aperture other than the illuminated one (an incorrect response); and if animals failed to nosepoke any aperture within 5 s of stimulus light illumination (a response omission). All of these unrewarded trials were associated with a 5s time-out punishment period during which the houselight was illuminated and new trials could not be initiated and thus reward could not be earned. Following the time-out, the tray light illuminated to signal that the rat could begin the next trial.

Behavioural Measures

Percent choice (rather than the absolute number of choices) was used to determine preference for lever/trial type, in order to minimize the influence of variation in the number of trials completed. Percent choice was calculated as follows: (number of choices of a particular lever / total number of choices) * 100. When baseline

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performance on the rCET was deemed statistically stable (no effect of session for choice, accuracy, and premature responding over the last three sessions when analyzed with a repeated-measures ANOVA; see "Data Analysis" below), the mean choice of the HR option was 69%. Animals were grouped as "workers" if they choice HR for >70% of trials (n = 17) and as "slackers" if they chose HR for ≤ 70% of trials (n = 14). One rat was removed from the study due to health complications and thus was not categorized as a worker or slacker, and two slacker rats suffered health complications shortly after classification and had to be removed from the study, so that n = 17 workers and n = 12 slackers remained. This subdivision was based on the mean split from the original rCET paper [2], where workers and slackers were categorized based on their preference for greater than or less than the average of 70% HR trials. To maintain consistency when discussing individual differences across studies, we held the worker/slacker distinction at 70% HR trials for this study. The following variables were analyzed separately for LR and HR trials: percent accuracy ((number of correct responses/ number of total responses made) * 100); percent response omissions ((number of trials omitted / number of correct, incorrect, and omitted trials) * 100); percent premature responses ((number of premature responses / total number of trials initiated) * 100); latency to choose between LR and HR levers (lever choice latency); latency to correctly nosepoke in the illuminated aperture (correct latency); latency to collect reward (collection latency). Failures to choose a lever at the beginning of the trial (choice omissions) and total number of trials completed were also

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analyzed.

Pharmacological Challenges

Once behavioural baseline was established, drugs were administered in the following order: the CB_1 receptor inverse agonist Rimonabant (0, 0.3, 1, 3 mg/kg), the CB_2 receptor antagonist AM 630 (0, 5 mg/kg), the fatty acid amide hydrolase inhibitor URB 597 (0, 0.1, 0.3, 1.0 mg/kg), delta-9-Tetrahydrocannabinol (dronabinol) (0, 0.3, 1, 2, 3 mg/kg), cannabidiol (CBD) (0, 5, 15 mg/kg), THC/CBD co-administration (0-0, 0-2, 2-0.2, 2-2 mg.kg) and the CB_1 synthetic receptor agonist WIN 55, 212-2 (0, 1, 2, 3 mg/kg). Rimonabant, AM 630 and URB697 were purchased from Cedarlane (Burlington, ON, Canada), THC and cannabidiol were purchased from THC Pharm GmbH (Frankfurt, Germany) and WIN-55, 212-2 was purchased from Tocris (Minneapolis, MN, USA). Rimonabant, THC, WIN 55212-2, and cannabidiol were dissolved in a mixture of ethanol, Tween80, and sterile saline (1:1:8) in a manner similar to that described previously [3]. Vehicle alone tests suggested that this solution did not affect rCET performance, and doses of ethanol 12-fold higher than what has been used here were previously shown to not affect rCET behavioural measures [2]. AM 630 was dissolved in a mixture of DMSO, Tween80, and sterile saline, while URB 597 was dissolved in 15% DMSO, a drop of Tween80, and sterile saline. All drugs were administered in a volume of 1 ml/kg via intraperitoneal injection. Animals were given a minimum of one week drug-free testing between compounds to minimize carry-over effects.

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All drugs were prepared fresh daily and administered according to a Latin-square within-subjects design. The three-day injection schedule started with a baseline session, followed by a vehicle or drug injection session, and then by a non-testing day. In the case of the THC, THC/CBD, and WIN55, 212-2 Latin squares, another baseline session was added between drugs sessions to exclude potential carryover effects. Injections for rimonabant, AM 630, THC, CBD, and WIN55, 212-2 were administered 30 minutes before testing; URB 597 injections were administered 45 minutes prior to testing. For the co-administration studies, THC and CBD were injected successively 30 minutes prior to testing, with order counterbalanced across subjects.

Tissue Extraction and Membrane Preparation

Following the last drug challenge, rats were housed and food restricted for three weeks. There is no evidence to suggest that any changes in intracellular signalling caused by acute injections should be evident after such an extended time period. In the unlikely event that brain biochemistry was permanently altered by this series of drug challenges, this should be evident across all rats, and should not significantly confound our analyses. Animals were sacrificed by rapid decapitation and the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) were dissected using brain matrix and tissue punches. Tissue samples were frozen immediately on dry ice and stored at -80°C. Tissue from eight workers and eight slackers were processed for CB_1 receptor radioligand binding. Membranes were collected from isolated brain regions by the

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homogenization of frozen tissue in 20 volumes of TME buffer (50 mM Tris–HCl, pH 7.4;1 mM EDTA and 3 mM MgCl2). Homogenates were centrifuged at 18,000g for 20 min and the resulting pellet, which contains a crude membrane fraction, was resuspended in 20 volumes of TME buffer. Protein concentrations were determined by the BCA method using a commercially available kit (Pierce Biotechnology, Rockville, IL, USA).

CB_1 Receptor Radioligand-Binding Assay

CB_1 receptor agonist binding parameters were determined via radioligand binding using a Multiscreen Filtration System with Durapore 1.2-□M filters in 96-well filter plates (Millipore, Bedford, MA). Incubations (total volume = 0.2 mL) were carried out using TME buffer containing 1 mg/mL bovine serum albumin (TME/BSA). Incubations (total volume = 0.2mL) were carried out using TME buffer containing 1mg/mL bovine serum albumin (TME/BSA). Membranes (10μg protein per incubate) were added in triplicate to wells containing 0.1, 0.25, 0.5, 1.0, 1.5 or 2.5nM [^{3}H]CP 55,940 (American Radiochemicals, St. Louis, MO USA), a cannabinoid CB_1 receptor agonist, and incubated for 60 min at room temperature on an orbital shaker. 10μM AM251 (Tocris Biosciences, Minneapolis MN, USA) was used to determine non-specific binding. B_{max} (maximal binding site density) and K_D (binding affinity) values were determined by nonlinear curve fitting of specific binding data to the single site binding equation using GraphPad Prism (San Diego, CA, USA). Samples from the top eight workers and eight slackers (highest and lowest HR choice, respectively) were processed for CB_1 receptor radioligand binding.

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Four NAc samples were not of adequate size, leaving 16 mPFC and 12 NAc samples available for analysis.

Data Analysis

All data were analyzed in SPSS (version 22.0; SPSS/IBM, Chicago, IL, USA). Variables expressed as a percentage were arcsine transformed to minimize the effects of an artificially imposed ceiling. Data were analyzed with a two-way repeated measures ANOVA with session (three levels: baseline sessions 1-3) or dose (vehicle, plus 2-5 drug doses depending on drug, see above) as within-subjects factors, and group (two levels: worker or slacker) was included as a between-subjects factor for all analyses. Groups proved stable across the experiment: at rCET baseline and all vehicle injections for rCET drug challenges, workers chose a significantly greater percentage of HR trials than slackers (Group: all Fs > 20.747, $p < .001$). Choice (two levels: LR or HR) was included as a within-subjects factor for most analyses, except for the cannabidiol/THC and WIN 55, 212-2 analyses, where the subjects reflect a subset (top workers and top slackers) of the entire sample. A criteria was set wherein a subject had to have selected a given trial type at least five times in order for behavioural measures associated with that lever to be analyzed (i.e. collect latencies, response omissions, choice latencies, premature responding). Given the top workers selected the HR option almost exclusively, behavioural measures for the LR trials were often unavailable. Thus for these

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experiments behavioural measures were analyzed for each trial type (LR or HR) separately. At the highest dose of THC, 11 rats (eight workers and three slackers) did not complete any trials, and so this dose was analyzed separately from the other three doses. Violations of sphericity were assessed using Mauchly's test, and when violated degrees of freedom were adjusted to more conservative values using the Greenhouse-Geisser correction. Corrected degrees of freedom are shown to the nearest integer. Any main effects or interactions of significance ($p < .05$) were further analyzed via *post hoc* one-way ANOVA or paired samples t-tests with a bonferonni correction for the number of comparisons made. CB_1 receptor binding data were analyzed with a one-way between-subjects ANOVA with Group (worker or slacker) as a fixed factor. Pearson correlations were conducted to assess how choice shifts induced by THC were related to CB_1 receptor properties. For these analyses, an "average" sensitivity score was calculated, in which the choice shift at each dose of THC relative to vehicle was calculated ((choice of HR option at *x* dose THC – choice of HR option at vehicle)/ choice of HR option at vehicle*100). These values were then averaged across the number of available doses to develop this composite score. Any *p*-values > .05 but < .09 were reported as a statistical trend.

Supplementary Results

Baseline and Rimonabant Administration

Choice behaviour, accuracy, and premature responses. Baseline behaviour on the rCET has been discussed in detail previously (see [2], and so will only be briefly

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discussed here. As per previous reports, animals chose the high-effort/high-reward (HR) trials more than low-effort/low reward (LR) trials following a vehicle injection (Vehicle only -Choice: $F(1, 27) = 44.378$, $p < .001$), with workers choosing a significantly higher proportion of HR trials relative to slackers (Vehicle only-Group: $F(1, 27) = 20.747$, $p < .001$). The CB_1 receptor inverse agonist rimonabant had no effect on animals' choice of HR or LR trials (Figure 1a; Dose- $F(3, 81) = .480$, NS).

Animals were more accurate on LR trials relative to HR trials (Vehicle only-Choice: $F(1, 25) = 76.885$, $p < .001$), and as per previous reports, workers and slackers performed the rCET equally well (Vehicle only- Group / Group x Choice: all Fs < 1.455, NS). Thus the distinct choice profile of both groups was not driven by the subjects' ability to perform the task. Rimonabant had no effect on animals' accuracy (Figure 1b; Dose / Dose x Group / Dose x Choice / Dose x Choice x Group: all Fs < 1.65, NS).

Premature responding was generally higher for HR versus LR trials (Vehicle only- Choice: $F(1, 25) = 4.480$, $p = .044$), and there was no difference in this measure between workers and slackers (Group/ Group x Choice: all Fs < 1.742, NS). Rimonabant did not influence animals' rates of premature responding (Supplementary Figure 2a; Dose / Dose x Group / Choice x Dose / Choice x Dose x Group: all Fs < 1.454, NS).

Other behavioural measures. In general subjects took a longer time to initiate LR trials (Vehicle only- Choice: $F(1, 25) = 4.526$, $p = .043$), and this did not differ between workers or slackers (Group / Group x Choice: all Fs < .903, NS) (supplementary Table

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2). Across groups and trial types, Rimonabant increased choice latencies (Dose: $F(3, 72) = 4.912$, $p = .004$; Dose x Group / Dose x Choice / Dose x Group x Choice: all Fs < 1.935, NS). Correct responses were faster for HR trials across both groups (Vehicle only- Choice: $F(1, 25) = 13.076$, $p = .001$; Group / Dose x Group: all Fs < 1.949, NS), and rimonabant increased these latencies for both trial types (Dose: $F(3, 72) = 2.833$, $p = .044$; Dose x Group / Dose x Choice / Dose x Choice x Group: all Fs < 1.892, NS). The time to collect reward was similar for LR and HR trials and did not differ between groups (Vehicle only- Choice / Choice x Group / Group: all Fs < 2.645, NS). Rimonabant did not affect collect latencies in either group (Dose / Dose x Group / Dose x Choice / Dose x Choice x Group: all Fs < 1.089, NS). All animals failed to respond to HR trials to a greater extent compared to LR trials (Vehicle only- Choice (1, 25) = 4.877, $p = .037$; Group / Choice x Group: all Fs < 1.944, NS). Rimonabant tended to increase response omissions across both trial types (Dose: $F(3, 72) = 2.642$, $p = .056$; Dose x Choice: $F <$ .265, NS), and this effect was true for both groups (Dose x Group / Dose x Choice x Group: all Fs< 1.196, NS). Workers and slackers did not differ in the number of trials completed or the number of choice (lever) omissions made (Vehicle only- Group: all Fs < .780, NS). Rimonabant dose-dependently decreased trials completed (Dose: $F(3, 81) = 16.912$, $p < .001$; Dose x Group: $F < 1.451$, NS) and increased choice omissions (Dose: $F(3, 81) = 4.491$, $p = .010$; Dose x Group: $F < .832$, NS).

AM 630 Administration

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Choice behaviour, accuracy, and premature responses. The CB_2 receptor antagonist AM 630 had no effect on choice, accuracy, or premature responding (Figure 1 c-d; Dose/ Dose x Group / Dose x Choice / Dose x Choice X Group: all *F*s < 2.572, NS).

Other behavioural measures. Across both groups, AM 630 did not affect latencies to make a choice of LR or HR trials (Dose/ Dose x Group / Dose x Choice x Group: all *F*s < .379, NS; Dose x Choice: $F(1, 21) = 4.360$, $p = .049$; LR trials or HR trials- Dose: all *Fs* < 1.590, NS) (supplementary Table 3). In general, the drug did not affect latencies to make a correct response or the latencies to collect reward for either trial type (Dose/ Dose x Group / Dose x Choice / Dose x Choice X group: all *F*s < 1.662, NS). There was a tendency for AM 630 to increase omissions on LR trials in slackers (Dose x Choice x Group: $F(1, 21) = 6.207$, $p = .021$; LR trials slackers only- Dose: $F(1, 11) = 3.681$, $p = .081$; Dose / Dose x Choice / Dose x Group: all *F*s < 1.888, NS), but otherwise the drug did not affect trials completed or choice omissions in either group (Dose / Dose x Group: all *F*s < 2.358, NS).

URB 597 Administration

Choice behaviour, accuracy, and premature responses. The FAAH inhibitor URB 597 had no effect on choice, accuracy, or premature responding (Figure 1e-f; Dose/ Dose x Group / Dose x Choice / Dose x Choice X Group: all *F*s < 1.857, NS).

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Other behavioural measures. URB 597 increased latencies to make a correct response across both trial types in workers (Dose x Group: $F(3, 66) = 3.556$, $p = .019$; Workers only- Dose: $F(3, 33) = 4.537$, $p = .009$; Slackers only- Dose: $F(3, 33) = 1.106$, NS; Dose / Dose x Choice / Dose x Choice x Group: all Fs < 1.580, NS), but generally had no effect on latencies to make a choice or on latencies to collect reward following a correct detection (Dose/ Dose x Group / Dose x Choice / Dose x Choice X group: all Fs < 1.371, NS) (supplementary Table 4). URB 597 did not affect the number of choice omissions made, did not affect omissions once a lever was chosen, and did not affect the number of trials completed (Dose/ Dose x Group / Dose x Choice / Dose x Choice X group: all Fs < 0.668, NS).

WIN 55, 212-2 Administration

Choice behaviour, accuracy, and premature responses. Regardless of group, the synthetic CB_1 receptor agonist WIN 55 212-2 (WIN) had no effect on trial choice or on accuracy (Figure 2g-h; Dose / Dose x Group: all Fs < 1.780, NS). There was a trend for the lowest dose of WIN to increase premature responding on LR, but not HR trials, across subjects (Supplementary Figure 2d; LR trials- Dose: $F(3, 18) = 2.954$, $p = .06$; Veh vs. 1.0 mg.kg: $F(1, 7) = 10.046$, $p = .048$; Veh vs. 2.0 mg.kg and Veh vs. 3.0 mg.kg: all Fs < 0.579, NS; HR trials- Dose / Dose x Group: all Fs < 0.576, NS).

Other behavioural measures. WIN increased latencies to initiate LR and HR trials (LR trials- $F(3, 21) = 4.241$, $p = .017$; Dose x Group: $F(3, 21) = 1.682$, NS; HR trials-

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Dose: $F(3, 45) = 2.76$, $p = .053$; Dose x Group: $F(4, 35) = 0.969$, NS), but otherwise did not affect correct response latencies or latencies to collect reward (all Fs < 2.914, NS) (supplementary Table 5). The highest dose of WIN increased choice omissions (Dose: $F(3, 54) = 8.016$, $p < .001$; Dose x Group: $F(3, 54) = 0.957$, NS; Veh vs. 1.0 mg.kg: $F(1, 19) = 1.181$, NS; Veh vs. 2.0 mg.kg: $F(1, 19) = 5.602$, $p = .087$; Veh vs. 3.0 mg.kg: $F(1, 19) = 27.500$, $p < 001$), and the highest dose decreased the number of trials completed (Dose: $F(2, 32) = 19.094$, $p < .001$; Dose x Group: $F(2, 32) = 0.937$, NS; Veh vs. 3.0 mg.kg: $F(1, 19) = 23.707$, $p < .001$; Veh vs 1.0 mg.kg and Veh vs 2.0 mg.kg: all Fs < 0.922, NS).

THC Administration

Choice behaviour, accuracy, and premature responses. At the 3 mg.kg dose of THC, 11 rats (eight workers and three slackers) failed to initiate any trials, and so this dose was analyzed separately from the first four doses, unless otherwise specified. Across both groups, THC decreased choice of HR trials at all but the lowest dose tested (Figure 2a; Dose: $F(3, 75) = 8.610$, $p < .001$; Veh vs. 0.3 mg.kg- $F(1, 28) = 5.171$, $p = .093$; Veh vs. 1.0 mg.kg- $F(1, 28) = 6.508$, $p = .048$; Veh vs. 2.0 mg.kg- $F(1, 26) = 20.241$ $p < .001$; Dose x Group: $F(3, 75) = 1.780$, NS; Veh vs. 3.0 mg.kg- Dose: $F(1, 16) = 11.769$, $p = .004$; Dose X Group: $F(1, 16) = .011$, NS). This reduction in choice of HR trials remained significant even when the non-responders were removed from the analysis (Dose: $F(2, 64) = 5.945$, $p = .007$; Dose x Group: $F(2, 64) = .348$, NS). This shift

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in choice was not due to an impaired ability to complete HR trials, as accuracy was not affected following the first three doses of THC (Figure 2b; Dose/ Dose x Group / Dose x Choice / Dose x Choice X group: all *F*s < 1.205, NS), and the trending attentional impairment at the 3 mg.kg dose was limited to workers only (Dose x Group: $F(1, 11) = 4.783$, $p = 0.051$; Dose / Dose x Choice /Dose x Choice x Group: all *F*s < 3.279, NS; Workers only- Dose: $F(1, 4) = 14.848$, $p = .018$; Slackers only- Dose / Dose x Group: all *F*s < .402, NS). Subsequent analysis revealed that this attentional impairment in workers was driven by reduced accuracy on LR (10.53% decline) relative to HR trials (2.47% decline) at the 3 mg.kg dose. Thus, across both groups THC decreased the willingness to exert cognitive effort for HR trials, even though the capacity to complete these trials was generally intact. THC administration did not affect rates of premature responding for either trial type (Supplementary Figure 2e; Dose / Dose x Choice: all *F*s < 1.248, NS; Veh vs. 3.0 mg.kg:- Dose / Dose x Choice: all *F*s < .318, NS) nor did the drug differentially affect either group on this measure (Dose x Group / Dose x Group x Choice: all *F*s < 1.050, NS; Veh vs. 3.0 mg.kg- Dose x Group / Dose x Group x Choice: all *F*s < .409, NS).

Other behavioural measures. Across both groups, THC decreased the total number of trials completed at the 2 mg.kg and 3 mg.kg doses (Dose: $F(2, 41) = 11.481$, $p < .001$; Dose x Group: $F(2 , 41) = 0.257$, NS; Veh vs. 0.3 mg.kg- Dose: $F(1, 28) = 0.907$, NS; Veh vs. 1.0 mg.kg- Dose: $F(1, 28) = .032$, NS; Veh vs. 2.0 mg.kg- Dose: $F(1, 28) = 13.262$, $p = .003$; Veh vs. 3 mg.kg- Dose: $F(1, 27) = 51.916$, $p < .001$; Dose x

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Group: $F(1, 27) = 0.980$, NS) (supplementary Table 6). At the high THC doses this was also accompanied by an increase in choice omissions (Dose: $F(2, 36) = 9.951$, $p = .001$; Dose x Group: $F(2 , 36) = 0.745$, NS; Veh vs. 0.3 mg.kg- Dose: $F(1, 28) = 0.261$, NS; Veh vs. 1.0 mg.kg- Dose: $F(1, 28) = .03$, NS; Veh vs. 2.0 mg.kg- Dose: $F(1, 28) = 12.022$, $p = .006$; Veh vs. 3 mg.kg- Dose: $F(1. 27) = 7.995$, $p = .009$; Dose x Group: $F(1, 27) = 0.071$, NS), and by a modest increase in response omissions once a trial was initiated (Dose: $F(2, 32) = 5.507$, $p = .012$; Dose x Group / Dose x Choice / Dose X Group X Choice: all Fs < .0882, NS; Veh vs. 0.3 mg.kg- Dose: $F(1, 22) = 0.805$, NS; Veh vs. 1.0 mg.kg- Dose: $F(1, 22) = 6.216$, $p = .063$; Veh vs. 2.0 mg.kg- Dose: $F(1, 20) = 6.589$, $p = .054$; Veh vs. 3.0 mg.kg- Dose: $F(1, 12) = 6.368$, $p = .027$; Dose x Choice / Dose x Group / Dose x Choice x Group: all Fs < 1.539, NS). This behavioural profile may suggest that THC decreased motivation to engage in the task at higher doses. This seems unlikely, however, given that latencies to collect reward were not affected at any dose (Dose / Dose x Group / Dose x Choice / Dose x Group x Choice: All Fs < 1.313, NS), and this measure has long been used as an index of motivation for food reward in operant testing. Latencies to make a trial choice were unchanged (all Fs < 3.426, NS), and latencies to make a correct response were only affected at the highest dose of THC (Dose / Dose x Choice / Dose x Choice X Group: all Fs < 3.109, NS; Veh vs. 3 mg.kg- Dose: $F(1 ,11) = 33.361$, $p < .001$; Dose x Group / Dose x Choice / Dose x Group / Choice: all Fs < 3.746, NS). When all behavioural measures are considered together, THC appeared to make subjects less likely to initiate rCET trials (as evidenced by

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increased choice omissions), and when trials were initiated a shift to the easier, LR trials occurred. However, once a trial was started rats were able to complete it successfully (as evidenced by the generally unimpaired accuracy, correct latency, and collect latency measures).

Cannabidiol Administration

Choice behaviour, accuracy, and premature responses. Cannabidiol (CBD) in isolation had no effect on choice, accuracy, or on premature responding (Figure 2c-d; Dose/ Dose x Group / Dose x Choice / Dose x Choice X Group: all *F*s < 2.997, NS).

Other behavioural measures. Across all subjects and trial types, CBD had no effect on any latency measure (Dose/ Dose x Group / Dose x Choice / Dose x Choice X Group: all *F*s < 3.275, NS) (supplementary Table 7). CBD generally did not affect choice omissions, response omissions, or the number of trials completed (Dose/ Dose x Group / Dose x Choice / Dose x Choice X Group: all *F*s < 2.938, NS).

THC /CBD Administration

Choice behaviour, accuracy, and premature responses. Nine workers and nine slackers were initially selected to receive 2mg.kg THC alone and in combination with varying ratios of CBD. Of these, one slacker failed to initiate any trials on the rCET following an injection, and so was removed from this analysis. As described previously, administration of 2 mg.kg THC decreased choice of HR trials across groups (Dose: F(1,

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15) = 14.19, p = .002; Dose x Group: F(1,15) = .303, NS). However, co-administration of THC/CBD had distinct effects on workers and slackers, as indicated by a significant Dose x Group interaction (F(3, 45) = 3.90, p = .015; Dose: F(3, 45) = 6.25, p = .001; Figure 2e). In workers, THC still decreased choice of HR trials when administered in combination with CBD at a 10:1 or 1:1 ratio (Workers only-Dose: F(3, 24) = 6.53, p = .002; Veh vs. 10:1 THC/CBD- F(1, 8) = 9.56, p = .045; Veh vs. 1:1 THC/CBD- F(1, 8) = 8.93, p = .051). Although the main effect of dose in slackers was only a trend (Slackers only- Dose: F(3, 21) = 2.84, p = .063), subsequent analysis revealed the effects of THC were attenuated in slackers when administered with CBD at a 1:1, but not 10:1, ratio (Veh vs. 10:1 THC/CBD- F(1, 7) = 11.39, p = .036; Veh vs. 1:1 THC/CBD- F(1, 7) = .023, p = 1.0). While this analysis is compromised by a smaller n and thus lower power, it suggests that CBD may partially ameliorate THC-induced decision making impairments in select individuals. While THC previously had no effect on accuracy when administered alone (see above), here THC administered alone or in combination with CBD impaired accuracy for HR trials (Figure 2f; HR trials- Dose: F(3, 32) = 4.91, p = .012; Veh vs. THC- F(1, 16) = 7.60, p = .042; Veh vs. 10:1 THC/CBD- F(1, 16) = 12.59, p = .010; Veh vs. 1:1 THC/CBD- F(1, 16) = 31.54, p < .001; Dose x Group: F(3, 32) = 0.13, NS). This might suggest that attentional impairments associated with THC may manifest in some individuals, but that these effects are not robust when considered amongst a larger sample of individuals. Indeed, an analysis of HR trials from the original THC Latin square revealed a trending decline in accuracy among these subjects (Dose: $F(2, 26) = 3.528$, p

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= .051). In contrast, THC alone or in combination with CBD had no effect on premature responding for LR or HR trials (Supplementary Figure 3g; LR trials- Dose / Dose x Group: all *F*s < 1.678, NS; HR trials- Dose / Dose x Group: all *F*s < 2.213, NS).

Other behavioural measures. THC alone or in combination with CBD decreased the number of trials completed (Dose: *F*(3, 45) = 6.083, p = .001; Dose x Group: *F*(3, 45) = 0.378, NS; Veh vs. THC- *F*(1, 16) = 8.47, *p* = .030; Veh vs. 10:1 THC/CBD- *F*(1, 16) = 17.58, *p* < .001; Veh vs. 1:1 THC/CBD- *F*(1, 16) = 15.52, *p* < .005) and increased choice omissions across groups (Dose: *F*(3, 45) = 4.664, p = .006; Dose x Group: *F*(3, 45) = 0.639, NS; Veh vs. THC- *F*(1, 16) = 11.49, *p* = .012; Veh vs. 10:1 THC/CBD- *F*(1, 16) = 9.381, *p* = .021; Veh vs. 1:1 THC/CBD- *F*(1, 16) = 15.768, *p* < .001). Similarly, THC in combination with CBD increased the number of response omissions for HR trials (HR trials- Dose: *F*(3, 45) = 4.388, *p* = .009; Dose x Group: *F*(3, 45) = 0.188, NS; Veh vs. THC- *F*(1, 16) = 6.185, *p* = .072; Veh vs. 10:1 THC/CBD- *F*(1, 16) = 6.325, *p* = .070; Veh vs. 1:1 THC/CBD- *F*(1, 16) = 10.452, *p* = .015; LR trials- Dose / Dose x Group: all *F*s < 0.679, NS).

In general, THC/CBD challenges appeared to increase latencies associated with LR, but not HR, trials, but these differences did were not significant following correction for multiple comparisons (Choice latency: LR trials- Dose: *F*(2, 12) = 5.512, *p* = .029; Dose x Group: *F*(2, 12) = 2.796, NS; Veh vs. THC- *F*(1, 9) = 0.103, NS; Veh vs. 10:1 THC/CBD- *F*(1, 9) = 0.089, NS; Veh vs. 1:1 THC/CBD- *F*(1, 9) = 5.831, *p* = .12; HR trials- Dose / Dose x Group: all *F*s < 1.5256, NS; Collect latency: LR trials- Dose: *F*(2,

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11) = 6.02, $p = .027$; Dose x Group: $F(2, 11) = 3.018$, NS; Veh vs. THC- $F(1, 9) = 0.563$, NS; Veh vs. 10:1 THC/CBD- $F(1, 9) = 6.955$, $p = .081$; Veh vs. 1:1 THC/CBD- $F(1, 9) = 4.735$, $p = .174$; HR trials- Dose / Dose x Group: all Fs < 2.459, NS). Latencies to make a correct response were not affected (LR trials- Dose / Dose x Group: all Fs < 2.043, NS; HR trials- Dose / Dose x Group: all Fs < 2.602, NS). Administration of CBD did not potentiate the behavioural effects of THC alone on any measure (THC vs. 10:1 THC/CBD- Dose: all Fs < 1.755, NS; THC vs. 1:1 THC/CBD- Dose: all Fs < 2.769, NS) (supplementary Table 8).

CB_1 Receptor Binding

CB_1 receptor *Bmax* and and K_d values for the mPFC and NAc are listed in Supplementary Table 9. Workers and slackers did not differ in any measure of receptor binding (all Fs < .743, NS). However, the choice shift induced by THC was correlated with mPFC *Bmax* values, $r(15) = -.567$, $p = .022$, such that greater sensitivity to THC's effects on choice across the four doses was associated with higher CB_1 receptor density in this region (Figure 4). mPFC K_d values ($r(15) = .04$, NS) and binding parameters from NAc samples (B_{max}: $r(11) = .25$, NS; K_d: $r(11) = .18$, NS) were not related to THC-induced changes in behaviour.

Supplementary Tables

Table 1. Doses of cannabinoid drugs

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Cannabinoid Type (In order of administration)	**Drug Name**	**Dose (mg/kg)**
CB_1 inverse agonist	Rimonabant	0, 0.3, 1, 3
CB_2 antagonist	AM 630	0, 5
Fatty acid amide hydrolase (FAAH) inhibitor	URB 597	0, 0.1, 0.3, 1.0
CB_1 partial agonist	□⁹-tetrahydrocannabinol (THC)	0, 0.3, 1, 2, 3
Unknown	Cannabidiol (CBD)	0, 5, 15
	THC/CBD Co-administration	vehicle-vehicle vehicle- 2 THC 2 THC – 0.2 CBD (10:1) 2 THC- 2 CBD (1:1)
Synthetic CB_1 full agonist	WIN 55, 212-2	0, 1, 2, 3

Table 2. Behavioural rCET measures following administration of Rimonabant

Measure	**Dose**	**Workers** *(M)*	**Workers** *(SEM)*	**Slackers** *(M)*	**Slackers** *(SEM)*
Trials	Vehicle	**134.88**	6.35	**142.42**	4.64
	0.3	**134.88**	5.57	**129.25**	7.59

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	1	**125.53**	6.12	**127.33**	8.45
	3	**116.82**	6.89	**116.67**	9.41
Choice omissions	Vehicle	**3.06**	2.04	**1.08**	0.60
	0.3	**3.12**	1.42	**3.25**	1.26
	1	**6.53**	2.28	**4.17**	1.89
	3	**5.00**	0.91	**5.17**	1.75
Easy choice latency (s)	Vehicle	**3.33**	0.40	**3.38**	0.32
	0.3	**3.38**	0.37	**3.81**	0.35
	1	**3.59**	0.32	**3.57**	0.38
	3	**3.47**	0.22	**3.73**	0.31
Hard choice latency (s)	Vehicle	**2.94**	0.15	**2.59**	0.20
	0.3	**3.03**	0.22	**2.56**	0.18
	1	**3.20**	0.20	**2.61**	0.23
	3	**3.28**	0.15	**2.87**	0.24
Easy correct latency (s)	Vehicle	**0.48**	0.02	**0.50**	0.02
	0.3	**0.48**	0.03	**0.51**	0.02
	1	**0.49**	0.02	**0.54**	0.02
	3	**0.53**	0.03	**0.57**	0.02
Hard correct latency (s)	Vehicle	**0.40**	0.01	**0.45**	0.04
	0.3	**0.41**	0.02	**0.47**	0.03
	1	**0.44**	0.02	**0.47**	0.02
	3	**0.44**	0.02	**0.45**	0.03
Easy collect latency (s)	Vehicle	**1.70**	0.21	**1.55**	0.08
	0.3	**1.85**	0.32	**1.63**	0.10
	1	**1.57**	0.16	**1.48**	0.08
	3	**1.78**	0.24	**1.74**	0.10
Hard collect latency (s)	Vehicle	**1.31**	0.05	**1.49**	0.12
	0.3	**1.30**	0.05	**1.45**	0.10
	1	**1.38**	0.09	**1.48**	0.11
	3	**1.31**	0.06	**1.38**	0.10
Easy response	Vehicle	**1.85**	0.88	**1.74**	0.79

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omissions (%)					
	0.3	**4.90**	1.82	**1.99**	0.59
	1	**3.09**	1.07	**1.20**	0.48
	3	**3.60**	1.90	**2.83**	0.83
Hard response omissions (%)	Vehicle	**2.91**	0.74	**1.85**	0.60
	0.3	**5.28**	1.33	**3.09**	0.97
	1	**5.39**	1.10	**3.17**	1.08
	3	**4.76**	0.90	**4.46**	0.96

Table 3. Behavioural rCET measures following administration of AM 630

Measure	Dose	Workers *(M)*	Workers *(SEM)*	Slackers *(M)*	Slackers *(SEM)*
Trials	Vehicle	**136.18**	5.28	**132.25**	8.59
	5.00	**132.18**	5.89	**127.58**	7.93
Choice omissions	Vehicle	**3.88**	1.54	**3.58**	1.18
	5.00	**4.24**	1.89	**5.58**	2.04
Easy choice latency (s)	Vehicle	**3.48**	0.37	**3.76**	0.41
	5.00	**3.46**	0.38	**3.57**	0.37
Hard choice latency (s)	Vehicle	**3.16**	0.21	**2.58**	0.23
	5.00	**3.22**	0.19	**2.92**	0.25
Easy correct latency (s)	Vehicle	**0.49**	0.02	**0.50**	0.03
	5.00	**0.50**	0.04	**0.52**	0.03
Hard correct latency (s)	Vehicle	**0.40**	0.01	**0.47**	0.03
	5.00	**0.44**	0.02	**0.46**	0.02
Easy collect latency (s)	Vehicle	**1.37**	0.08	**1.90**	0.17
	5.00	**1.88**	0.43	**1.92**	0.29
Hard collect latency (s)	Vehicle	**1.28**	0.05	**1.37**	0.12
	5.00	**1.41**	0.12	**1.46**	0.11
Easy response	Vehicle	**5.26**	2.53	**0.74**	0.37

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omissions (%)					
	5.00	**3.21**	2.00	**1.91**	0.66
Hard response omissions (%)	Vehicle	**2.18**	0.66	**2.34**	0.43
	5.00	**3.75**	0.92	**2.48**	0.75

Table 4. Behavioural rCET measures following administration of URB 597

Measure	Dose	Workers (M)	Workers (SEM)	Slackers (M)	Slackers (SEM)
Trials	Vehicle	**137.94**	6.35	**142.92**	5.62
	0.1	**141.06**	5.65	**146.08**	5.81
	0.3	**142.06**	5.39	**145.67**	5.85
	1	**139.29**	6.13	**143.50**	5.75
Choice omissions	Vehicle	**2.41**	1.26	**1.50**	0.61
	0.1	**3.06**	2.20	**1.17**	0.42
	0.3	**2.71**	1.73	**1.92**	1.08
	1	**2.76**	1.54	**1.83**	0.94
Easy choice latency (s)	Vehicle	**2.98**	0.28	**3.46**	0.33
	0.1	**3.04**	0.21	**3.39**	0.38
	0.3	**2.96**	0.21	**3.30**	0.39
	1	**3.08**	0.21	**3.12**	0.36
Hard choice latency (s)	Vehicle	**2.88**	0.14	**2.66**	0.17
	0.1	**2.75**	0.17	**2.67**	0.20
	0.3	**2.70**	0.14	**2.51**	0.20

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	1	**2.95**	0.12	**2.53**	0.18
Easy correct latency (s)	Vehicle	**0.45**	0.03	**0.50**	0.02
	0.1	**0.48**	0.03	**0.48**	0.01
	0.3	**0.47**	0.03	**0.50**	0.02
	1	**0.50**	0.04	**0.50**	0.02
Hard correct latency (s)	Vehicle	**0.40**	0.02	**0.44**	0.02
	0.1	**0.43**	0.02	**0.42**	0.02
	0.3	**0.41**	0.02	**0.41**	0.02
	1	**0.41**	0.02	**0.43**	0.02
Easy collect latency (s)	Vehicle	**1.43**	0.09	**1.76**	0.12
	0.1	**1.67**	0.28	**1.69**	0.13
	0.3	**1.60**	0.19	**1.56**	0.11
	1	**1.45**	0.07	**1.58**	0.11
Hard collect latency (s)	Vehicle	**1.35**	0.08	**1.43**	0.12
	0.1	**1.30**	0.06	**1.42**	0.14
	0.3	**1.30**	0.07	**1.43**	0.12
	1	**1.40**	0.12	**1.45**	0.13
Easy response omissions (%)	Vehicle	**3.16**	1.94	**1.16**	0.67
	0.1	**5.48**	3.00	**0.54**	0.21
	0.3	**3.31**	1.86	**1.43**	0.46
	1	**1.62**	0.81	**1.14**	0.35
Hard response omissions (%)	Vehicle	**3.64**	1.80	**1.29**	0.38
	0.1	**2.41**	0.76	**1.79**	0.40
	0.3	**2.40**	0.97	**0.76**	0.37
	1	**2.30**	0.65	**1.68**	0.42

Table 5. Behavioural rCET measures following administration of WIN 55, 212-2

Measure	Dose	Workers (M)	Workers (SEM)	Slackers (M)	Slackers (SEM)
Trials	Vehicle	**134.40**	8.48	**146.90**	11.80

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	1	**141.60**	7.21	**148.80**	6.53
	2	**142.70**	8.38	**118.90**	18.25
	3	**70.00**	11.37	**60.00**	17.58
Choice omissions	Vehicle	**5.60**	2.57	**3.40**	1.56
	1	**5.30**	2.01	**9.30**	3.12
	2	**10.50**	4.38	**6.30**	1.55
	3	**18.70**	3.15	**15.30**	3.31
Easy choice latency (s)	Vehicle	**4.70**	0.67	**2.73**	0.53
	1	**3.12**	0.13	**2.90**	0.34
	2	**3.66**	0.04	**2.49**	0.32
	3	**4.81**	0.95	**3.63**	0.23
Hard choice latency (s)	Vehicle	**3.21**	0.22	**2.27**	0.23
	1	**3.03**	0.23	**2.56**	0.18
	2	**3.50**	0.22	**2.53**	0.25
	3	**3.50**	0.28	**3.08**	0.43
Easy correct latency (s)	Vehicle	**0.42**	0.05	**0.45**	0.03
	1	**0.52**	0.10	**0.48**	0.03
	2	**0.73**	0.30	**0.49**	0.05
	3	**0.76**	0.29	**0.50**	0.06
Hard correct latency (s)	Vehicle	**0.40**	0.02	**0.38**	0.03
	1	**0.41**	0.03	**0.43**	0.02
	2	**0.45**	0.04	**0.40**	0.05
	3	**0.45**	0.03	**0.53**	0.10
Easy collect latency (s)	Vehicle	**1.32**	0.07	**2.26**	0.80
	1	**1.25**	0.06	**1.59**	0.15
	2	**1.24**	0.09	**3.46**	1.51
	3	**1.49**	0.09	**1.69**	0.12
Hard collect latency (s)	Vehicle	**1.91**	0.52	**1.49**	0.18
	1	**2.28**	0.63	**1.49**	0.16
	2	**1.37**	0.05	**1.45**	0.15

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	3	**1.57**	0.19	**1.60**	0.23

Table 6. Behavioural rCET measures following administration of THC

Measure	Dose	Workers *(M)*	Workers *(SEM)*	Slackers *(M)*	Slackers *(SEM)*
Trials	Vehicle	**141.47**	5.85	**139.83**	9.59
	0.3	**141.24**	5.74	**149.75**	6.74
	1	**138.41**	5.29	**142.17**	6.96
	2	**101.12**	10.13	**111.58**	16.08
	3	**47.41**	13.23	**68.50**	16.15
Choice omissions	Vehicle	**3.47**	1.77	**3.08**	1.25
	0.3	**3.65**	2.12	**2.00**	0.77
	1	**4.59**	2.04	**1.83**	0.55
	2	**11.12**	2.40	**6.92**	2.48
	3	**11.53**	2.75	**9.75**	3.52
Easy choice latency (s)	Vehicle	**2.94**	0.25	**3.25**	0.37
	0.3	**2.84**	0.20	**2.98**	0.27
	1	**3.10**	0.25	**2.99**	0.32
	2	**3.64**	0.36	**3.15**	0.43
	3	**4.23**	0.77	**3.03**	0.34
Hard choice latency (s)	Vehicle	**2.77**	0.16	**2.42**	0.21
	0.3	**2.69**	0.16	**2.35**	0.21
	1	**2.64**	0.14	**2.39**	0.19
	2	**2.85**	0.20	**2.81**	0.30
	3	**2.92**	0.24	**3.04**	0.20
Easy correct latency (s)	Vehicle	**0.44**	0.03	**0.46**	0.02
	0.3	**0.48**	0.06	**0.51**	0.03
	1	**0.47**	0.03	**0.51**	0.02
	2	**0.51**	0.05	**0.62**	0.06
	3	**0.48**	0.05	**0.64**	0.05
Hard correct latency (s)	Vehicle	**0.43**	0.03	**0.43**	0.03
	0.3	**0.38**	0.01	**0.43**	0.02

Appendix 1 to Silveira MM, Adams WK, Morena M, et al. Δ9-Tetrahydrocannabinol decreases willingness to exert cognitive effort in male rats. *J Psychiatry Neurosci* 2016.

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	1	**0.45**	0.02	**0.43**	0.02
	2	**0.51**	0.03	**0.43**	0.02
	3	**0.48**	0.02	**0.49**	0.04
Easy collect latency (s)	Vehicle	**1.50**	0.11	**1.87**	0.36
	0.3	**1.77**	0.40	**1.53**	0.09
	1	**2.04**	0.63	**1.51**	0.08
	2	**1.52**	0.11	**1.66**	0.15
	3	**1.63**	0.17	**1.67**	0.16
Hard collect latency (s)	Vehicle	**1.32**	0.05	**1.39**	0.12
	0.3	**1.28**	0.07	**1.38**	0.14
	1	**1.22**	0.04	**1.42**	0.09
	2	**1.36**	0.05	**1.76**	0.27
	3	**1.48**	0.06	**1.54**	0.14
Easy response omissions (%)	Vehicle	**1.42**	0.88	**3.08**	1.42
	0.3	**1.03**	0.56	**1.35**	0.55
	1	**5.37**	2.07	**3.74**	1.25
	2	**5.74**	2.02	**6.56**	4.04
	3	**7.95**	1.72	**23.30**	10.40
Hard response omissions (%)	Vehicle	**1.52**	0.16	**2.42**	0.13
	0.3	**2.05**	0.16	**2.35**	0.13
	1	**3.85**	0.14	**2.39**	0.11
	2	**7.54**	0.20	**2.81**	0.17
	3	**6.89**	0.24	**3.04**	0.15

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Table 7. Behavioural rCET measures following administration of cannabidiol

Measure	Dose	Workers *(M)*	Workers *(SEM)*	Slackers *(M)*	Slackers *(SEM)*
Trials	Vehicle	**136.24**	6.17	**136.42**	7.86
	5	**127.24**	7.16	**141.58**	8.64
	15	**125.71**	5.86	**137.42**	7.34
Choice omissions	Vehicle	**3.41**	1.83	**2.83**	1.02
	5	**2.18**	1.00	**2.92**	1.10
	15	**3.53**	1.32	**2.92**	1.06
Easy choice latency (s)	Vehicle	**3.43**	0.39	**3.34**	0.36
	5	**2.76**	0.29	**3.22**	0.35
	15	**3.26**	0.60	**3.43**	0.38
Hard choice latency (s)	Vehicle	**2.97**	0.18	**2.76**	0.31
	5	**2.85**	0.23	**2.54**	0.24
	15	**3.07**	0.17	**2.64**	0.27
Easy correct latency (s)	Vehicle	**0.45**	0.03	**0.48**	0.02
	5	**0.44**	0.02	**0.47**	0.02
	15	**0.47**	0.02	**0.49**	0.02
Hard correct latency (s)	Vehicle	**0.42**	0.02	**0.43**	0.03
	5	**0.40**	0.02	**0.41**	0.02

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	15	**0.42**	0.02	**0.43**	0.02
Easy collect latency (s)	Vehicle	**1.77**	0.19	**1.56**	0.10
	5	**1.67**	0.28	**1.57**	0.09
	15	**1.74**	0.27	**1.57**	0.11
Hard collect latency (s)	Vehicle	**1.27**	0.05	**1.54**	0.14
	5	**1.41**	0.15	**1.35**	0.09
	15	**1.38**	0.11	**1.56**	0.13
Easy response omissions (%)	Vehicle	**1.30**	0.23	**2.08**	0.52
	5	**2.83**	1.07	**1.76**	0.57
	15	**3.35**	1.47	**2.34**	0.78
Hard response omissions (%)	Vehicle	**0.10**	0.01	**0.12**	0.02
	5	**0.13**	0.03	**0.10**	0.03
	15	**0.13**	0.03	**0.12**	0.03

Table 8. Behavioural rCET measures following co-administration of THC and cannabidiol (V-V, V- 2.0 mg.kg THC, 10:1 THC/CBD (2.0/0.2 mg/kg), 1:1 THC:CBD (2.0/2.0 mg/kg))

Measure	**Dose**	**Workers** *(M)*	**Workers** *(SEM)*	**Slackers** *(M)*	**Slackers** *(SEM)*
Trials	Veh-Veh	**129.56**	9.73	**148.50**	9.17
	Veh-THC	**113.56**	12.39	**125.63**	11.34
	10:1 THC:CBD	**95.89**	13.41	**126.50**	9.60
	1:1 THC:CBD	**93.56**	10.94	**112.63**	11.10
Choice omissions	Veh-Veh	**4.89**	2.85	**2.13**	0.81

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	Veh-THC	**9.11**	3.48	**8.63**	3.05
	10:1 THC:CBD	**12.89**	4.04	**7.38**	3.53
	1:1 THC:CBD	**13.33**	3.95	**7.88**	1.92
Easy choice latency (s)	Veh-Veh	**3.42**	1.29	**2.84**	0.31
	Veh-THC	**3.41**	0.49	**2.98**	0.28
	10:1 THC:CBD	**3.92**	0.54	**3.12**	0.30
	1:1 THC:CBD	**3.74**	0.71	**3.39**	0.30
Hard choice latency (s)	Veh-Veh	**3.31**	0.25	**2.47**	0.22
	Veh-THC	**2.96**	0.28	**2.63**	0.29
	10:1 THC:CBD	**3.02**	0.26	**2.63**	0.24
	1:1 THC:CBD	**2.92**	0.30	**2.86**	0.16
Easy correct latency (s)	Veh-Veh	**0.38**	0.02	**0.51**	0.03
	Veh-THC	**0.46**	0.07	**0.52**	0.02
	10:1 THC:CBD	**0.61**	0.06	**0.53**	0.02
	1:1 THC:CBD	**0.56**	0.10	**0.57**	0.05
Hard correct latency (s)	Veh-Veh	**0.41**	0.02	**0.44**	0.03

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	Veh-THC	**0.47**	0.03	**0.46**	0.04
	10:1 THC:CBD	**0.49**	0.03	**0.50**	0.04
	1:1 THC:CBD	**0.51**	0.06	**0.50**	0.05
Easy collect latency (s)	Veh-Veh	**1.58**	0.24	**1.46**	0.12
	Veh-THC	**1.44**	0.06	**1.56**	0.11
	10:1 THC:CBD	**1.48**	0.11	**1.56**	0.10
	1:1 THC:CBD	**1.99**	0.33	**1.69**	0.08
Hard collect latency (s)	Veh-Veh	**1.26**	0.05	**1.37**	0.12
	Veh-THC	**1.48**	0.14	**1.42**	0.10
	10:1 THC:CBD	**1.52**	0.19	**1.53**	0.12
	1:1 THC:CBD	**1.97**	0.40	**1.50**	0.11
Easy response omissions (%)	Veh-Veh	**5.00**	5.00	**2.19**	0.66
	Veh-THC	**5.56**	3.51	**5.47**	2.30
	10:1 THC:CBD	**6.45**	3.24	**5.54**	2.67
	1:1 THC:CBD	**18.45**	5.70	**7.54**	3.39
Hard response omissions (%)	Veh-Veh	**1.74**	0.43	**1.94**	0.70

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	Veh-THC	**5.01**	1.66	**5.39**	1.75
	10:1 THC:CBD	**5.99**	2.57	**9.34**	3.72
	1:1 THC:CBD	**8.66**	3.55	**12.77**	7.12

Table 9. CB_1 receptor B_{max} (maximal binding site density, pmol/mg protein) and K_d (binding affinity, nM) values for workers and slackers. CB_1 receptor parameters did not differ between the two groups. Data are expressed as mean ± SEM.

	Workers	Slackers
mPFC *Bmax*	.581 ± .024	.582 ± .034
mPFC K_d	1.992 ± .391	1.844 ± 0.234
NAc *Bmax*	.437 ± .054	.422 ± .031
NAc K_d	1.603 ± 0.222	2.050 ± .256

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Supplementary Figure

Figure 1. Schematic diagram showing the trial structure of the rCET. The task began with illumination of the tray light. A nose-poke response in the food tray extinguished the tray light, commencing a new trial and extending the levers. These levers were permanently designated to initiate either low-effort/LR or high-effort/HR trials. If one of the two levers was pressed, the levers retracted and a 5-s ITI would begin. Following the ITI, one of five stimulus lights would be briefly illuminated: 1.0 s for a LR trial and 0.2 s for a HR trial. A nose-poke response in the illuminated hole (ie, correct response) led to a sugar reward-one pellet for a LR trial and two pellets for a HR trial-and the tray light would illuminate, indicating the opportunity to start the subsequent trial. A number of behaviors led to a 5-s time-out, signaled by house-light illumination: failure to make a lever response (choice omission); failure to withhold responding during the ITI (premature response); nose poke in an unlit hole following the stimulus (incorrect response); failure to make a nose-poke response following the stimulus (response omission). Reprinted with permissions from Cocker et al., 2012

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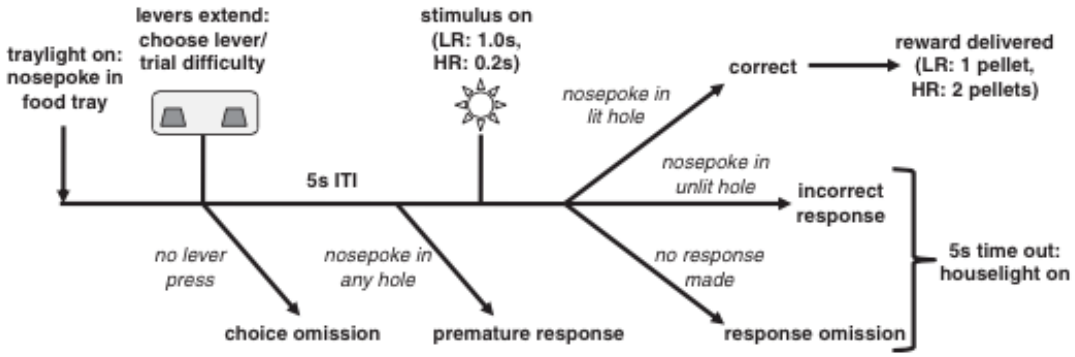

Figure 2. Premature responding on the rCET.

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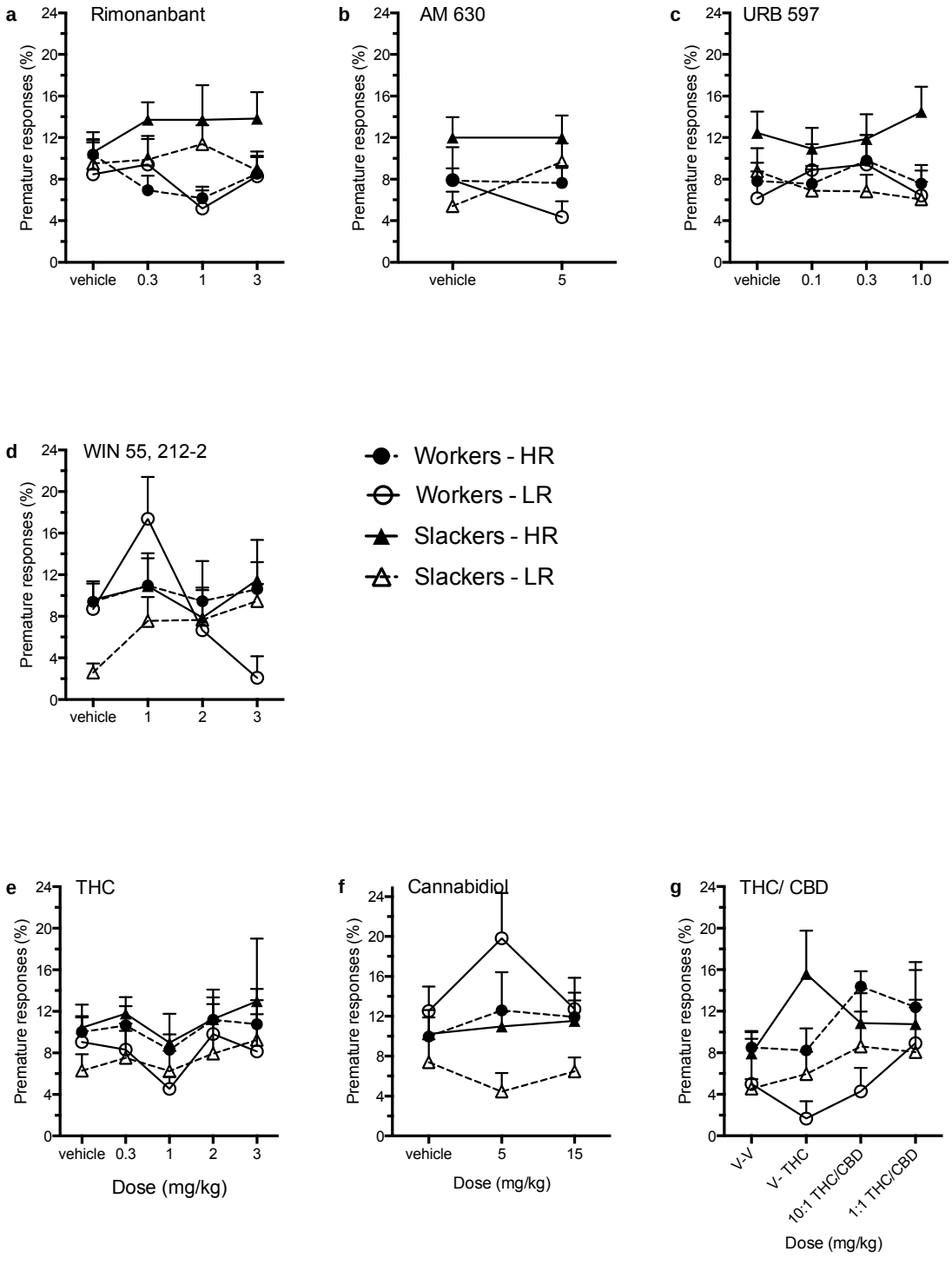

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