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ORIGINAL INVESTIGATION

# CB1 receptor antagonism in capuchin monkeys alters social interaction and aversive memory extinction

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## Abstract

**Rationale** The endocannabinoid system (eCS) is an important modulator of social anxiety and social reward, as well as memory functions.

**Objectives** The present study evaluated the role of eCS in social interactions and aversive memory extinction in capuchin monkeys (*Sapajus* spp.) by blocking the cannabinoid type 1 receptor ($CB_{1r}$).

**Methods** In experiment 1, spontaneous social and non-social behaviors of five capuchin males, each one living in triads with two other females, were observed after AM251 treatment (vehicle, 0.3, 1.0, and 3.0 mg/kg; i.m.). In experiment 2, seven male capuchin monkeys were trained to reach for a reward inside a wooden box. After training, they were given either vehicle or a 3.0-mg/kg i.m. dose of AM251 before a single aversive encounter with a live snake in the box. The latency to return to reach the reward inside the box in subsequent trials was measured.

**Results** The 3.0-mg/kg dose significantly increased the time spent performing self-directed behaviors, while decreasing that of social interactions. No changes were observed in vigilance or locomotion. AM251 increased the latency to reach the reward after the aversive encounter.

**Conclusion** Taken together, these results suggest that $CB_{1r}$ antagonism induces social deficits without increasing anxiety levels and impairs the extinction of aversive memories. This behavioral profile in monkeys underscores the potential involvement of eCS signaling in the deficits observed in autism spectrum disorders.

**Keywords** Endocannabinoid system · AM-251 · Aversive memory · Social interaction · Capuchin monkey

## Introduction

The endocannabinoid system (eCS) has emerged in recent years as an important neuromodulator of social interactions. The eCS has been hypothesized to modulate such social interactions either by controlling social anxiety or by increasing the rewarding properties of social exchanges (Wei et al. 2017). For instance, strengthening endogenous endocannabinoids' signaling by injecting the anandamide hydrolysis inhibitor URB597, either systemically or directly into brain limbic areas (amygdala and nucleus accumbens), has been reported to increase the social activity of rats (Trezza et al. 2012). Conversely, deletion of cannabinoid type 1 receptor ($CB_{1r}$) in mice induces context-dependent alterations in social interaction (Haller et al. 2004; Litvin et al. 2013).

Several lines of investigation have linked the social impairments in autism spectrum disorders (ASD) with disorders in the eCS. Rodent models of ASD, including valproic acid

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(Kerr et al. 2013) and Fmr1 (Jung et al. 2012) or Neuroligin3 gene knockouts (Speed et al. 2015), have been associated with pervasive changes in eCS signaling. Indeed, social deficits in these animal models have been improved or reversed by modulating $CB_{1r}$ activity or general eCS transmission (Speed et al. 2015; Wei et al. 2015; Kerr et al. 2016). Valproate and Fmr1 knockout models of ASD have also revealed impaired extinction of negative/aversive memories (Qin et al. 2015; Kerr et al. 2016). Once again, eCS seems to modulate several aspects related to the acquisition, consolidation, and extinction of memories (Marsicano et al. 2002; Varvel et al. 2007; De Oliveira Alvares et al. 2010). Importantly, Karhson et al. (2018) reported earlier this year that autistic children have a lower plasma concentration of anandamide, consolidating the previous findings in rodent models of ASD and disrupted eCS.

While most rodent models of social impairments display malfunctions in eCS modulation (see Zamberletti et al. 2017, for review), research on non-human primates (NHPs) have so far remained largely silent on this issue (see Bauman and Schumann 2018, for a recent review on this topic). It is still unclear whether the social deficits observed in these models stem from augmented social anxiety or reduced incentive salience of social cues (i.e., rewarding cues), both of which can be modulated by the eCS. It has been shown, nonetheless, that cannabinoids modulate the perception of social threats in humans (Phan et al. 2008) and that facilitation of anandamide signaling improves social impairments in adolescent rats (Doenni et al. 2016). Given that complex human disorders such as ASD cannot be completely represented in animal models, NHP models are a critical translational step to clinical studies due to the closer phylogenetic proximity among primates. Therefore, the present study evaluated the effects of $CB_{1r}$ antagonism, by systemic injections of AM251, on ASD-related social interactions and memory in capuchin monkeys.

## Methods and materials

### Ethical approval

All procedures herein described were carried out in compliance with the Brazilian regulations for the scientific use of laboratory animals (Lei Arouca 11.794/2008), as well as the CONCEA/Brazil guidelines for the care and use of laboratory animals, under the approval of the Animal Ethics Committee of the University of Brasilia (CEUA-UnB, no. 46060/2014).

### Subjects

Capuchin monkeys (Mammalia; Cebidae; *Sapajus* spp.) were group housed in large home-cages (4 m × 3 m × 2 m) of the Primate Center of the University of Brasilia, Brazil. Prior to testing, all subjects were housed in triads (one male and two females) for at least 5 months receiving food and water ad libitum, and remained so throughout the present study (except during aversive memory trials as explained below). In total, 12 adult capuchin monkeys (4 females and 8 males), weighing between 3 and 5 kg, were scored in this study.

### Social impairment test

Five adult male capuchin monkeys from the abovementioned triads were employed in the present study. Female monkeys were not subject to any behavioral measurement, capture, or drug administration.

Three different doses of AM251 (0.3, 1.0, and 3.0 mg/kg, Sigma-Aldrich, USA) were dissolved in a 1:9 solution of Tween 80 (Sigma-Aldrich, Brazil) and phosphate-buffered saline. All doses were injected intramuscularly (i.m.), in a volume of 1 mL/kg, 30 min before the test sessions. Each male capuchin was subjected to all four treatment trials, totaling 4 administrations, 48 h apart. The order of the treatments was pseudo-randomly assigned for each subject.

All experimental sessions were conducted between 07:30 and 11:30 a.m. Initially, five 30-min habituation sessions were carried out to acclimatize the focal subjects and females to the presence of the experimenter team and the general procedure. In these sessions, the subjects were not manipulated in any way (e.g., capture, drug administration), and spontaneous behavior was recorded with a digital video camera placed outside the home-cage. The experimenter left the area around the cages immediately after the recording started. Following the habituation sessions, four test sessions were carried out, one with each of the three doses of AM251, and one with the vehicle. In each session, the male capuchin was captured in its home-cage, by means of a net, and briefly immobilized (< 1 min) for the i.m. injection (similarly to the routine capture procedure, the animals are regularly subjected for veterinary purposes). After the subject received its preestablished treatment, it was immediately returned to its home-cage. Behavioral recording began 30 min after this procedure. The test sessions lasted 30 min.

The behaviors were recorded via focal animal observations (Altmann 1974), with continuous recording (duration in seconds) made for social and non-social behaviors performed by the males. All behavior scoring was performed *off-line* by the same experimenter, who was blind to the treatment. Social and non-social behavior was based on the following definitions (Boinski et al. 1999; Fragaszy et al. 2004; Campos and Fedigan 2009).

The non-social behaviors observed were as follows:

– Locomotion: time spent (in seconds) in motion, or movement of the animal, around the home-cage

– Vigilance: aerial and terrestrial scanning (aerial scanning: time that the animals spent scanning the environment from the horizontal plane upwards, persisting for at least five seconds, while the animal remained stationary; terrestrial scanning: time that the animals spent scanning the environment below the horizontal plane, persisting for at least five seconds while the animal remained stationary)

The social behaviors recorded were as follows:

– Approach: to move toward another individual and staying within arm's length of it for at least one second
– Accept proximity: to remain stationary, for at least one second, following the approach behavior of another individual
– Follow: to move around the home-cage for at least one second by following the route of another animal
– Allogroom: slow and precise repetitive movements of the hand through the fur of another individual, either giving or receiving
– Play: physically vigorous interaction, such as chase and play fighting (rough-and-tumble)

The self-directed behaviors observed were as follows:

– Scratching: to use the hands or feet to rub a part of its body
– Self-grooming: slow and precise repetitive movements of the hand through its own fur

### Aversive memory extinction test

In this experiment, seven adult subjects (capuchin monkeys; *Sapajus* spp.; none of which were subjects in experiment 1) were employed, being four females and three males. The animals were later divided into two experimental groups: vehicle ($n = 3$; 1 female and 2 males) and AM251 ($n = 4$; 2 females and 2 males).

The experiment was carried out in a test-cage (2.50 m × 1.70 m × 2.15 m), located near the subjects' home-cages. On one of the test-cage's wire-mesh walls, a "surprise box" (60 cm × 70 cm × 30 cm) was placed near the ceiling. The surprise box had wooden walls on all sides, except on the side that faced the test-cage's mesh wire, allowing the experimenter to observe, from outside the test-cage, what transpired inside of the surprise box. The surprise box was partially divided in two, with an entrance quadrant and a reward quadrant separated by an opaque wall (45 cm × 30 cm; Fig. 1a). The subject could only access the box through a circular opening (15 cm diameter) that could be remotely closed by a metal door. In the reward quadrant, a transparent acrylic box (27 cm × 27 cm × 15 cm) was fixed to the floor of the surprise box.

This experiment was conducted from 08:00 to 10:00 a.m. The animals were food deprived overnight (approximately 12 h) prior to each trial. Before each trial (see below), the subject was individually led through connecting corridors from its home-cage to the test-cage. No capture procedure (i.e., no physical restraint) was performed, except on the snake confrontation trial, when AM251 was administered. Each session started when the subject entered the test-cage, and lasted for 5 min. During this period, the subject had free access to the entire surprise box and test-cage. All trials were recorded for later analyses using a digital camera.

This experiment was divided into three consecutive phases: habituation, snake confrontation, and extinction. For the initial habituation phase, at least 15 trials, each 24 h apart, were held for each subject. During this phase, a grape was placed on top of the acrylic box located in the reward quadrant of the surprise box. The snake confrontation phase was held 24 h after the last habituation trial. It consisted of a single trial aimed at creating an unexpected aversive event. Therefore, before the trial, a live rainbow boa (*Epicrates cenchria*) was placed and locked inside the acrylic box (Fig. 1b). The lid on this box was tightly sealed to prevent the exchange of air between the box and the outside environment (i.e., presence of olfactory cues). For this session, the animals were divided in two groups: vehicle and AM251. The former received a 1:9 Tween 80 and phosphate-buffered saline solution (1 mL/kg), while the AM251 group was injected with a 3-mg/kg dose of AM251. This dose was chosen based on the results of experiment 1. Each subject was captured by means of a net, briefly immobilized, and then injected with its preestablished treatment 30 min prior to the start of the session. Also, the entrance of the surprise box was closed immediately after the subject's entrance. Visual contact with the snake was only possible after fully entering the box. Each subject was maintained in close proximity with the snake for 5 s, after which the entrance door was opened and the subject could spontaneously return to the test-cage for the remainder of the 5-min trial. The extinction phase started the following day. For this, five consecutive trials, held 24 h apart from each other, were held exactly as those described above for the habituation phase of this experiment. As such, a grape was once again placed on top of the acrylic box, yet in the absence of the snake. The latency to enter the surprise box was measured on all trials.

## Statistics

For the statistical analysis in experiment 1, the *Shapiro-Wilk* test was employed to check for data normality. Since non-parametric samples were detected, the *Friedman* test was used to identify possible between-treatment differences. Subsequent pairwise comparisons were performed using Dunn's multiple comparison test whenever significant

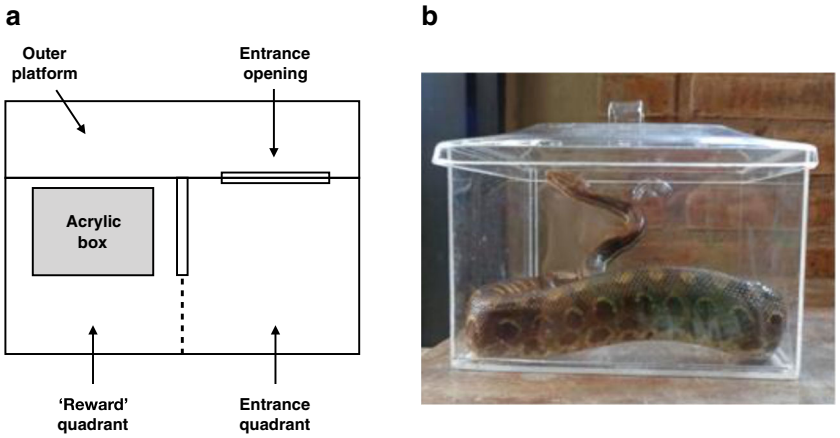


**Fig. 1** **a** Top view schematics of the surprise box designed for the capuchin monkeys' aversive memory extinction test. **b** Acrylic box containing a live rainbow boa (*Epicrates cenchria*)

differences were detected. In the case of clustered behaviors (i.e., self-directed and social behaviors), total time spent performing each behavior (as defined above) was pooled together for each individual in a given trial. In experiment 2, the latency to enter the box in the last habituation trial and all five extinction trials were analyzed by a two-way ANOVA (factors: trial × treatment). Tukey's multiple comparison test was used for subsequent pairwise comparison. An alpha value of 0.05 was used in all analyses.

## Results

In the social impairment test, none of the AM251 treatments significantly altered the subjects' locomotor activity ($p > 0.05$, Friedman's $Q = 0.6$; Fig. 2a). Similarly, changes in vigilance behavior duration were not observed ($p > 0.05$, Friedman's $Q = 2.52$; Fig. 2b). In spite of the normal exploratory behavior (locomotion and vigilance), AM251 administration significantly increased the time spent on self-directed behaviors at the highest dose (3.0 mg/kg, i.m.) in comparison to the vehicle treatment ($p < 0.05$, Friedman's $Q = 12.12$; Fig. 3a). On the other hand, the same dose of AM251 decreased the time spent on social behaviors between the subject and the two co-housed females ($p > 0.05$, Friedman's $Q = 9.24$; Fig. 3b). Table 1 shows the average scores for uncollapsed social and self-directed behaviors. Play and allogroom behaviors were not observed in the subjects.

In the aversive memory extinction test, subjects in the AM251 group showed longer latencies to return to the surprise box, after the snake confrontation phase. There was a significant main effect in latency for treatment ($F_{1,30} = 12.2$; $p < 0.01$), AM251 vs. vehicle (Fig. 4), and session ($F_{5,30} = 4.969$; $p < 0.01$) factors, but no factor interaction ($F_{5,30} = 0.753$; $p > 0.05$). Pairwise comparison yielded no significant difference within individual sessions ($p > 0.05$).

## Discussion

In the present study, the systemic administration of AM251 in adult male capuchin monkeys induced a decrease in social and an increase in self-directed behaviors and resistance to aversive memory extinction. This profile was detected at the highest dose employed here (3.0 mg/kg), yet with no concomitant changes in the

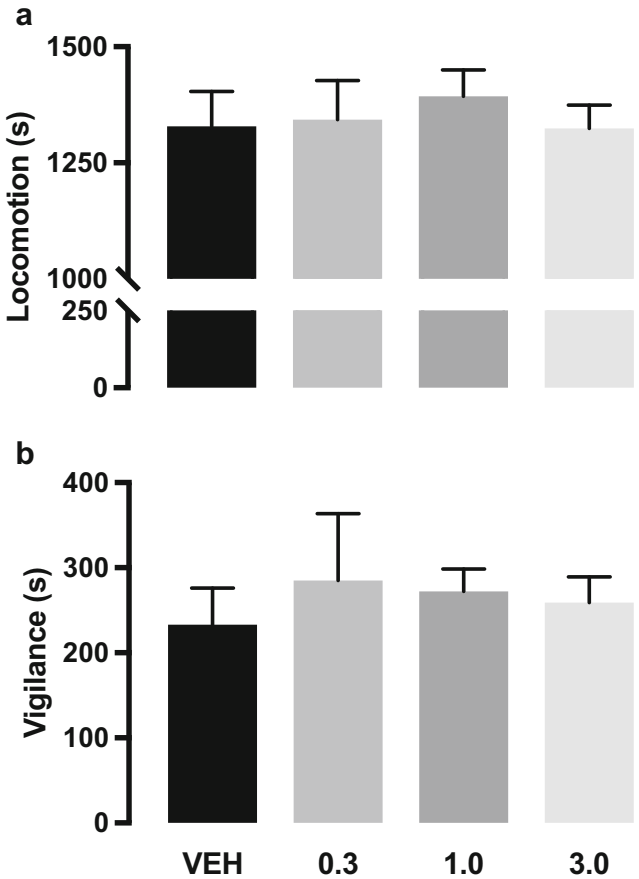


**Fig. 2** The effects of AM251 (mg/kg; i.m.) on **a** locomotor behavior and **b** vigilance behaviors during 30-min trials of capuchin monkeys ($n = 5$)

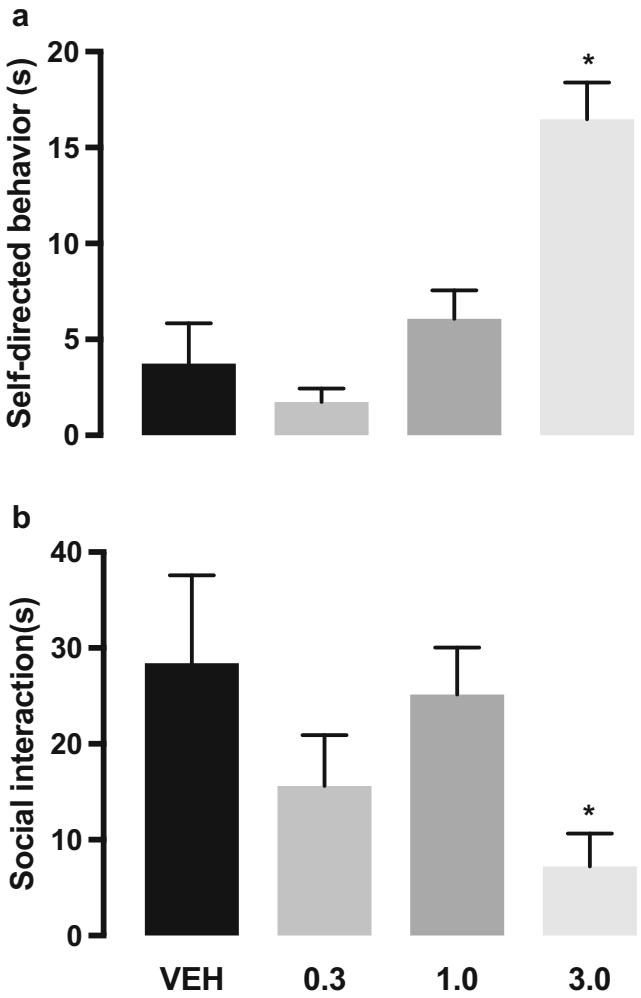


**Fig. 3** The effects of AM251 (mg/kg; i.m.) on the time spent on **a** self-directed behaviors and **b** social interaction behaviors during 30-min trials of capuchin monkeys ($n = 5$). *$p < 0.05$ vs. VEH

subjects' locomotor activity or vigilance behavior. To our knowledge, this is the first study to assess the $CB_{1r}$ modulation of such behaviors in a non-human primate (NHP), and therefore, our findings are mostly discussed in the context of the rodent literature.

The reduced social interaction observed here is in keeping with the results from previous studies with mice and rats. For instance, $CB_{1r}$ blockade by AM251 was shown to decrease the social interaction time of rats (Seillier et al. 2013) and to reduce the preference for social context in mice (Wei et al. 2015). Using both $CB_{1r}$ knockout mice and systemic AM251 blockade, Litvin et al. (2013) suggested that the ensuing social interaction impairment could stem from higher levels of (social) anxiety. In this sense, the increased levels of self-directed behaviors found here in capuchins may corroborate this hypothesis. However, prior studies with marmoset monkeys showed that 2.0 mg/kg of AM251 induced a moderate anxiolytic profile in the open-field test, with no changes in vigilance behavior or locomotor activity (Cagni and Barros 2013; Cagni et al. 2014). In both cases, the subjects were individually tested, so the anxiolytic effect detected is unlikely related to social anxiety. Nonetheless, all AM251 treatments used in the present study also failed to change the vigilance and locomotion of the capuchin monkeys, and thereby does not seem to support an anxiogenic effect in a social context. Although self-grooming and scratching may be interpreted as displays of anxiety in some contexts (Barros and Tomaz 2002), Wei et al. (2015) suggested that $CB_{1r}$ signaling may regulate incentive salience of social cues independent of its role in modulating anxiety. Also, no increase in aggressiveness among subjects was detected (data not shown). Taken together, the results observed here (i.e., increased self-directed behaviors, decreased social behaviors, and no changes in vigilance and locomotion or aggressiveness) suggest that $CB_{1r}$ antagonism decreases social interaction in capuchins possibly by reducing the rewarding properties of social cues rather than by increasing social anxiety. A definitive answer to this question, however, might require a comparison between social and non-social tests of anxiety in this species.

In the aversive memory extinction test, all monkeys behaved as if in extreme distress during the brief confrontation period with the live snake, trying to force their way out of the surprise box. Nevertheless, the subjects which received a single dose of AM251 prior to the aversive encounter showed longer latencies to enter the surprise box during the subsequent extinction trials, in comparison to the vehicle group (Fig. 4). Either systemic $CB_{1r}$ antagonism or $CB_{1r}$ deficiency impairs memory extinction in rodents, but seems to have no impact on acquisition (Marsicano et al. 2002; Varvel et al. 2007). Here, we administered AM251 systemically in a single injection shortly before confrontation with the live snake. The increase in latencies during subsequent extinction trials suggests that AM251 may have enhanced acquisition/consolidation of the aversive event. On the other hand, centrally administered antagonists in

**Table 1** Duration (±SEM) of social and self-directed behaviors

| | VEH | 0.3 mg/kg | 1.0 mg/kg | 3.0 mg/kg |
|---|---|---|---|---|
| Social | | | | |
| Approach | 20.2 (11.79) | 12 (5.4) | 19.4 (5.61) | 7.4 (3.54) |
| Accept proximity | 3.4 (1.72) | 3.2 (3.2) | 5.2 (2.33) | 0 (0.0) |
| Follow | 1.2 (0.80) | 0.7 (0.44) | 0.6 (0.4) | 0 (0.0) |
| Self-directed | | | | |
| Scratching | 1.4 (2.61) | 0.8 (1.1) | 5.6 (6.73) | 13.6 (11.76) |
| Grooming | 5.8 (3.56) | 2.6 (1.47) | 6 (3.21) | 15.2 (6.75) |

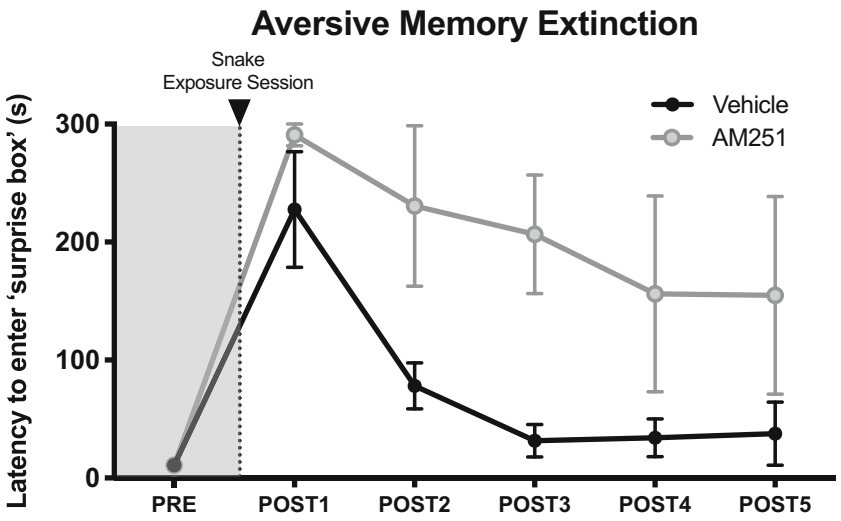


**Fig. 4** The effects of AM251 (3.0 mg/kg, i.m.) on aversive memory extinction of capuchin monkeys ($n = 7$). AM251 was administered 30 min prior to the snake session. PRE-EXP = last habituation trial; POST1–5 = extinction trials 1 through 5

rodents were found to either induce deficits in consolidation (in the hippocampus, De Oliveira Alvares et al. 2010) or acquisition (amygdala; Tan et al. 2011). These conflicting results may reflect important differences in brain anatomy and neurochemistry between rodents and primates. Alternatively, it could be argued that AM251 may have strengthened memory trace of the aversive event and therefore made it more resistant to extinction. Regardless of the mechanism in place, the behavioral profile observed here suggests that extinction of the snake's memory was impaired.

Besides acting as a $CB_{1r}$ inverse agonist (Pertwee 2005), AM251 is also a GPR55 agonist (Ryberg et al. 2007) and adenosine type 1 receptor antagonist (Savinainen et al. 2003). Currently, very little is known on the consequences of the interaction of AM251 with these pharmacological targets. It is thus plausible that some of the effects reported here were mediated/influenced by either or both of these targets. Although it would be hard to rule them out in this kind of experiment, AM251 has indeed been shown to block anandamide-induced increases in social preference (Wei et al. 2015), further suggesting $CB_{1r}$ as the main target of the observed effects.

Finally, most efforts to establish a putative eCS model for ASD have centered in genetic knockout studies (fragile × syndrome, Neuroligin3, and BTBR models) or fetal/early exposure to contaminants (valproate and LPS injection) in rodents (Zamberletti et al. 2017). To date, despite considerable recent advances, no putative ASD model in NHPs has been put forward (see Bauman and Schumann 2018, for review). Promising alternatives, such as the prenatal exposure of rhesus monkeys to maternal antibodies, still lack a detailed analysis of the possible impairments to the eCS—as has been done in rodent models (e.g., Jung et al. 2012). Since the changes in social behavior reported here in the capuchin monkeys mirror some of the social impairments observed in NHP models of ASD, further investigation into the involvement of eCS, especially the impact $CB_{1r}$ antagonism, in such models is warranted.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that there is no conflict of interest.

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