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Cannabinoid inhibition improves memory in food-storing birds, but with a cost

Michael W. Shiflett[1], Alexander Z. Rankin, Michelle L. Tomaszycki and Timothy J. DeVoogd[*]

Department of Psychology, 212 Uris Hall, Cornell University, Ithaca NY 14853, USA

Food-storing birds demonstrate remarkable memory ability in recalling the locations of thousands of hidden food caches. Although this behaviour requires the hippocampus, its synaptic mechanisms are not understood. Here we show the effects of cannabinoid receptor (CB1-R) blockade on spatial memory in food-storing black-capped chickadees (*Poecile atricapilla*). Intra-hippocampal infusions of the CB1-R antagonist SR141716A enhanced long-term memory for the location of a hidden food reward, measured 72 h after encoding. However, when the reward location changed during the retention interval, birds that had received SR141716A during initial learning showed impairments in recalling the most recent reward location. Thus, blocking CB1-R activity may lead to more robust, long-lasting memories, but these memories may be a source of proactive interference. The relationship between trace strength and interference may be important in understanding neural mechanisms of hippocampal function in general, as well as understanding the enhanced memory of food-storing birds.

Keywords: hippocampus; cannabinoid; spatial memory; proactive interference; chickadee; *Poecile atricapilla*

1. INTRODUCTION

Food-storing birds are able to accurately recall the location of thousands of hidden food caches. These memories are encoded spatially and require activity of the hippocampal formation (HF) (Sherry & Vaccarino 1989; Hampton & Shettleworth 1996*a*; Shiflett *et al.* 2003). At a gross level, the enhanced memory capacity in food-storing species may result from an overall expansion in the size of memory-related brain regions, such as the HF and septum (Krebs *et al.* 1989; Sherry *et al.* 1989; Healy & Krebs 1992, 1996; Hampton *et al.* 1995; Smulders & DeVoogd 2000; Shiflett *et al.* 2002). However, the neural mechanisms underlying the enhanced spatial memory of food-storing species remain poorly understood. Ultimately, changes in the strength of synaptic connections are believed to underlie the formation of long-term memory (Martin *et al.* 2000; Abel & Lattal 2001; Dudai 2002). This suggests that factors that modulate synaptic plasticity in memory-related brain regions may contribute to food storing species' enhanced long-term spatial memory.

In mammals, blockade of cannabinoid receptors (CB1-R) produces memory-enhancing effects on spatial and associative memory tasks (Terranova *et al.* 1996; Reibaud *et al.* 1999; Lichtman 2000; Wolff & Leander 2003). Mice deficient in CB1-R show enhanced long-term potentiation induction in the hippocampus (Pertwee 1997; Paton *et al.* 1998; Sullivan 1999). Cannabinoid receptors are also present in avian HF, and have similar signalling properties as mammalian CB1-Rs (Soderstrom & Johnson 2000, 2001); however, their function in memory formation has not been investigated. We studied the role of CB1-Rs during spatial learning in food-storing black-capped chickadees (*Poecile atricapilla*). We infused the CB1-R antagonist SR141716A into the chickadees' HF before they learned the location of a hidden food reward. We first examined whether, as in mammals, blockade of CB1-R activity would improve chickadees' spatial memory. Second, we investigated the influence of CB1-R blockade on memory interference. Training with stimuli related to the item that is being assessed commonly results in interference with retention of the test stimulus. Interfering stimuli disrupts memory in food-storing birds to a lesser degree than such stimuli do in non-storing birds (Clayton & Krebs 1994; Hampton & Shettleworth 1996b). Our results suggest that although inhibition of CB1-R activity promotes longer-lasting spatial memory, it also promotes interference in food-storing birds.

2. MATERIAL AND METHODS

(a) *Subjects*

Twelve black-capped chickadees were caught near Ithaca, NY, under state and federal permits. Five birds were caught between September and October 2001, and were used in experiment 1. An additional seven birds were caught between July and September 2002, and were used in experiments 1 and 2. Experiments were performed from December 2001 to January 2002, and November 2002 to December 2002. Approximately two weeks before performing the experiments described here, both cohorts of birds completed a similar set of experiments, which involved memory tests paired with intra-hippocampal infusion of the *N*-methyl D-aspartate receptor antagonist DL-2-amino-5-phosphonopentanoic acid (Shiflett *et al.* 2004). At the onset of the present experiments birds had extensive experience with the testing environment, task requirements and experimental procedures, and had undergone cannulation surgery.

Birds were fed daily on a diet of mealworms, and a mix consisting of ground beef, carrot baby food, hardboiled eggs, wheat germ and turkey pellets. Water was provided *ad libitum*. Birds were

[*] Author for correspondence (tjd5@cornell.edu).
† Present address: Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA 15260, USA.

housed in 60.96 cm × 40.64 cm × 40.64 cm wire cages and kept on a 10 L : 14 D cycle.

(b) *Testing apparatus*

Memory tests took place in a 4.5 m × 4 m × 2.5 m testing room (figure 1). Nineteen wooden feeders were arranged on the walls of the testing room. Each feeder consisted of a wooden block containing a 9 mm deep hole and a 10 cm dowel protruding from the base. We inserted one-half of a mealworm into one feeder hole. All feeders were fitted with a string attached to the dowel, the end of which was knotted and covered the feeder hole. This prevented subjects from casually observing whether or not a feeder was baited. Subjects entered the room from their home cages through a trapdoor in the wall.

(c) *Reference memory task*

The memory task consisted of a training episode and a memory test (figure 1). In the training episode, birds first found a single visible mealworm placed in one of the 19 feeders. When the birds retrieved the mealworm they were allowed to eat it, after which we turned off the lights in the testing room and the birds returned to their cages before three rehearsal trials. For each of these trials, birds remained in their cage for 2 min while we re-baited the feeder that previously contained the mealworm, and hid this and all other food storage sites by placing knots over all the feeder holes. After 2 min, we released birds into the testing room where they searched for the concealed mealworm by removing knots from feeders.

Memory tests took place either 72 h (experiment 1) or 48 h (experiment 2) after the training episode. We baited the location that contained a reward during the training episode and recorded the number of knots the birds removed from unbaited feeders (errors) before finding the reward. Only initial visits to feeders were scored. Revisits to feeders whose knots had already been removed were not counted because it was not possible to determine whether the bird was rechecking a feeder or merely perching at the feeder.

(d) *Cannulation surgery*

Birds were anaesthetized (5 mg kg^{-1} xylazine, and 87.5 mg kg^{-1} ketamine, injected intramuscularly) and bilateral cannulae (26 gauge, 4 mm long) were implanted for intra-cranial infusion. Cannulae were affixed to the skull with cyanoacrylate glue and dental cement, using standard stereotaxic techniques. Cannulae were positioned 2.2 mm rostral to the site in the brain where the midline meets the cerebellum, 1 mm lateral to the midline, and with the ventral tip of each cannula in contact with the dorsal surface of the HF. Birds were allowed 2 days to recover.

(e) *Intra-hippocampal infusions*

The cannabinoid antagonist SR141716A (National Institute of Drug Abuse) was dissolved in 100% dimethylsulphoxide (DMSO), and the solution was diluted with 0.8% saline and one drop of Tween-80 to a final concentration of 15% DMSO and 0.104 M SR141716A. The dose of SR141716A used was based on previous research in mice (Marsicano *et al.* 2002). During infusion, subjects were restrained by hand, and a 32 gauge needle attached to a 2.5 µl Hamilton syringe was inserted into each cannula. Infusions were delivered gradually over the course of 1 min. The needle was left in the cannula for an additional minute to allow for fluid dispersal. All birds used in each experiment were run in all experimental conditions, including control trials in which the drug vehicle was injected.

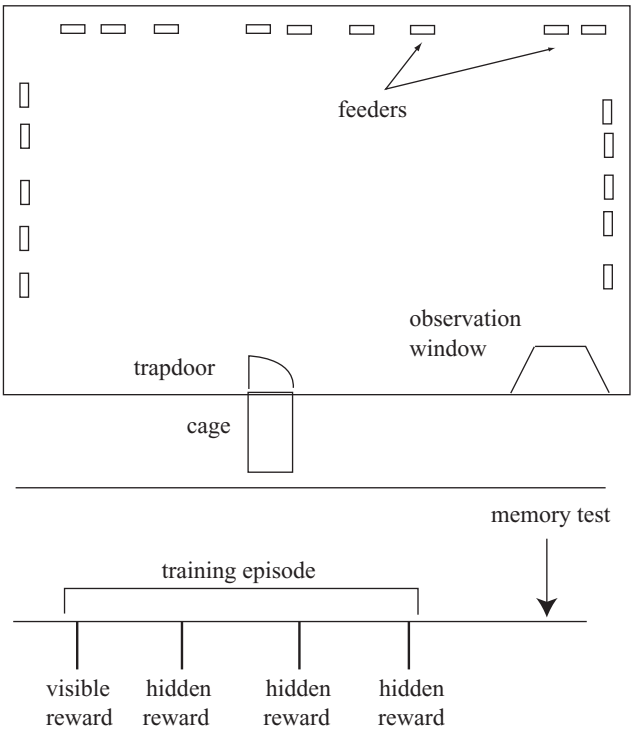

Figure 1. Memory tests took place in a 4.5 m × 4 m × 2.5 m testing room. Nineteen wooden feeders were arranged on the walls of the testing room. Birds entered the room from their home cage through a trapdoor on one wall. Observations took place through a Plexiglass window located in the corner of the testing room. The memory task consisted of a training episode and a memory test. In the training episode, birds first found a single visible mealworm placed in one of 19 feeders. Two minutes after finding the visible reward, birds performed three rehearsal trials (separated by 2 min) in which the reward was hidden from view by covering the holes of each feeder with a knot. The birds' memory for the hidden reward was tested 48 h or 72 h after the training episode.

Statistical comparisons of mean errors for each treatment were made using a within-subject general linear model analysis of variance (GLM-ANOVA). Because some of the birds were caught and tested 1 year after the others, we included cohort as a dichotomous fixed factor in the analysis. All values are reported as mean values ± standard errors of the mean.

3. EXPERIMENT 1: DOES BLOCKING HIPPOCAMPAL CB1-R INFLUENCE LONG-TERM SPATIAL MEMORY FOR A SINGLE REWARD LOCATION?

In this experiment we blocked CB1-R activity before the birds learned the location of a single reward contained in one of the 19 feeders. If blocking CB1-R activity improves long-term memory, we expect that when birds receive SR141716A before learning, they should make fewer errors in later locating the hidden reward than when birds receive vehicle infusions before learning.

(a) *Design*

Birds performed the reference memory task as described above. Five minutes before the training episode, birds received bilateral intra-HF infusions of SR141716A or vehicle. A single memory test was conducted 72 h after the training episode. We rearranged the placement of feeders in the testing room between treatment conditions to decrease interference between tests, and randomized the

order of treatments for each bird. Approximately one week separated the two treatment conditions.

(b) *Results*

After infusion of either SR141716A or vehicle, birds rapidly learned the location of the food item during the training episode. As shown in figure 2, birds were substantially better than chance on the third rehearsal trial during the training episode, and their performance did not differ whether they received SR141716A or vehicle before the training episode (SR141716A mean = 2.0 ± 0.56; vehicle mean = 2.33 ± 0.61).

After receiving either of the two infusates, birds found the food reward at better than chance levels when tested 72 h after training. However, birds differed in the accuracy of their memory, depending or whether they had received SR141716A or vehicle before the training episode (treatment effect: $F_{1,9} = 18.98$, $p < 0.01$; treatment × cohort interaction: $F_{1,9} = 3.46$, n.s.). Birds that received SR141716A before learning made significantly fewer errors to locate the hidden reward than birds that received the vehicle (vehicle = 6.09 ± 1.76; SR141716A = 2.45 ± 1.01; paired $t_{10} = 3.76$, $p < 0.01$; figure 2).

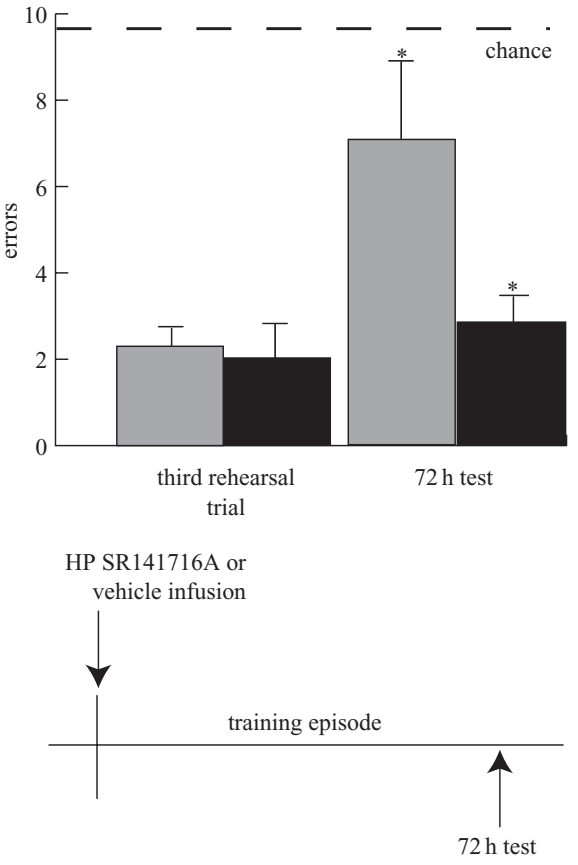

Figure 2. In experiment 1, birds received infusions of SR141716A or vehicle before a training episode. Memory for the hidden reward was evaluated 72 h later. The number of errors on the third rehearsal trial of the training episode and the 72 h memory test was compared when birds received vehicle (grey bars) or SR141716A (black bars) prior to the training episode. The hatched line indicates chance performance on the task. Similar rapid learning occurred in the two treatment conditions. However, birds that had received SR141716A prior to the training episode, made significantly fewer errors on the 72 h test than when they had received vehicle before learning ($^{*}p < 0.01$).

4. EXPERIMENT 2: DOES BLOCKING HIPPOCAMPAL CB1-R INFLUENCE LONG-TERM SPATIAL MEMORY FOR SEQUENTIAL REWARD LOCATIONS?

In this experiment, we examined how CB1-R blockade before learning one reward location can influence memory for a second reward location. Sequential learning of spatial locations is especially important for food-storing birds that serially deposit food caches. We were therefore interested in whether memory enhancement during a particular learning episode would interfere with memory for subsequent reward locations. To test this hypothesis, birds first learned the location of a single reward location while CB1-R activity in the HF was blocked. Twenty-four hours after this first learning episode, birds learned that the previous reward location no longer contained a reward, and that a new location now contained a reward. No drug infusions occurred before this second learning episode. Twenty-four hours after this second learning episode (48 h after the original learning episode), we tested birds' memory for both locations. If birds remembered the shift in reward locations from one day to the other, then they should first visit the reward location learned on day 2, and avoid the location learned on day 1. If CB1-R blockade is promoting interference between successive memories, then memory for the second rewarded location should be reduced.

(a) *Methods*

(i) *Subjects*

Seven of the black-capped chickadees used in experiment 1 were used in this experiment.

(ii) *Memory task*

On day 1, birds received intra-hippocampal infusions of the CB1-R blocker SR141716A or vehicle 5 min before a training episode. Birds found a single visible reward placed in one of 19 feeders (location A in figure 3) and then received three rehearsal trials with the mealworm concealed, with a 2 min interval separating these trials.

On day 2, birds found a single visible reward placed in one of the 19 knotless feeders (location B in figure 3). The feeder array was in the same configuration as on day 1 but the reward was placed in a different feeder from that used on the previous day. The feeder that had contained the reward on day 1 no longer contained a reward. After the birds retrieved and ate the mealworm they received three rehearsal trials with the mealworm concealed in this new location, with a 2 min interval separating these trials. No infusions were given on day 2.

On day 3, the birds' memory for both reward locations was tested. Knots concealed all of the feeder holes and birds were released into the testing arena. We placed mealworms in both previously baited locations. We tallied the number of errors birds made before finding each of the two rewards. A cumulative count of errors was made for the two reward locations. For example, if birds made three errors before visiting one of the two reward locations and two more errors before visiting the other reward location, the number of errors the bird made before visiting the first location visited was three, and the number of errors for the second location was five. Because there are no constraints on which rewarded feeder the bird chooses first, this error counting method should not bias the

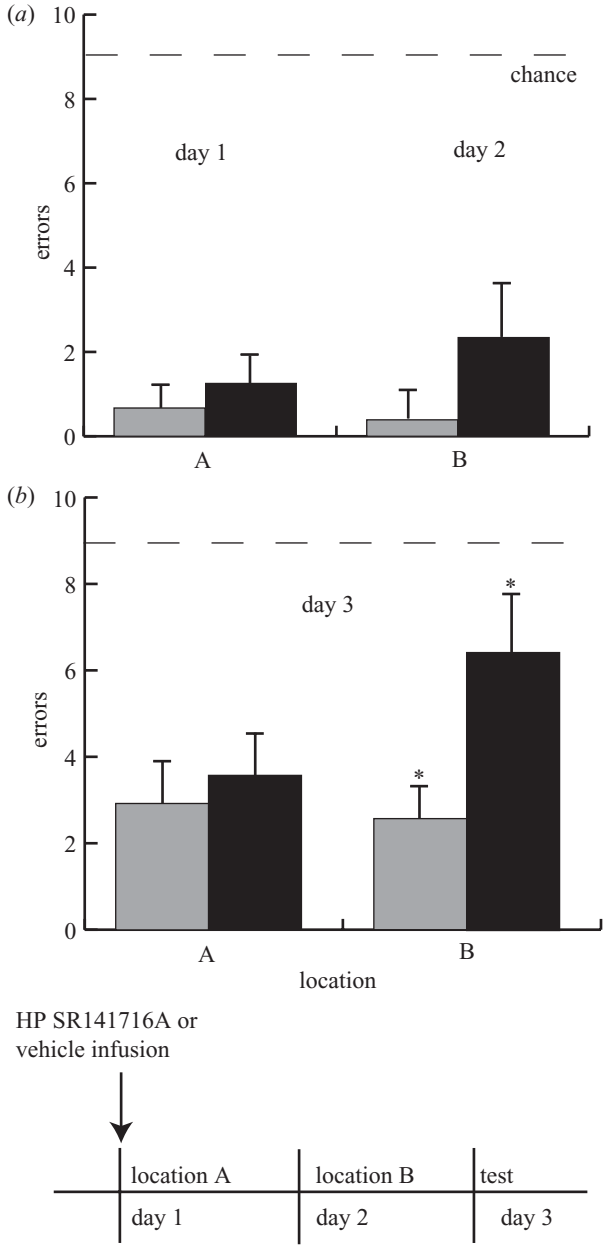

Figure 3. In experiment 2, birds received infusions of SR141716A or vehicle on day 1 prior to a training episode. They then had three rehearsal trials to learn the reward location (location A). On day 2, they learned that this location no longer contained a reward but another did (location B). No infusions occurred on day 2. (*a*) Acquisition performance on the third training trial was similar whether learning location A on day 1 or B on day 2, and whether birds had received SR141716A (black bars) or vehicle infusion (grey bars) before the training episode of day 1. (*b*) On day 3, the number of errors birds made prior to visiting locations A and B was assessed. Birds that had received vehicle on day 1 made similar numbers of errors prior to retrieving the A and B rewards. Birds that received SR141716A on day 1 made significantly more errors in retrieving the B reward compared with birds that received vehicle ($^{*}p < 0.05$).

results for or against one of the reward locations learned on day 1 or day 2.

Each bird experienced both treatment conditions (SR141716A or vehicle infusion) and the order of the infusates was chosen randomly for each bird, resulting in four of the seven birds experiencing SR141716A first. The arrangement of the feeders differed for the two treatment conditions and at least one week separated each treatment condition.

(b) *Results*

Before initial learning of location A on day 1, birds received infusions of either SR141716A or vehicle followed by three rehearsal trials. By the third rehearsal trial, both SR141716A and vehicle-infused birds had accurately learned the location of the hidden reward, and the groups did not differ in the number of errors committed on this third training trial (SR141716A = 1.38 ± 0.75; vehicle = 0.67 ± 0.77, n.s.). As in experiment 1, we found no effects of SR141716A on this short-term memory.

On day 2, birds received three training trials to learn the new reward location (location B in figure 3). Birds received no infusions before learning B. Both birds that had received SR141716A on day 1 and birds that had received vehicle on day 1 learned quickly and did not differ in the number of errors before finding location B (third training trial for B: SR141716A = 2.34 ± 1.44; vehicle = 0.39 ± 0.75, n.s.). Based on their training performance, birds accurately learned the new reward location on day 2. Furthermore, every bird visited the feeder that had been rewarded the previous day (location A), at least once during the three rehearsal trials on day 2, with an average of 1.8 ± 0.40 visits for vehicle-infused birds, and 1.5 ± 0.34 visits for SR141716A-infused birds. Therefore all birds had a similar experience on day 2 of learning that location A no longer contained a reward.

Accuracy of retrieval for both A and B locations was measured on day 3. The number of errors before finding A and B were tallied for each bird in each condition. A multiple measures repeated-measures GLM-ANOVA was used to analyse performance on day 3. The two dependent variables were the errors made before locating A and B. The drug used before learning location A (SR141716A or vehicle) was a within-subject factor. There was no effect of drug on the number of errors birds made before retrieving A ($F_{1,6} = 0.53$, n.s.; figure 3). However, there was an effect of the drug on the number of errors birds made before retrieving B ($F_{1,6} = 6.74$, $p = .04$). Birds that received SR141716A before initial learning made more errors locating the reward in B than in A (SR141716A: A = 2.57 ± 0.57; B = 6.43 ± 0.99; paired $t = 2.59$, $p < 0.05$), whereas birds that initially received vehicle did not differ in their errors to locate A and B. Therefore, CB1-R blockade before learning location A led to poor retrieval of reward location B.

We also examined the order in which birds visited the A and B locations during the day 3 test. Four of seven vehicle-treated birds visited A before visiting B, whereas six of seven SR141716A-treated birds visited A before visiting B. A χ^2 test revealed non-significant differences from chance for the vehicle group (χ^2 vehicle = 0.14, $p = 0.71$) and values that approached significance for the SR141716A-treated group (χ^2 = SR141716A = 3.57, $p = 0.06$).

(c) *Verification of infusion sites*

After experiment 2, the birds were anaesthetized with an overdose of chloropent and were perfused transcardially with 0.8% saline, followed by 10% formalin/0.8% saline. The brains were removed from the skulls, and transferred to 30% sucrose/10% formalin for 48 h. Brains were then

embedded in 10% gelatin/30% sucrose and cut at 40 mm on a freezing microtome. Sections were stained with cresyl violet, coverslipped, and examined with a light microscope. Cannulae for all birds were located within the HF.

5. DISCUSSION

The experiments described here show that CB1-R activity in the HF of black-capped chickadees is important in modulating long-term memory for the location of a hidden reward. The first experiment shows that pharmacological blockade of CB1-Rs facilitates 72 h retention of a single reward location. The second experiment demonstrates a consequence of such memory facilitation on subsequent learning. Memories formed while CB1-R activity was blocked interfere with retention of similar memories formed 24 h later. This behavioural pattern can be attributed to proactive interference. Thus, cannabinoid signalling in the avian HF may play an important role in modifying features of synaptic plasticity underlying memory consolidation, so as to reduce interference between related memories.

We found no motivational effects resulting from HF CB1-R blockade. Both groups of birds behaved similarly during the training episode, suggesting that CB1-R blockade did not influence their motivation to obtain food rewards. Also, because the birds in this experiment had extensive experience with the testing apparatus, experimental procedures and task requirements, we find it unlikely that our treatment was influencing the bird's ability to perform the task. We feel the present results can best be explained in terms of a modulatory effect of hippocampal CB1-R blockade on the acquisition of new spatial information. Although our experiments lack a non-spatial control task, we and others have shown that the avian hippocampus is typically not involved in such cue–reward learning (Sherry *et al.* 1989; Shiflett *et al.* 2003).

Previous research in animals and humans has linked cannabinoids with alterations in learning and memory. Exogenous CB1-R ligands, such as the synthetic cannabinoid agonist WIN55,212-2, as well as Δ^9–tetrahydrocannabinol, the psychoactive agent found in marijuana, have been shown to disrupt performance of spatial and delayed-match to sample memory tasks (Heyser *et al.* 1993; Lichtman *et al.* 1995; Mallet & Beninger 1996; Varvel *et al.* 2001; Egashira *et al.* 2002). Also, pharmacological blockade of CB1-Rs results in improved long-term associative memory (Mansbach *et al.* 1996; Terranova *et al.* 1996; Reibaud *et al.* 1999; Lichtman 2000; Wolff & Leander 2003). These results suggest that endocannabinoid signalling normally occurs during learning, and prevention of this signalling enhances single-item memory relative to control animals.

Our study is the first, to our knowledge, to demonstrate an involvement of CB1-R activity in memory in an avian species. Cannabinoid signalling has been studied in one other avian species, the zebra finch (*Taeniopygia guttata*), in the context of song-related behaviour. In the zebra finch brain, CB1-Rs are expressed in regions associated with song perception and production (Soderstrom & Johnson 2000). WIN55,212-2 reduces the number of song bouts produced by zebra finches (Soderstrom & Johnson 2001). Furthermore, zebra finches injected systemically with WIN55,212-2 before hearing a song showed reduced expression of the immediate-early gene *zenk* in brain areas associated with song perception (Whitney *et al.* 2003). These studies demonstrate that CB1-Rs are conserved in the avian brain and appear to have similar physiological and behavioural functions as in mammals.

Whereas CB1-R blockade may facilitate long-term memory retention, it may hinder the ability of new information to modify existing memories. Our second experiment demonstrates that birds that had received the CB1-R antagonist before learning one reward location had difficulty in remembering a new reward location in the same context. By contrast, when birds received vehicle infusions they were equally likely to go to either of the previously rewarded locations. Similar findings have been reported in mice deficient in CB1-R tested in the Morris water maze, which show impairments in reversal learning (Varvel & Lichtman 2002). Also, CB1-R activation has been shown to be necessary for the extinction of conditioned fear memories (Marsicano *et al.* 2002; Suzuki *et al.* 2004). This pattern of memory deficits suggests that CB1-R signalling may be necessary for maintaining flexible representations in memory, and that blockade of CB1-Rs at the time of memory acquisition may provide a source of proactive interference.

Proactive interference is a problem faced by any organism attempting to remember multiple features of its environment, but it is especially relevant to food-storing species. Food-storing black-capped chickadees serially deposit a few thousand caches each year, and must remember the location of each of their caches to retrieve them (Cowie *et al.* 1981; Shettleworth & Krebs 1982). Thus, it is especially important that a chickadee's memory of its existing caches does not disrupt its ability to encode new cache locations. Also, when it retrieves caches, it should be able to extinguish the previous memory trace and avoid revisiting emptied cache sites. Food-storing birds are indeed less susceptible to proactive interference than other bird species (Clayton & Krebs 1994; Hampton & Shettleworth 1996*b*). If cannabinoid signalling is important for the learning of cache locations in food-storing birds, then one might expect adaptations in the components of cannabinoid signalling in the brains of these animals. It is not known whether food-storing species have adaptations in the properties of endogenous cannabinoid signalling or CB1-R expression in the memory related brain regions.

This experiment demonstrates that cannabinoid signalling in the avian HF is important for modulating long-term memory formation. Blockade of HF CB1-Rs improves long-term memory retention; however, such enhancement may also promote proactive interference, which suggests that normal CB1-R activity may function during learning to reduce proactive interference. This further suggests that the reduced proactive interference demonstrated by food-storing birds may result from modification of cannabinoid signalling in the HF, either through increased levels of endogenous cannabinoids, or increased CB1-R expression in the avian HF. The role of cannabinoids in balancing a memory's trace strength and interfering effects may be important in understanding neural mechanisms of hippocampal function in general, as well as understanding more specifically, the enhanced memory of food-storing birds.

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