Published in final edited form as:

Exp Clin Psychopharmacol. 2013 October ; 21(5): 416–425. doi:10.1037/a0033668.

Effects of a Novel CB1 Agonist on Visual Attention in Male Rats: Role of Strategy and Expectancy in Task Accuracy

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Abstract

The effects of cannabinoid CB1 agonists (including 9-tetrahydrocannabinol, the main psychoactive component of marijuana) on attention are uncertain, with reports of impairments, no effects, and occasionally performance enhancements. To better understand these effects, we sought to uncover a role of changing online (within-session) strategy as a possible mediator of the effects of the novel, potent CB1 agonist AM 4054, on a model of sustained attention in male Sprague–Dawley rats. In this operant, two-choice reaction time (RT) task, AM 4054 decreased accuracy in an asymmetric manner; that is, performance was spared on one lever but impaired on the other. Furthermore, this pattern was enhanced by the outcome of the previous trial such that AM 4054 strengthened a win-stay strategy on the “preferred” lever and a lose-shift strategy on the “nonpreferred” lever. This pattern is often found in tests of expectancy; therefore, in a second experiment AM 4054 enhanced expectancy that we engendered by altering the probability of the

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All authors declare no conflict of interest.

two stimulus cues. Accuracy was impaired in reporting the less frequent cue, but only after two or more presentations of the more frequent cue. Taking the results of the experiments together, AM 4054 engendered expectancy by increasing the role of previous trial location and outcome on performance of future trials, diminishing stimulus control (and therefore, accuracy). This novel effect of CB1 receptor agonism may contribute to the deleterious effects of cannabinoids on attention.

Keywords

attention; cannabinoids; decision making; marijuana; operant conditioning

Cannabinoid CB1 agonists are often found to affect performance of cognitive and attentional tasks; however, the nature of these effects is poorly understood and equivocal results have been found. Chronic marijuana users, as well as participants given Δ^9 -tetrahydrocannabinol (THC) in the lab, often show lengthened response times and increased errors in cognitive tasks (Hunault et al., 2009; Wadsworth, Moss, Simpson, & Smith, 2006). However, several reports found no differences between these groups and control participants on accuracy (Aragona et al., 2009; Chang, Yakupov, Cloak, & Ernst, 2006; Gruber & Yurgelun-Todd, 2005; Vadhan et al., 2007). Self-reports indicate both enhancements and impairments in concentration (Green, Kavanagh, & Young, 2003).

Because of this, it is important to understand components of attentional task performance that may be sensitive to cannabinoid use. Acute and chronic marijuana use is associated with impaired behavioral flexibility and errors in shifting strategy in accordance with task demands in humans (Hart et al., 2010; Hester, Nestor, & Garavan, 2009; Hill, Froese, Morrish, Sun, & Floresco, 2006; Lane, Cherek, Tcheremissine, Lieving, & Pietras, 2005). A trial-by-trial analysis of performance of the Iowa Gambling Task revealed that marijuana users were similar to controls at the start of the task, but developed performance deficits by poorly evaluating wins and losses during the session (Wesley, Hanlon, & Porrino, 2011). This analysis of online strategy can be applied situations of high attentional demand to elucidate the role of such within-session factors in cannabinoid-induced attentional deficit. It is possible that such a deficit may be mediated, at least in part, by such a shift in online strategy, or by an enhancement in expectancy, which can be defined as a preparation or “tuning” (Bushnell, 1998, p. 238) of the nervous system to respond to certain stimuli, based upon frequency and repetition (Pang, Merkey, Egeth, & Olton, 1992).

In an operant animal model of sustained attention in which subjects chose between two levers to report the location of brief, unpredictable visual stimuli, the novel CB1 agonist AM 411 ((-)-adamantyl- Δ^8 -tetrahydrocannabinol) produced an impairment at high doses that was independent of the duration of the target stimulus (McLaughlin, Brown et al., 2005). This suggests that the drug did not impair performance by directly affecting sustained attention. It is interesting to note that AM 411 instead led to an asymmetric effect on accuracy. Rather than being equally accurate in reporting stimuli on either lever, animals were correct more often on one side (termed the *preferred lever*) than on the other (the *nonpreferred lever*), and the highest dose tested (2.0 mg/kg) impaired performance by

increasing the number of runs of multiple consecutive errors on the nonpreferred lever. These findings indicate that AM 411 may have affected accuracy via an alteration in strategy: higher doses impaired shifting away from the preferred lever, even when the cue for the nonpreferred lever was illuminated. As the reinforcing lever was selected at random on every trial, optimal performance can only be achieved by eliminating lever preference. A similar effect was found with CB1 agonists THC and WIN 55,212–2 (Hampson & Deadwyler, 1998, 1999) and hippocampal lesion (Hampson, Jarrard, & Deadwyler, 1999) on delayed nonmatch-to-sample (DMNTS), a similar two-choice operant task that models working memory. The CB1 antagonist SR 141716A reversed the effects of WIN 55,212–2, implicating the CB1 receptor (Hampson & Deadwyler, 1999). We therefore hypothesized that CB1 agonists alter online strategy, which is perhaps mediated by changes in expectancy, impairing performance when attention or memory are taxed.

Both experiments reported here utilized AM 4054 (9 β -(Hydroxymethyl)-3-(1-adamantyl)-hexahydrocannabinol; Bergman et al., 2008; Desai et al., 2013; Kangas et al., 2013; McLaughlin et al., 2013; Paronis et al., 2013; Thakur et al., 2013). This novel compound, an analog of AM 411, is highly potent and has approximately threefold binding preference for the CB1 receptor, compared with CB2. It has been found to induce behavioral changes typical of a CB1 agonist that were reversed by the CB1 inverse agonist AM 251 (McLaughlin et al., 2013). Experiment 1 used a sustained attention task in which one of two cue lamps would illuminate briefly (50–500 ms) and unpredictably to indicate which of two levers was reinforcing, similar to that used previously (McLaughlin, Brown et al., 2005). It was expected that AM 4054 would impair accuracy, and that this effect would be apparent only on the nonpreferred lever, with sparing of accuracy on the preferred lever. Furthermore, this asymmetrical impairment would be mediated by an increase in control of behavior by the location (i.e., side of cue and lever) and outcome (correct or error) of the most recent trial. Therefore, we also predicted that AM 4054 would facilitate responding on the preferred lever following a correct response on that lever (a win-stay strategy), and shifting away from the nonpreferred lever following an error (a lose-shift strategy). If subjects' choices were related to aspects of recent trials, it may be indicative of an enhancement of expectancy. Because of this, we investigated the effect of AM 4054 in an expectancy task in Experiment 2.

General Method

Subjects

Male Sprague–Dawley rats (Hilltop, Scottdale, PA) were used (initial weights = 250–290g). Separate groups of rats were used for Experiments 1 (sustained attention task, $n = 8$) and 2 (expectancy task, $n = 10$). Rats were housed doubly in an animal colony with a 12-hr light–dark cycle (lights on 08.00–20.00), and food-restricted prior to training. Animals were fed approximately 14 g of lab chow following sessions, with additional supplemental feeding if their weights were at or below 85% of free-feeding weight. Experiments were conducted during the light part of the cycle. Animal protocols were approved by the Edinboro University Institutional Animal Care and Use Committee, and the methods were in accord with the *Guide for the Care and Use of Laboratory Animals*.

Apparatus

Rats were trained in Coulbourn Instruments (Whitehall, PA) operant chambers under control of a PC computer using Graphic State 2 software. All training sessions were 30 min in length, and training and testing were conducted 5 days per week. One wall of each chamber held a recessed food tray into which 45 mg Noyes pellets (TestDiet, Richmond, IN) were delivered for reinforcement. The food tray was equipped with infrared sensors that detected head entries into the tray; such responses were used to initiate trials in Experiment 2. On either side of the food tray were fixed response levers, with a corresponding white LED stimulus light 9 cm above each lever. Chambers were housed in sound-attenuating cubicles with fans that provided continuous white noise.

Experiment 1—Sustained Attention Task

Drug

AM 4054 was synthesized at the Center for Drug Discovery (Northeastern University, Boston, MA). AM 4054 was dissolved in a solution of dimethyl sulfoxide (DMSO; Fisher Scientific, Pittsburgh, PA), Tween-80 (Fisher Scientific), and 0.9% saline, for a final concentration of 1:2:7 DMSO: Tween-80: saline. This solution was also used as the vehicle treatment. Doses of 0.01, 0.02, 0.04, 0.08, and 0.16 mg/kg were prepared via serial dilution. These doses were selected because they approximated the ED₅₀ for suppressing fixed-ratio 5 (FR5) lever pressing (0.1 mg/kg; McLaughlin et al., 2013). Each rat received drug treatments (doses described below) via the intraperitoneal route once per week in a counterbalanced, within-subjects fashion 30 min prior to testing. Drug testing took place on the fourth or fifth session each week and data from the intervening sessions were analyzed to ensure that there was no carryover of drug effect.

Procedure

Four training stages were used to shape performance on the task. On Day 1, both stimulus lights were illuminated continuously, and subjects received magazine training in which a pellet was delivered unconditionally every 30 s. Each response on either lever also resulted in delivery of one pellet. Beginning with Day 2, subjects were required to alternate between levers. Only the active lever (i.e., the lever that could be pressed for reinforcement) was cued by the stimulus light. Third, once subjects achieved a criterion of 100 or more reinforced responses on each lever, the schedule was changed so that the cued lever was randomly selected on a trial-by-trial basis, rather than following an alternation rule. The first response on the cued lever was reinforced and resulted in termination of the cue. A response on the noncued lever or lack of responding within 15 s of light onset (referred to as an *omission*) also resulted in termination of the cue but was not reinforced. A 15 s intertrial interval (ITI) was used, and each incorrect response or omission resulted in a 15 s timeout (an additional 15 s before the start of the next trial). Responses during timeout or ITI were recorded but had no programmed consequences. When an animal's accuracy on one lever was below 50% for two or more sessions, a correction rule was implemented to eliminate side bias. While the correction rule was in place, an incorrect response would result in a repeat of the same kind of trial until a correct response was made. When subjects maintained 85% overall accuracy for three consecutive days, the final training program was

implemented in which the cue was shortened to 1 s. When accuracy stabilized (i.e., no more than three consecutive sessions of increasing accuracy), subjects were advanced to the final experimental protocol.

The testing protocol was similar to the last training stage, except that ITI values of 7, 11, 15, 19, and 23 s and stimulus duration values of 50, 150, and 500 ms were varied randomly on a per-trial basis. Testing sessions began approximately 2 weeks after onset of this program, when performance reached a criterion of no more than three consecutive sessions with increasing accuracy. Testing sessions were 40 min in length.

Statistical Analysis

Session-wise measures—The main measure of performance was accuracy, calculated as correct trials/(correct trials + incorrect trials). Omissions were analyzed separately as explained below. For each session, the lever on which each animal was more accurate was defined as the preferred lever, while the other lever was defined as nonpreferred. A $6 \times 2 \times 3$ (Dose AM 4054 $\times$ Lever [preferred vs. nonpreferred] $\times$ Stimulus Duration) repeated-measures ANOVA was performed. An interaction of dose and duration would be taken to indicate a selective effect of AM 4054 on attention, while an interaction of dose and lever would be interpreted as a selective effect of drug on lever preference. Main effects of lever and duration were highly anticipated; the former was expected because preferred lever performance was superior by definition, while the latter was expected to confirm that shorter stimulus durations were associated with more difficult task demands.

Where significant interactions were found, analyses of simple main effects were performed on the dose factor, followed by post hoc tests using Bonferroni-corrected t tests in which each dose of AM 4054 was compared with vehicle. As five doses were used, five tests were performed with testwise $\alpha = .01$.

Omissions (trials with no response within 15 s after stimulus onset), reaction times (RT; time in ms from cue onset to response on either lever), and overall responses (all lever presses, during or between trials, regardless of consequence) were also divided into trials in which the preferred lever was correct, and those in which the nonpreferred lever was indicated for reinforcement, and a Dose $\times$ Lever ANOVA was run. Where dose effects were found, post hoc tests were conducted as described above.

Because levers were fixed (i.e., nonretractable), responses between trials were analyzed to assure that the effects of AM 4054 were not mediated by such responding immediately prior to trial onset. A $6 \times 2 \times 2$ (Dose $\times$ Lever $\times$ Outcome; i.e., whether the subsequent trial was correct or incorrect) was performed, and interactions of dose and outcome, or dose, lever and outcome, would be interpreted as evidence that AM 4054 affected task performance by altering the pattern of responding prior to each trial.

Trial-by-trial analysis—This analysis determined whether the outcome of the previous trial, or the lever pressed on the previous trial (or the interaction of the two) affected the lever selected by the subject on the current trial. A Dose $\times$ Lever (preferred vs. nonpreferred) $\times$ Last Trial Outcome (LTO; correct vs. error) repeated-measures ANOVA

was performed on a *percent staying* measure, defined as the percentage of trials in which animals responded on the same lever as the previous trial. Interactions involving dose were interpreted as evidence that AM 4054 altered strategy based on aspects of the previous trial.

Where a significant three-way interaction was found, repeated-measures ANOVAs were run for the effect of AM 4054 on percent staying for each of the four combinations of lever and LTO: Correct preferred (in which the preferred lever was reinforcing for the previous trial and was correctly selected); Incorrect preferred (the animal incorrectly responded on the preferred lever when the nonpreferred lever was indicated for reinforcement); Correct non-preferred (the animal correctly responded on the nonpreferred lever); and Incorrect nonpreferred (the preferred lever was indicated but the animal incorrectly responded on the nonpreferred lever). To assess whether percent staying varied from chance (i.e., ideal) performance, one-sample *t* tests were performed in each condition that tested the null hypothesis that percent staying = 50%, and used as its error term the standard error of the mean of the overall analysis.

Results

A three-factor repeated measures ANOVA of accuracy indicated significant main effects for the factors of dose, $F(5, 30) = 10.05, p < .001, \eta_p^2 = .63$, stimulus duration, $F(2, 12) = 35.43, p < .001, \eta_p^2 = .86$, and lever (preferred vs. nonpreferred), $F(1, 6) = 29.65, p < .002, \eta_p^2 = .83$.

A significant interaction of dose and lever was also found, $F(5, 30) = 6.69, p < .001, \eta_p^2 = .53$. Because of this, analyses of simple main effects of dose were conducted for accuracy on each lever. As can be seen in Figure 1, accuracy on the preferred lever was not affected, but AM 4054 did significantly impair accuracy on the nonpreferred lever, $F(5, 35) = 18.40, p < .001, \eta_p^2 = .72$. Post hoc comparison of each dose with vehicle using Bonferroni-corrected *t* tests indicated a significant difference between the 0.16 mg/kg dose and vehicle. Neither the two-way interaction of lever and stimulus duration, nor of dose and duration, nor the three-way Dose $\times$ Duration $\times$ Lever interaction were significant ($ps > .2$).

AM 4054 also increased trial omissions, $F(5, 35) = 16.12, p < .001, \eta_p^2 = .70$, lengthened RT, $F(5, 35) = 18.28, p < .001, \eta_p^2 = .72$, and decreased overall responding, $F(5, 35) = 14.97, p < .001, \eta_p^2 = .68$; comparing the preferred to the nonpreferred side, number of omissions and RT were similar, but animals made more responses overall on the preferred lever, $F(1, 7) = 27.90, p = .001, \eta_p^2 = .80$. Post hoc tests of dose indicated a significant difference from vehicle at the 0.16 mg/kg dose. The Dose $\times$ Lever interaction was nonsignificant ($ps > .6$) for all three measures. Data averaged between levers, as well as means for each lever, are presented in Table 1. An analysis of lever pressing between trials indicated an overall dose-dependent decrease in ITI responding, $F(5, 35) = 2.81, p = .031, \eta_p^2 = .29$; however, dose of AM 4054 did not interact with either the outcome (correct vs. error) or the side (preferred vs. nonpreferred) of the subsequent trial ($ps > .4$).

A $6 \times 2 \times 2$ (Dose $\times$ Lever [preferred vs. nonpreferred] $\times$ LTO [correct vs. error]) ANOVA was performed on percent staying (see Figure 2). No main effects were significant, nor did

dose interact with lever or LTO ($p > .2$). However, both the Lever $\times$ LTO, $F(1, 6) = 44.47$, $p < .001$, $\eta_p^2 = .88$, and the three-way Dose $\times$ Lever $\times$ LTO, $F(5, 30) = 2.97$, $p = .027$, $\eta_p^2 = .33$, interactions were significant. Because the interaction was significant, simple main effects of dose were conducted for each of the four combinations of lever and LTO. AM 4054 significantly increased the likelihood of staying on the preferred lever following a correct trial, $F(5, 35) = 8.50$, $p < .001$, $\eta_p^2 = .55$. Furthermore, at the 0.16 mg/kg dose, likelihood of staying on the preferred lever following a correct trial was significantly higher than chance (i.e., 50%), $t(6) = 4.39$, $p = .005$, and likelihood of staying on the nonpreferred lever following an error was lower than chance, $t(6) = -4.59$, $p = .004$. To investigate the possibility that the role of previous trials on percent staying at the 0.16 mg/kg dose may decrease over longer ITI values, percent staying values were separated by the five ITI values (range: 7 to 23 s); however, this technique resulted in few or no trials in many cells, which prevented statistical analysis. Inspection of the means suggested that even after the longest ITI, the Correct Preferred ($M = .67$, $SD = .39$), Incorrect Preferred ($M = .63$, $SD = .48$), Correct Nonpreferred ($M = .42$, $SD = .50$), and Incorrect Nonpreferred ($M = .38$, $SD = .48$) previous trial conditions were similar to the overall values displayed in Figure 2 at this dose ($M = .73$, $SD = .13$; $M = .64$, $SD = .23$; $M = .49$, $SD = .36$; $M = .28$, $SD = .19$, respectively).

Discussion

AM 4054 impaired performance in a manner that was not dependent on the duration of the stimulus. That is, the most brief stimuli (50 ms) theoretically taxed attentional processing the most, and therefore responding to 50 ms cues should have been more sensitive to the effects of a drug that impaired attention (as was found for the anticholinergic scopolamine; McLaughlin, Brown et al., 2005). In a similar design, 2.0 mg/kg THC impaired accuracy in reporting only the shortest visual cues (Presburger & Robinson, 1999), suggesting that CB1 agonists may impair sustained attention within a narrow dose range. However, this was not found in the present study, which used five doses over a wide range. The impairment found here was also not confounded by ITI responding: AM 4054 suppressed all ITI responding and did not specifically alter patterns of responding before left, right, correct, or incorrect responses.

Rather, the drug increased the discrepancy between preferred and nonpreferred lever accuracy regardless of attentional demand. This was found with the CB1 agonist AM 411 (McLaughlin, Brown et al., 2005), but Experiment 1 confirmed that the outcome of each trial was partly determined by the location and outcome of the previous trial, and that AM 4054 enhanced this effect. Reinforced responses on the preferred lever were significantly more likely to be repeated, while animals shifted away from the non-preferred lever following an incorrect response. As the computer designated the correct lever for each trial at random and regardless of previous events, these tendencies therefore likely led to the overall drug-induced impairment in accuracy.

Facilitating or inhibiting choice of a lever based on the location and success of recent trials is often found in tests of expectancy. In these tasks, stimulus probabilities are manipulated, and the effect of consecutive trials of the same type is to increase accuracy and decrease RT on each subsequent trial of the same type (Pang et al., 1992; Pang, Williams, Egeth, &

Olton, 1993; Stoehr et al., 1997). Moreover, the more that trials of the same type were presented consecutively, the fewer errors were committed. We therefore hypothesized that AM 4054 altered expectancy in the sustained attention task, and that this effect was mediated or strengthened by alterations in online strategy. That is, expectancy of either the cue or the response on the preferred lever increased following each correct response on that lever (leading to a win-stay strategy on that lever), and each error on the nonpreferred lever (causing a lose-shift strategy on that lever). If an inappropriate, internally generated expectancy effect were responsible for the impairment in the sustained attention task, then AM 4054 may enhance sensitivity to changes in trial probability. Specifically, a high-probability cue may be associated with greater accuracy relative to a low-probability cue (Pang et al., 1992). Moreover, if a trial on one lever is presented following several consecutive trials on the other, performance may be impaired. Meanwhile, as the number of consecutive trials on one lever increases, accuracy may increase, or at least remain unaffected, even by higher doses of AM 4054.

Experiment 2 employed an expectancy task adapted from that of Pang and colleagues (1992, 1993). Like Experiment 1, animals were to respond on the lever closest to the illuminated cue lamp. However, subjects were required to begin each trial by maintaining a nose poke response in a food tray equidistant from each lever, and the probability of each cue lamp illuminating varied between test sessions, with values (left-right) of 85%–15%, 50%–50%, and 15%–85%. While a decrease in accuracy on the less frequent side was expected, AM 4054 was predicted to exacerbate this impairment while sparing or improving performance on the lever associated with the more frequent cue. Furthermore, AM 4054 was hypothesized to enhance the influence of recent trials, impairing performance on one lever when the other had been recently cued.

Experiment 2—Expectancy Task

Drug

AM 4054 was prepared and administered as in Experiment 1, with two exceptions. Based on the results of Experiment 1 and pilot studies with the solubility of AM 4054, Experiment 2 utilized doses of 0.08, 0.12, and 0.16 mg/kg, and vehicle of 8% DMSO, 8% Tween-80, and 84% saline.

Procedure

The first two stages of training (magazine training and cued alternation) were identical to Experiment 1. Cued alternation was then modified, in that animals were required to maintain a nose-poke response in the central food tray for at least 1 s after each reinforced lever press. After 1 week, the hold time was extended to 2 s and varied between 1 and 2 s for the remainder of the study. The criterion to advance to the expectancy training task was the attainment of at least 100 pellets with responses on either lever no greater than 20% more than the other; this was met by all animals in approximately 20 sessions.

In the expectancy training task, stimulus probabilities (left-right) of 100%–0% or 0%–100% were used, alternating each day. Expectancy training required animals to initiate a nosepoke response to start each trial. A magazine light illuminated to indicate when a trial could

begin, and the nosepoke was to be maintained for a randomly selected duration (1, 1.5, or 2 s). After this, the magazine light extinguished and the cue light above one of the two adjacent response levers illuminated, indicating that reinforcement was available and contingent upon response on that lever. The duration of the cue light illumination, and therefore the availability of reinforcement, was 10 s at the start of expectancy training, and was gradually reduced to 3 s over approximately 12 weeks of training. *Premature responses* were defined as tray exits before the magazine light extinguished; such responses ended the trial and initiated a 5 s timeout, which was cued by the house light. To reduce premature responding, 40% of trials were *catch trials*, in which the magazine light was illuminated for 3 s following the initial nose-poke, and responses maintained for that duration were immediately reinforced without the lever press requirement. During training, animals ending more than 50% of trials with premature responses were subjected to a remedial schedule in which reinforcement was delivered following each 2 s nosepoke. For all trials, there was a 2 s ITI before the magazine light illuminated to permit the start of the subsequent trial.

The test program was identical to the final training protocol in terms of the length of the ITI and the nosepoke hold period. The cue light also illuminated for 3 s following this hold period. Premature responses, incorrect responses on the uncued lever, and failure to execute a lever press within 3 s (omissions) resulted in a 5 s timeout, during which the house light illuminated. However, the test protocol used 85%–15%, 50%–50%, and 15%–85% left-right probabilities, rather than 100%–0% and 0%–100%. There were 12 test sessions consisting of all combinations of four doses and three probability values, in counterbalanced format. Drug testing took place on the second and fifth session each week and data from the intervening sessions (which utilized the alternating 100%–0% or 0%–100% probabilities of the training task) were analyzed to ensure that there was no carryover of drug effect. Test sessions lasted 30 minutes.

Statistical Analysis

Because stimulus probabilities varied between test sessions, data from the first 20 trials were discarded. Levers were defined by position (left vs. right) rather than preference, and all analyses were conducted separately for each of the three left-right stimulus probability conditions. As in Experiment 1, the main measure of performance was accuracy, as analyzed by a two-factor (Dose $\times$ Lever) repeated measures ANOVA, with simple main effects of dose planned following significant interactions. Post hoc tests of dose were Bonferroni-corrected *t* tests with testwise $\alpha = .017$.

Where significant Dose $\times$ Lever interactions were found, accuracy was further analyzed by separating trials into four or five categories based on locations of recent trials. For the 50%–50% condition, trials were divided into five categories based on whether they followed three or more, two, or one trial on the opposite lever, or followed one, or more than one, trial on the same lever. A $4 \times 2 \times 5$ (Dose AM 4054 $\times$ Lever $\times$ Recent Trial) repeated-measures ANOVA was planned for the measure of accuracy. For both the 85%–15% and 15%–85% conditions, near-perfect performance on the 85% lever caused a ceiling effect; therefore, accuracy was only analyzed on the 15% lever. In both conditions, there were few consecutive trials on the 15% lever, and almost no runs of three or more of such trials.

Therefore, to analyze accuracy in more detail, we created four categories of three or more, two, or one preceding trial on the 85% lever, or one or more trial on the 15% lever. Accuracy was then compared across these conditions with a 4×4 (Dose $\times$ Recent Trial) ANOVA.

Reaction time (RT) was defined, as in Experiment 1, as time from cue onset to response, and analyzed in the same fashion as accuracy. Omissions were also defined as failure to respond during the 3 s cue and analyzed with a 4×2 (Dose $\times$ Lever) repeated-measures ANOVA. Unlike Experiment 1, trials were subject-initiated and therefore number of trials completed may have been affected by AM 4054. *Completed trials* were therefore defined as those terminating in a correct or incorrect response, or an omission, and excluded catch trials (number of successful 3 s nose pokes which occurred at random on 40% of all trials) and premature responses (nose pokes terminated prior to offset of the magazine lamp on either completed or catch trials). Effects of AM 4054 on completed trials, catch trials, and premature responses were analyzed with repeated-measures ANOVA.

Results

The three left-right probabilities (85%–15%, 50%–50%, 15%–85%) were analyzed separately.

85%–15% left-right probabilities—An overall main effect of dose, $F(3, 18) = 9.87$, $p < .001$, $\eta_p^2 = .62$, and lever, $F(1, 6) = 126.21$, $p < .001$, $\eta_p^2 = .96$, were found, as was a Dose $\times$ Lever interaction, $F(3, 18) = 11.10$, $p < .001$, $\eta_p^2 = .65$. As seen in Figure 3a, performance was nearly perfect on the 85% lever at all doses. Meanwhile, a significant repeated-measures ANOVA of dose on the 15% lever, $F(3, 18) = 10.59$, $p < .001$, $\eta_p^2 = .64$, was followed by post hoc comparisons indicating a difference only between the 0.16 mg/kg dose and vehicle.

As shown in Figure 3b, accuracy data on the 15% lever were separated by the locations of the preceding trials. In a 4×4 (Dose $\times$ Previous Trial) repeated-measures ANOVA, the main effect of dose failed to reach significance, $F(3, 18) = 2.70$, $p < .076$, $\eta_p^2 = .31$, but the main effect of previous trial was significant, $F(3, 18) = 16.81$, $p < .001$, $\eta_p^2 = .74$, as was the interaction of dose and previous trial, $F(9, 54) = 2.41$, $p = .022$, $\eta_p^2 = .29$. Because the interaction was significant, separate analyses of dose were performed for each of the previous trial type categories. As shown in Figure 3b, AM 4054 impaired 15% lever accuracy when preceded by two, $F(3, 18) = 3.62$, $p = .033$, $\eta_p^2 = .38$, or three or more, $F(3, 18) = 7.61$, $p = .002$, $\eta_p^2 = .56$, consecutive 85% lever trials, but performance was not affected when preceded by only one 85% lever trial, or by a 15% lever trial. For both significant conditions, post hoc analysis revealed significant differences only between vehicle and the 0.16 mg/kg dose.

RT was not slowed by AM 4054, but animals were slower to respond to 15% lever trials, $F(1, 5) = 13.25$, $p = .015$, $\eta_p^2 = .73$; likewise, AM 4054 did not increase trial omissions, although there were more omissions on the more-frequent 85% lever trials, $F(1, 6) = 19.54$,

$p = .004$, $\eta_p^2 = .77$. The Dose $\times$ Lever interaction was not significant for either measure, therefore further analyses were not conducted. Numbers of completed trials, catch trials, and premature responses were not affected by AM 4054 in any probability condition ($ps > .08$).

50%–50% left-right probabilities—The main effect of dose approached significance, $F(3, 18) = 2.83$, $p = .068$, $\eta_p^2 = .32$. The factors of dose and lever did not interact, and as expected, the main effect of lever was not significant. The main effect of previous trial also approached significance, $F(4, 20) = 2.82$, $p = .053$, $\eta_p^2 = .36$. AM 4054 did not affect secondary measures of behavior ($ps > .1$), and unlike sessions with unequal probabilities, RT and omissions did not differ by lever.

15%–85% left-right probabilities—85% lever performance was superior, $F(1, 6) = 29.74$, $p = .002$, $\eta_p^2 = .83$. There was an overall main effect of drug dose, $F(3, 18) = 9.34$, $p = .001$, $\eta_p^2 = .61$, and an interaction of dose and lever, $F(3, 18) = 10.31$, $p < .001$, $\eta_p^2 = .64$ that is shown in Figure 4a. Similar to the 85%–15% left-right condition, accuracy on the 85% (right) lever was found to be at or near perfect in all cases; therefore, further analysis of accuracy on the right lever was not performed. Analysis of dose on the 15% (left) lever revealed a significant effect, $F(3, 18) = 10.17$, $p < .001$, $\eta_p^2 = .63$, and post hoc testing indicated an impairment at the 0.16 mg/kg dose. When accuracy at each dose was sorted by recent trials, two-way ANOVA revealed differences in accuracy based on dose, $F(3, 18) = 4.44$, $p = .017$, $\eta_p^2 = .43$ and recent trial type, $F(3, 18) = 9.31$, $p = .001$, $\eta_p^2 = .61$, as well as an interaction of these two factors that is shown in Figure 4b, $F(9, 54) = 2.37$, $p = .025$, $\eta_p^2 = .29$. AM 4054 impaired accuracy on the 15% lever following three or more consecutive 85% lever trials $F(3, 18) = 10.56$, $p < .001$, $\eta_p^2 = .64$, but not after one or two such trials, nor after another 15% lever trial. Again, only the 0.16 mg/kg dose differed from vehicle.

Analysis of RT, omissions, completed trials, catch trials, and premature responses yielded no effect of drug or interaction of drug and lever ($ps > .2$). As 85% lever trials were more numerous, there were more omissions of these trials, $F(1, 6) = 9.62$, $p = .021$, $\eta_p^2 = .62$.

Discussion

As seen in Figures 3 and 4, the effects of AM 4054 in the 85%–15% condition mirrored that of the 15%–85% condition; therefore, findings in these two versions of the task can be considered together. On the 50%–50% version of the task, AM 4054 did not significantly impair accuracy, RT, or any other parameter. This is surprising in light of the fact that animals anecdotally displayed overt motor slowing at the 0.12 and 0.16 mg/kg doses, and suggests that AM 4054 impaired performance specifically by inhibiting selection of the 15% lever. Moreover, this inhibition was only evident following runs of two or more trials on the 85% lever. No impairment was evident on the 15% lever when it had been cued recently. A nonsignificant trend toward improved accuracy with repetitions of the same trial was seen in the 50%–50% condition ($p = .053$), but no interaction with dose was evident. AM 4054 may therefore enhance sensitivity to recent events in this task; when subjects combine data from

recent trials with information about overall session stimulus probability, they may show a bias away from the 15% lever. Likewise, one may expect an enhancement of 85% lever performance, but this may be masked by a ceiling effect. It is clear, however, that AM 4054 spared accuracy on levers cued with 50% or 85% probability.

General Discussion

As predicted, the novel CB1 agonist AM 4054 impaired performance in both two-choice operant tasks by allowing the location and outcome of recent events to control behavior at the expense of control by the visual stimuli. In both cases, accuracy decreased on one lever, with sparing of performance on the other. In Experiment 1, stimuli were presented briefly and unpredictably, but with equal frequency. Nevertheless, the highest dose tested (0.16 mg/kg), enhanced the asymmetry between the preferred and nonpreferred levers, as has been found with other CB1 agonists (Hampson & Deadwyler, 1998, 1999; McLaughlin, Brown et al., 2005). The trial-by-trial analysis (see Figure 2) revealed that this drug-induced deficit was particularly evident when the most recent trial was a reinforced response on the preferred lever or an incorrect response on the nonpreferred lever. Similarly, in Experiment 2 we manipulated response preference by altering the relative frequency of the stimuli, and confirmed that AM 4054 enhanced sensitivity to this frequency. That is, AM 4054 impaired performance on the 15% lever, but only after a run of recent trials on the 85% lever (Figures 3b and 4b). A recent (i.e., at least once in the past two or three trials) 15% trial negated the drug-enhanced expectancy effect that impaired performance.

Since target stimuli in both tasks were selected randomly on each trial, ideal choice behavior would be under stimulus control and without regard to the location or success of recent trials. Therefore, AM 4054 allowed an inefficient strategy to control behavior at the expense of control by the external stimulus. Difficulties in switching from an inefficient strategy have also been found for ethanol (Devenport, Stidham, & Hale, 1989) and scopolamine (Soffie, Bronchart, & Lebailly, 1986). The effect of AM 4054 may, therefore, be more analogous to ineffective strategies during games such as the Iowa Gambling Task, where response allocation may also not match the expected payout of each option. Indeed, chronic marijuana smokers were found to make riskier choices that led to decreased payoff over time (Whitlow et al., 2004). In contrast, marijuana did not acutely affect strategy in experienced users (Vadhan et al., 2007), although it is possible that tolerance reduced performance deficits.

The results of Experiment 2 suggest that the strategy may have been guided by an alteration in expectancy. It remains to be seen whether AM 4054 affected stimulus or response expectancy. However, the fact that animals in the sustained attention task directed 14–62% more overall responses to the preferred lever compared with the nonpreferred (depending on dose, see Table 1) suggests that the effect may have been driven by response expectancy. This may stand in contrast to undrugged human participants, who are guided by anticipation of the stimulus, rather than changes in response preparation (Hinrichs & Krainz, 1970).

It must be noted, however, that these effects are not caused by motor slowing or a strategy of expending minimal effort by disregarding one of the two response options. Several lines of

evidence support this. First, in the extreme, such a strategy would involve chance performance; that is, accuracy of 100% and 0% on the preferred and nonpreferred levers, respectively, whereas non-preferred lever accuracy reported here and in other studies (Hampson & Deadwyler, 1998, 1999; McLaughlin, Brown et al., 2005) is approximately 40–70% following CB1 agonist administration. Curiously, the asymmetric effects of AM 411 (McLaughlin, Brown et al., 2005) were not associated with changes in measures of bias adapted from signal detection theory and choice theory for use in similar tasks. A lack of effect of AM 411 on responsivity index (Bushnell, Kelly, & Crofton, 1994; Presburger & Robinson, 1999), log b (Herremans, Huzen, & Slangen, 1994; Steckler, 2001), and Index y (Dudchenko & Sarter, 1991; Sahgal, 1987; Sahgal, Keith, & Lloyd, 1990) suggests that these bias measures are not sensitive to this type of effect. Second, while AM 4054 increased RT and trial omissions and decreased overall responding in the sustained attention task, no Dose $\times$ Lever interactions were found for these measures (see Table 1), indicating that the non-preferred lever was not simply neglected at the effective dose of AM 4054. AM 4054 had no effect on RT and trial omissions in the expectancy task (likely because trials were subject-initiated and far more temporally predictable), which is also incompatible with an explanation of simple motor slowing. Lastly, there was no main effect of dose on percent staying in the sustained attention task. In other words, AM 4054 did not globally enhance the likelihood of repeating a response; in fact, the drug caused shifting away from incorrect nonpreferred lever responses.

While the impairment does not result from motor slowing, a reduction in effort expenditure, or a simple bias toward one type of response, it may be revealed only with high attentional demand. AM 4054 did not asymmetrically affect performance in the 50%–50% condition of the expectancy task, even though this version of the task was similar to the sustained attention test used in Experiment 1. The main procedural difference of the expectancy task is that its 3 s stimulus duration and subject-initiated trials were designed to minimize demands on sustained attention. The 50%–50% condition of Experiment 2 revealed nearly significant main effects of dose and recent trial history on accuracy ($ps < .07$, $\eta_p^2 > .32$), but these did not interact, indicating that the drug-induced impairment was not related to previous trial history. Performance was also not significantly different between levers, unlike in Experiment 1. The impairment may also emerge at only high doses; the effective dose of 0.16 mg/kg induces catalepsy (McLaughlin et al., 2013), as does 2.0 mg/kg AM 411 (McLaughlin, Lu et al., 2005), which produced similar effects on a sustained attention task (McLaughlin, Brown et al., 2005). We piloted higher doses (not shown) that frequently resulted in few or no trials completed.

In the DNMTS, the CB1 agonist WIN 55,212–2 produced a symmetric delay-dependent impairment at lower doses than those that produced a similar asymmetric effect (Hampson & Deadwyler, 1998) to that shown in the current paper. This may be due to a specific short-term memory (STM) effect that is evident in the DNMTS, whereas the sustained attention task was designed to minimize mnemonic demand. There may also be differences in baseline strategy between the two tasks that are enhanced by CB1 agonists; under control conditions, the magnitude of lever preference (i.e., preferred side accuracy—nonpreferred side accuracy) was found to be <5 percentage points in the DNMTS task (Hampson &

Deadwyler, 1999), but 11 points under vehicle conditions in Experiment 1 (see Figure 1). However, to the extent that the effects found in Experiment 1 depend on memory of the location and outcome of the previous trial, a very durable memory trace is evident. Although a low number of trials per condition prevented statistical analysis by ITI value, the role of previous trial outcome in choice behavior appears to remain high at the effective dose, even after a 23 s ITI, comparable to longer memory delays used in DNMTS tasks in rats.

In addition to these qualifying factors, other aspects of this altered online strategy remain to be elucidated. For instance, our findings indicate that AM 4054 enhanced lever preference, but it is not known whether the preferred lever is determined in any systematic manner. The preferred lever frequently changed between sessions, as was found previously (Hampson & Deadwyler, 1998). Similarly, it was found that accuracy asymmetry in the DNMTS task produced by hippocampal lesion was not related to prelesion performance (Hampson & Deadwyler, 1999). Chronic THC administration did not induce any asymmetry in attentional performance (Verrico, Jentsch, Roth, & Taylor, 2004).

These results highlight a cannabinoid-induced inappropriate weighting of recent performance on future decisions and imply a previously understudied type of impairment of marijuana and other CB1 agonists. That is, in situations with heavy demand on attention, cannabinoids increase the likelihood that attention will be guided by expectancy based on previous experience, rather than by currently relevant external stimuli. The importance of trial-by-trial analyses to determine the influence of recent outcomes is also emphasized to elucidate the effects of CB1-acting drugs on attention and memory.

Acknowledgments

This research was supported in part by a grant from the Edinboro University Senate. The funding source had no other role than financial support. All authors contributed in a significant way to the manuscript. All authors have read and approved the final manuscript.

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Figure 1.

Accuracy in the two-choice sustained attention task. Error bars represent standard error of the mean. ** $p < .01$ AM 4054 difference from vehicle.

Figure 2.

Likelihood of staying at a particular response choice given different outcomes of the preceding trial. Ideal, stimulus-controlled behavior = 50% probability (dashed line). Error bars represent standard error of the mean. ** $p < .01$ significant difference from 50% probability.

Figure 3.

Accuracy on each response choice given 85%–15% left-right stimulus probability and on the right (15% probability) lever on trials immediately preceded by runs of three or more, two, or one left lever trial, or by one or more right lever trials. Error bars represent standard error of the mean. * $p < .05$.

Figure 4.

Accuracy on each response choice given 15%–85% left-right stimulus probability and on the left (15% probability) lever on trials immediately preceded by runs of three or more, two, or one right lever trial, or by one or more left lever trials. Error bars represent standard error of the mean. ** $p < .01$.

Table 1

Means (and Standard Error of the Mean) for Secondary Measures of Sustained Attention Task Performance

	Dose AM 4054 (mg/kg)					
	Vehicle	0.01	0.02	0.04	0.08	0.16
Trial omissions						
Overall	.4 (.2)	.4 (.3)	.6 (.2)	.6 (.4)	6.4 (2.6)	23.8 (5.1)**
Preferred lever	.5 (.3)	.1 (.1)	.3 (.1)	.6 (.4)	6.9 (2.9)	23.0 (4.8)
Nonpreferred lever	.3 (.2)	.8 (.5)	.9 (.3)	.6 (.4)	5.9 (2.3)	24.6 (5.6)
Reaction time (ms)**						
Overall	1412.0 (123.6)	1392.8 (57.4)	1394.3 (124.6)	1414.8 (116.7)	1679.1 (135.2)	3108.9 (326.2)**
Preferred lever	1360.8 (138.5)	1422.4 (117.6)	1345.1 (100.0)	1428.8 (129.6)	1698.4 (130.2)	3281.6 (398.4)
Nonpreferred lever	1463.1 (172.2)	1363.3 (58.1)	1443.4 (179.8)	1400.8 (121.4)	1659.9 (191.5)	2936.1 (386.5)
Total responses**						
Overall	333.1 (28.3)	329.4 (24.5)	343.2 (32.2)	343.0 (22.2)	271.4 (28.1)	141.9 (42.1)**
Preferred lever	382.9 (38.4)	381.4 (31.0)	365.8 (34.7)	373.6 (29.6)	323.8 (34.5)	175.5 (50.4)
Nonpreferred lever	283.3 (23.2)	277.4 (29.6)	320.6 (35.5)	312.4 (44.2)	219.1 (23.1)	108.4 (34.4)

**
 $p < .01$.