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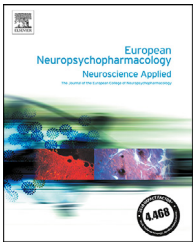

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Modulation of object memory consolidation by heroin and heroin-conditioned stimuli: Role of opioid and noradrenergic systems

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Abstract
There is recent evidence that cocaine, nicotine, and their conditioned stimuli have the ability to enhance memory consolidation. The present study compared the effects of post-training heroin and of a heroin contextual conditioned stimulus (CS+) on consolidation of object recognition memory and investigated the roles of opioid and beta-adrenergic receptors in heroin/CS+ memory modulation by co-administering the respective antagonists, naltrexone (NTX) and propranolol (PRO). Three experiments were performed in male Sprague-Dawley rats demonstrating that immediate, but not delayed, post-sample exposure to heroin (0.3, 1 mg/kg), or exposure (30 min) to a contextual CS+ paired with 1 mg/kg heroin (5 pairings, each 120 min), equally enhanced object memory. Importantly, while the memory enhancing effects of 1 mg/kg heroin and of the contextual CS+ were not altered by post-training co-administration of 3 mg/kg naltrexone, they were blocked by post-training co-administration of 10 mg/kg propranolol. Taken together, these data suggest that a context paired with heroin shares the memory enhancing effect of heroin itself and that these unconditioned and conditioned drug stimuli may modulate memory through the activation of beta-noradrenergic receptors.
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1. Introduction

Drugs of abuse have powerful effects on behavior in part because they enhance the consolidation of neural representations of learned events (White and Milner, 1992;

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McGaugh, 2000; White, 2002). Hence, drugs such as cocaine, nicotine, amphetamine, morphine, heroin, and alcohol, when administered post-training during the period of memory consolidation, generally enhance performance of various learning tasks, in various species (Introini-Collison and McGaugh, 1989; Saha et al., 1990; Puma et al., 1999; Simon and Setlow, 2006; Eddins et al., 2009; Iñiguez et al., 2012; Leri et al., 2013; Rkieh et al., 2014; Weafer et al., 2017; Wolter et al., 2019).

It is well known that neutral stimuli paired with the effects of addictive substances can acquire "conditioned" properties and, consequently, influence behavior. For example, environmental stimuli paired with the acute effects of these drugs consistently elicit approach (i.e., conditioned place preference; for review see Tzschentke, 1998), enhance operant responding maintained by incentive stimuli (Di Ciano et al., 2003), alter locomotion activity (i.e., conditioned locomotion; for review see Barr et al. (1983) and Damianopoulos and Carey (1994)), and stimulate physiological responses such as heart rate and respiratory rate (Bloch et al., 1973; Fitzgerald et al., 1984; Blanco et al., 2012). More importantly, accumulating experimental evidence suggests that conditioned stimuli paired with drugs of abuse can also affect memory consolidation. For example, Wolter et al. (2019) found that post-training exposure to a context paired with cocaine or nicotine enhanced memory in the object recognition (OR) task.

The experiments in this manuscript were designed to explore the effects of opioids on memory consolidation because, while these compounds are clearly reinforcing in people (Mello et al., 1981; Degenhardt et al., 2014) and animals (Kuntz et al., 2008), and opioid-paired stimuli elicit approach conditioned responses (i.e., conditioned place preference; (Tzschentke, 1998; Sticht et al., 2010), the acute effects of agonists (Castellano and Oliverio, 1975; White and Major, 1978; Mondadori and Waser, 1979; Castellano, 1980; Stäubli and Huston, 1980; Introini et al., 1985; Castellano et al., 1994; Cloke et al., 2014) and antagonists (Fulginiti and Cancela, 1983; Introini et al., 1985; Introini-Collison and Baratti, 1986; Introini-Collison and McGaugh, 1989) on memory consolidation have been more mixed, and the question of whether opioid-conditioned stimuli impact memory consolidation has never been explored.

Hence, three experiments were carried out using the object recognition memory task, which has been found sensitive to modulation by cocaine, nicotine, and their conditioned stimuli (Wolter et al., 2019). The first was designed to compare the effects of heroin and of a contextual heroin conditioned stimulus (CS+). Experiment 2 established whether naltrexone (NTX), a non-selective opioid receptor antagonist (Beatty, 1983), could alter the memory effects of post-training exposure to heroin or to the contextual CS+ paired with heroin. Because this experiment generated puzzling findings, a hot-plate test was employed to verify the pharmacological competition between NTX and heroin on analgesia. Finally, Experiment 3 investigated whether the effects of heroin or of the contextual heroin CS+ could be modified by administration of propranolol (PRO), a beta-noradrenergic antagonist that has been found to block the memory enhancing effects of various manipulations (Cahill et al., 1994; Lee and Ma, 1995; Schneider et al., 2011; Goode et al., 2016; Goodman and Packard, 2016). An effect of PRO was anticipated because this noradrenergic antagonist has been found to modulate the effects of opioid agonists and antagonists on consolidation of memory tested by inhibitory avoidance, Y-maze discrimination and Y-maze spatial recognition (Introini-Collison and Baratti, 1986; Introini-Collison et al., 1989; Zhang et al., 2008).

2. Experimental procedures

2.1. Subjects

A total of 124 male Sprague-Dawley rats (Charles River, Quebec, Canada), weighing between 225 and 250 g at the beginning of the experiments were individually housed in standard rat cages (polycarbonate; 50.5 × 48.5 × 20 cm) with standard bedding and environmental enrichment, and were maintained on a reverse light-dark schedule (lights off at 07:00; on at 19:00). All testing and injections were performed during their dark period. The rats had access to 25 g per day of standard rat chow, and water was available ad libitum in home cages. All procedures adhered to the guidelines of the Canadian Council on Animal Care and were approved by the University of Guelph Animal Care Committee.

2.2. Apparatus

2.2.1. Conditioning chambers

The chambers (30 cm × 40 cm × 26 cm) used for contextual conditioning were made of semi-transparent Plexiglass (University of Guelph, ON, Canada), differed in visual (half of the chambers had vertical black and white stripes and the other half had a checkered pattern) and tactual (half of the chambers included a ceramic tile on the floor) cues, and were covered by black wire mesh to enable automatic video tracking (EthoVision v11.5, Noldus, The Netherlands).

2.2.2. Object recognition task

This memory task is based on the natural tendency of rats to explore novel objects (Ennaceur and Delacour, 1988; Winters et al., 2004) and was selected because of our previous demonstration that OR 72 h after learning is improved by post-sample cocaine, nicotine or exposure to cocaine- or nicotine-contextual CSs (Wolter et al., 2019). The Y-apparatus was used for OR has been described previously by Winters et al. (2004). The objects used were of varying sizes, tactile qualities, visual qualities, shape, and height. On each object recognition trial, the rats experienced a new set of never before seen objects.

2.2.3. Hot plate latency

Analgesia was assessed using a hot plate apparatus (Model LE7406; LSI Letica. Spain, Barcelona). The heated surface (22 × 22 cm) was maintained at 50 ± 2.1 °C (Leri et al., 2007). The rats placed onto the apparatus were removed after they had licked one hind paw or 60 s of session time had elapsed (Carter, 1991).

2.3. Procedures

2.3.1. Experiment 1

A group of rats ($n = 28$) was used to assess the effect of acute post-sample injections of 0, 0.3, or 1 mg/kg heroin on OR memory. These rats were habituated to the empty Y-apparatus for 5 min on two consecutive days before the beginning of testing. The test

trials began 24 h after the second habituation session. Each trial consisted of two phases: a sample phase and a choice phase, separated by a 72-h retention interval. This retention interval was chosen as a "suboptimal" condition in which drug-naïve rats do not typically express memory (Melichercik et al., 2012; Rkieh et al., 2014; Wolter et al., 2019). Rats were always exposed to new, never-before-seen objects for each new trial.

During the sample phase, two identical novel objects were placed into the Y-apparatus at the end of each exploration arm. Each rat was placed in the start box, and the guillotine door was opened. Rats were allotted a maximum of 180 s to explore objects or were removed if 25 s of total object exploration was achieved, whichever came first. Object exploration was defined as directing the nose to the object at <2 cm and/or touching the object with the nose. The rats were injected immediately after the conclusion of the sample phase with vehicle or heroin (0.3 or 1 mg/kg). All animals were tested at each dose of heroin and the order of heroin doses was counterbalanced using a Latin Square Design. Following the 72-h retention interval, rats experienced the choice phase, for which the Y-apparatus contained a copy of the original sample object in one arm and a novel object in the other. The choice phase lasted 2 min, and the time spent exploring the novel and familiar objects was recorded. Different object pairs were used for each trial, and the order of exposure to object pairs, as well as the designated sample and novel objects for each trial were counterbalanced. Another group of 12 rats received vehicle or 1 mg/kg heroin 6-h following the conclusion of the sample phase to evaluate the time-dependency of any observed memory effect.

A separate group of 12 animals was used to assess the effects of post-sample exposure to a 1 mg/kg heroin conditioned context on OR memory. All rats were habituated to each of the chambers for 30 min, 24 h prior to the beginning of conditioning (0 mg/kg heroin in CS− and 1 mg/kg heroin in CS+). At the beginning of conditioning, rats received either 0 mg/kg heroin or 1 mg/kg heroin and were immediately placed in the CS− or CS+ chamber for 2 h, respectively. The chambers of the apparatus used as CS− and CS+ were counterbalanced across rats. All animals received a total of 5 conditioning sessions with the CS− and 5 with the CS+, alternating over 10 successive days. Conditioned locomotion was assessed on two separate tests. The first test occurred the day after the last conditioning session and half of the animals were placed in the CS− and the other half were placed into the CS+. The second test occurred 72 h later and the same animals were tested in the alternate chamber. The rats were habituated to the Y-apparatus on Days 9 and 10 of conditioning and were exposed to the sample phase prior to the first test of conditioned locomotion on Day 11. Therefore, 6 of these subjects were exposed to the CS− immediately following exposure to the two objects, and the other 6 were exposed to the CS+ immediately following exposure to the two objects. The choice phase of OR occurred 72 h later (Day 14). On Day 15, the same animals experienced another sample phase of OR with different objects, and right after they were confined to the alternative conditioning chamber (CS− or CS+). The final test of OR occurred 72 h later (Day 18). Finally, this experiment also included a separate group of 12 rats that were tested as described above, but exposure to the CS− and CS+ was delayed by 6 h following the two sample phases.

2.3.2. Experiment 2

A group of rats ($n = 12$) was used to access the effects of immediate post-training injections of 1 mg/kg heroin as well as co-administration of 1 mg/kg heroin and 3 mg/kg NTX on object recognition memory. The procedure used for this experiment was identical to that of experiment 1. A separate experiment was also conducted with the same group of rats tested the same as above, but only receiving injections of 1 or 3 mg/kg NTX post-training. Finally, this group of animals was also evaluated for heroin analgesia by testing their hind-paw lick latency on a hot-plate using the same drugs and doses as above. Rats were pre-treated (within group) with 0 mg/kg heroin, 1 mg/kg heroin or 1 mg/kg heroin & 3 mg/kg NTX. The rats placed onto the testing apparatus were removed after they licked one of their hind-paws or a maximum 60 s had elapsed.

A separate group of 12 rats was used to assess the effects of 3 mg/kg NTX on post-training exposure to compartments previously paired with 0 mg/kg heroin (the CS-) and compartments previously paired with 1 mg/kg heroin (the CS+). The procedures employed during conditioning and post-training exposure to the CS- and CS+ were identical to experiment 1, the only difference being that rats were also tested with injections of 3 mg/kg NTX in the CS- and CS+ post-training.

2.3.3. Experiment 3

A group of rats ($n = 12$) was used to assess the effects of post-training co-administration of 1 mg/kg heroin and 10 mg/kg PRO on OR. The procedures and testing parameters were the same as experiment 1 and 2; however, now rats were co-administered with 1 mg/kg heroin and 10 mg/kg PRO post-training. A separate group of animals ($n = 12$) were also evaluated using the same testing procedures as above but were injected with 5 or 10 mg/kg PRO post-training and assessed following a 24 h retention interval. A 24 h retention interval has been established as a sufficiently short interval at which normal rats should perform OR successfully when tested in a Y-apparatus (Winters et al., 2004, 2008). A separate group of rats ($n = 12$) were used to assess the effects of 10 mg/kg PRO on post-training exposure to compartments previously paired with 0 mg/kg heroin (the CS-) and 1 mg/kg heroin (the CS+). The procedures and testing parameters were the same as experiment 1 and 2, but the rats were injected with 0 mg/kg PRO or 10 mg/kg PRO prior to confinement in the CS- and CS+ post-training.

2.4. Drugs

Heroin (Diacetylmorphine hydrochloride, Almat Pharmachem, Concord, ON), naltrexone hydrochloride (Sigma Aldrich) and propranolol hydrochloride (Sigma Aldrich) were dissolved in 0.9% physiological saline and injected subcutaneously at a volume of 1.0 ml/kg. Vehicle (0.9% physiological saline) was injected at the same volume subcutaneously. The range of heroin doses utilized was selected on the basis of previous place conditioning and memory consolidation studies. Hence, both 0.3 (Leri and Rizos, 2005) and 1 mg/kg heroin (Leri and Rizos, 2005; Levy et al., 2009) reliably produce a conditioned place preference, and post-training administration of heroin enhanced acquisition of tasks involving fear conditioning, maze learning, and social learning (Levy et al., 2009; Leri et al., 2013). The range of doses of naltrexone utilized were selected on the basis of previous place conditioning and memory consolidation studies (Introini et al., 1985; Introini-Collison and Baratti, 1986; Introini-Collison et al., 1989; Leri et al., 2003). The range of doses of propranolol were selected on the basis of previous memory consolidation studies (Cahill et al., 1994; Lee and Ma, 1995; McGaugh, 2004).

2.5. Data analysis

Two-way repeated measures analyses of variance (ANOVA) were performed using SigmaPlot (v.12.5, Systat Software Inc). Significant main effects and/or interactions were further analyzed by Student Newman-Keuls post-hoc analysis. The significant alpha level for all analyses was set at 0.05. The values of non-significant analyses are not reported. Analyses of the OR task required the calculation of a discrimination ratio (DR) to standardize for differences in individual total exploration times between the rats. A DR is a ratio of object preference, where a score of 0 means the rat shows no preference between the two objects, a positive score indicates preference of the novel object, and a negative score indicates prefer-

ence for the familiar object. Exploration data were taken from the first minute of the choice phase to calculate the choice discrimination ratio [1 min novel object exploration – 1 min familiar object exploration / 1 min novel object exploration + 1 min familiar object exploration], as previous research indicates that novelty preference is most robust during the first minute of the choice phase (Dix and Aggleton, 1999). The sample DR was calculated using an if/then scenario: (If "novel side is left" (left arm exploration – right arm exploration) / (total object exploration) If "novel side is right" (right arm exploration – left arm exploration) / (total object exploration)). A minimum exploration time was not employed in these calculations.

3. Results

3.1. Experiment 1

Immediate post-sample heroin (0.3, 1 mg/kg) enhanced OR choice DRs (Fig. 1A). The ANOVA revealed a significant interaction between Dose and Phase [$F(2, 46) = 4.62$, $P < 0.05$], as well as significant main effects of Dose [$F(2, 46) = 4.29$, $P < 0.05$] and Phase [$F(1, 46) = 29.13$, $P < 0.01$]. Multiple comparisons further indicated that post-sample 0.3 and 1 mg/kg heroin significantly increased the choice discrim-

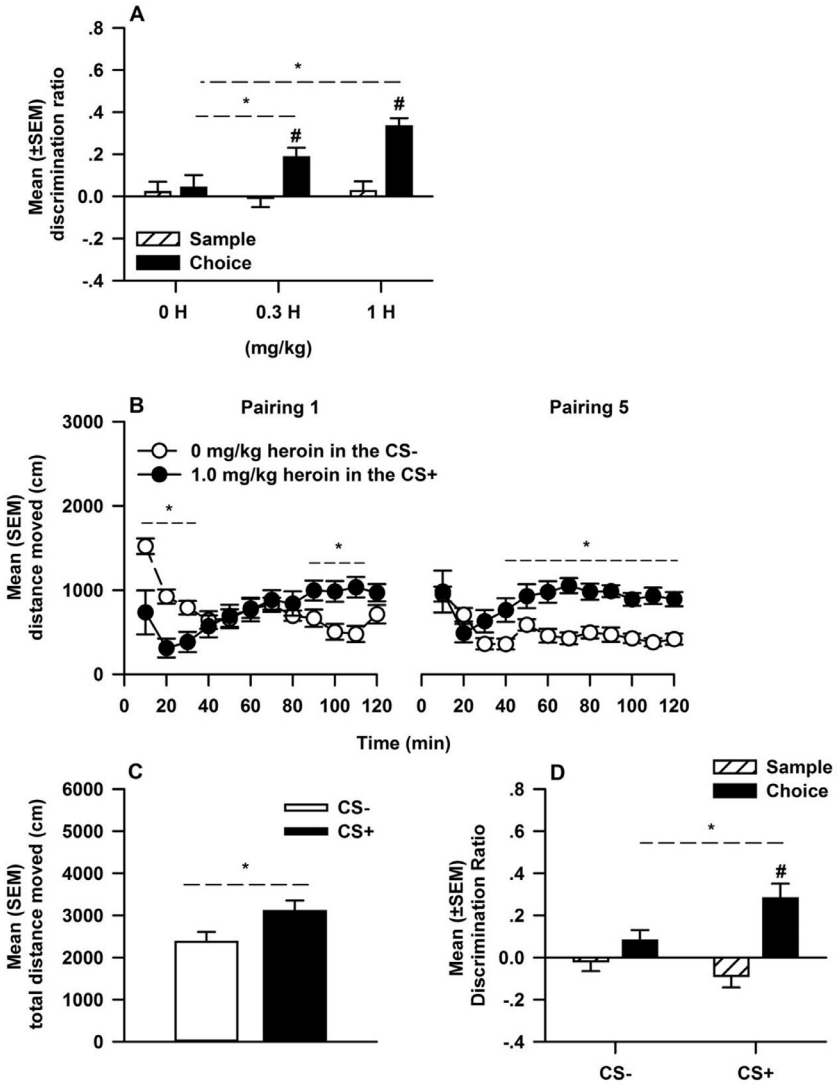

Fig. 1 **(A):** Mean (±SEM) discrimination ratios from sample and choice phases by the same rats ($n = 28$) following post-sample injections of 0, 0.3, and 1 mg/kg heroin. The * denotes a significant difference compared to 0 mg/kg heroin choice phase discrimination ratio. The # denotes a significant difference compared to sample discrimination ratio within dose. **(B):** Mean (SEM) distance moved by the same rats ($n = 12$) in compartments paired with injections of 0 mg/kg heroin (CS-) and 1 mg/kg heroin (CS+) during the first and last set of pairings. The * denotes a significant difference between compartments. **(C):** Mean (SEM) total distance moved in 30 min of confinement to the CS- and CS+, and the * denotes a significant difference between compartments. **(D):** Mean (±SEM) discrimination ratios during sample and choice phases of OR displayed by the same rats ($n = 12$) following confinement to CS- and the CS+. The * denotes a significant difference compared to the CS- choice phase DR. The # denotes a significant difference compared to the sample phase DR.

Table 1 Mean (±SEM) discrimination ratio (EXP. 1, 2, 3).

EXP	Group	Sample D.R (±SEM)	Choice D.R (±SEM)	Sample VS. Choice
1. 6-h del heroin (72-h ret)	0 mg/kg	0.02 (0.03)	0.04 (0.09)	ns
	1 mg/kg	−0.06 (0.05)	0.01 (0.07)	ns
6-h del CS (72-h ret)	CS-	−0.02 (0.05)	0.09 (0.07)	ns
	CS+	−0.01 (0.05)	0.11 (0.10)	ns
2. NTX (72-h ret)	0 mg/kg	0.17 (0.07)	0.05 (0.05)	ns
	1 mg/kg	−0.09 (0.06)	0.03 (0.12)	ns
	3 mg/kg	0.04 (0.05)	0.06 (0.08)	ns
3. PRO (24-h ret)	5 mg/kg	−0.00 (0.05)	0.48 (0.51)	P <0.01
	10 mg/kg	−0.00 (0.07)	0.43 (0.56)	P <0.01

EXP 1. Mean (±SEM) discrimination ratios from sample and choice phases by rats exposed to 0 and 1 mg/kg heroin ($n = 12$; within subject design), or exposure to the CS- or CS+ ($n = 12$; within subject design), 6 hr after the sample phase ("del") and tested following a 72 h retention interval. **EXP 2.** Mean (±SEM) discrimination ratios from sample and choice phases of object recognition by the same rats ($n = 12$) following injections of 0, 1 and 3 mg/kg naltrexone following the sample phase and tested following a 72 h retention interval. **EXP 3.** Mean (±SEM) discrimination ratios from sample and choice phases of object recognition by the same rats ($n = 12$) following injections of 5 and 10 mg/kg propranolol immediately post-sample and tested following a 24 h retention interval.

ination ratio compared to the sample discrimination ratio, as well as to the 0 mg/kg heroin choice discrimination ratio. When injections of 1 mg/kg heroin were delayed by 6 h, the choice discrimination ratio was not significantly altered ("del" - Table 1). The analyses of total object exploration for the sample and choice phases were not significant (data not shown).

Injections of 1 mg/kg heroin during conditioning had a bi-phasic effect on locomotion. Fig. 1B represents mean (SEM) distance moved by the same rats during the first CS- & 0 mg/kg heroin and CS+ & 1 mg/kg heroin pairings. In pairing 1, the ANOVA revealed a significant interaction between Dose and Time [$F(11, 121) = 14.66$, $P < 0.01$], as well as a significant main effect of Time [$F(11, 407) = 5.92$, $P < 0.01$]. Post-hoc analysis further indicated that, after receiving 1 mg/kg heroin, the animals moved significantly less during the initial 0–30 min and significantly more during the remaining 70–110 min of the session. In pairing 5, the ANOVA revealed a significant interaction between Dose and Time [$F(11, 121) = 4.57$, $P < 0.01$], as well as a significant main effect of Time [$F(11, 121) = 4.33$, $P < 0.01$] and Dose [$F(1, 121) = 15.01$, $P < 0.01$]. Post-hoc analysis further indicated that, after receiving 1 mg/kg heroin, the animals moved significantly more during the remaining 40–120 min of the session.

Hyperactivity was observed in the CS+ compartment previously paired with 1 mg/kg heroin. Fig. 1C represents mean (SEM) total distance moved by the same rats confined to the CS- and the CS+ compartments. The analysis of total distance moved was significant [$F(1,11) = 9.23$, $P < 0.05$], and the post-hoc analysis indicated that the same rats confined in the CS+ moved significantly more than when they were confined in the CS-.

Immediate post-sample confinement into the CS+ previously paired with heroin enhanced OR choice DRs. Fig. 1D represents mean (±SEM) discrimination ratios during the sample and choice phases of OR following exposure in the same animals confined post-sample to the CS- and the CS+. The ANOVA revealed a significant interaction between Compartment and Phase [$F(1, 11) = 9.04$, $p < 0.05$], as well as a significant main effect of Phase [$F(1, 11) = 31.64$, $p < 0.01$]. Multiple comparisons further indicated that immediate post-training confinement into the CS+ significantly enhanced the choice discrimination ratio in comparison to when the same animals were confined into the CS- post-training. When exposure to the CS+ was delayed by 6-h, the choice discrimination ratio was not significantly altered ("del" - Table 1). The analysis of total object exploration was not significant (data not shown).

3.2. Experiment 2

Naltrexone (3 mg/kg) did not alter the effects of 1 mg/kg heroin on choice DRs when co-administered post-training. Fig. 2A represents the mean (±SEM) discrimination ratio calculated during the sample and choice phases of OR following immediate post-sample injections of 0 mg/kg heroin, 1 mg/kg heroin or 1 mg/kg heroin and 3 mg/kg NTX. The ANOVA revealed a significant main effect of Drug [$F(2,22) = 11.33$, $P < 0.01$] and Phase [$F(1,22) = 8.71$, $P < 0.05$]. Multiple comparisons indicated that when rats were injected with 1 mg/kg heroin or co-administered 1 mg/kg heroin and 3 mg/kg NTX post-sample, their choice discrimination was significantly higher compared to their sample discrimination ratio. Immediate post-training injections of NTX (0, 1 or 3 mg/kg) did not significantly alter choice discrimination ratios (Table 1). The analyses of total object exploration for the sample and choice phases were not significant (data not shown).

The absence of a modulatory effect by 3 mg/kg NTX on 1 mg/kg heroin choice DRs was followed up by a test, using the same drugs and doses, of hot plate latency using the same animals. When the rats received 0 mg/kg heroin, the latency to lick the hind-paws was: [$M = 18.86$ s (SEM = 2.63 s)]. When the same rats were pre-treated with heroin, the latency was [$M = 52.11$ s (SEM = 2.73 s)]. And, finally, when they received 1 mg/kg heroin & 3 mg/kg NTX, the latency was [$M = 16.35$ s (SEM = 2.57 s)]. The analysis of variance was significant [$F(2, 22) = 111.95$, $P < 0.01$] and multiple comparisons revealed that when the rats were pre-treated with 1 mg/kg heroin they took significantly longer to lick their hind-paws than when the same rats were pre-treated with 0 mg/kg heroin or 1 mg/kg heroin & 3 mg/kg NTX.

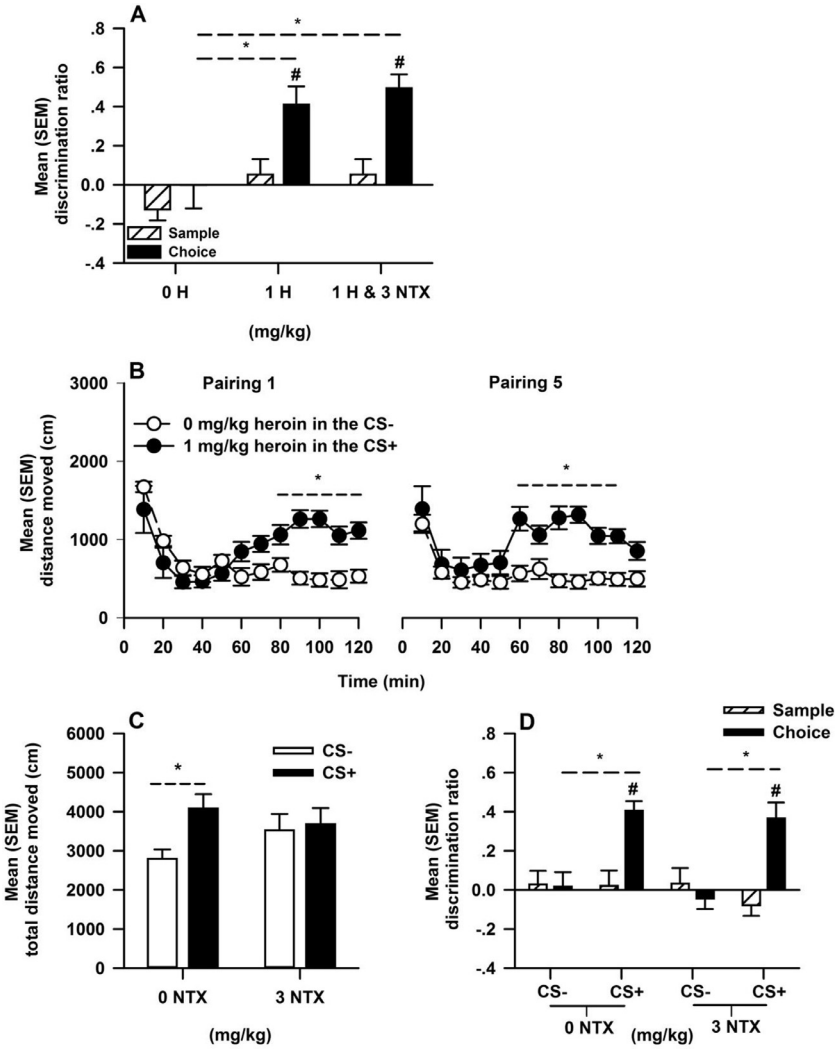

Fig. 2 **(A):** Mean (±SEM) discrimination ratios from sample and choice phases by the same rats ($n = 12$) following post-sample injections of 0 mg/kg heroin, 1 mg/kg heroin or co-administration of 1 mg/kg heroin and 3 mg/kg NTX. The * denotes a significant difference compared to 0 mg/kg heroin choice phase discrimination ratio. The # denotes a significant difference compared to sample discrimination ratio within dose. **(B):** Mean (SEM) distance moved by the same rats ($n = 12$) in compartments paired with injections of 0 mg/kg heroin (CS-) and 1 mg/kg heroin (CS+) during the first and last set of pairings. **(C):** Mean (SEM) total distance moved in 30 min of confinement into the CS- and CS+ of rats pre-treated with either 0 mg/kg NTX or 3 mg/kg NTX. The * denotes a significant difference between compartments. **(D):** Mean (±SEM) discrimination ratios during sample and choice phases of OR displayed by the same rats ($n = 12$) following injections of 0 mg/kg NTX or 3 mg/kg NTX prior to confinement into CS- and the CS+. The * denotes a significant difference compared to CS- choice phase discrimination. The # denotes a significant difference compared to the sample phase DR.

Injections of 1 mg/kg heroin during conditioning had a bi-phasic effect on locomotion. Fig. 2B represents mean (SEM) distance moved by the same rats during the first CS- & 0 mg/kg heroin and CS+ & 1 mg/kg heroin pairings. In pairing 1, the ANOVA revealed a significant interaction between Dose and Time [$F(11, 121) = 7.53$, $P < 0.01$], as well as a significant main effect of Time [$F(11, 121) = 13.16$, $P < 0.01$]. The post-hoc analysis further indicated that, after receiving 1 mg/kg heroin, the animals moved significantly more during the remaining 80–120 min of the session. In pairing 5, the ANOVA revealed a significant interaction between Dose and Time [$F(11, 121) = 4.45$, $P < 0.01$], as well as a significant main effect of Time [$F(11, 121) = 10.84$, $P < 0.01$] and Dose [$F(1, 121) = 9.88$, $P < 0.01$]. The post-hoc analysis further indicated that, after receiving 1 mg/kg heroin, the animals moved significantly more during the remaining 60–110 min of the session.

NTX (3 mg/kg) blocked hyperactivity in the CS+ previously paired with 1 mg/kg heroin. Fig. 2C represents mean (SEM) total distance moved by the same rats confined to the CS- and the CS+ compartments. The ANOVA revealed a significant interaction between CS and Dose [$F(1, 11) = 5.40$, $P < 0.05$], as well as a significant main effect of CS [$F(1, 11) = 9.88$, $P < 0.01$]. Multiple comparisons further indicated that rats only moved significantly more when injected with 0 mg/kg heroin prior to confinement into the CS+ com-

pared injections of 0 mg/kg heroin prior to confinement into the CS-.

NTX (3 mg/kg) did not alter the CS+ choice DRs. Fig. 2D represents mean (±SEM) discrimination ratio produced during the sample and choice phase of OR following exposure to CS compartments previously paired with 0 mg/kg (CS-) and 1 mg/kg heroin (CS+) and injections of 3 mg/kg NTX (in the CS- or CS+) post-sample. The ANOVA revealed a significant interaction between Group and Phase [$F(3,33) = 6.89$, $P = <0.01$], as well as significant main effects of Group [$F(3,33) = 5.54$, $P < 0.01$] and Phase [$F(1,33) = 20.71$, $P < 0.01$]. Multiple comparisons further indicated that when rats were injected with 0 or 3 mg/kg NTX prior to confinement into the CS+, their choice discrimination ratio was significantly higher than their sample discrimination ratio and the test discrimination ratio when the same rats were exposed to the CS- post-training. The analysis of total object exploration was non-significant (data not shown).

3.3. Experiment 3

Propranolol (10 mg/kg) blocked the effects of 1 mg/kg heroin on OR choice DRs. Fig. 3A represents the mean (±SEM) discrimination ratio calculated during the sample and choice phases of OR following immediate post-sample injections of heroin (0 or 1 mg/kg) or co-administration of 1 mg/kg heroin and 10 mg/kg PRO. The ANOVA revealed a significant interaction between Drug and Phase [$F(2,22) = 3.58$, $P < 0.05$] and a significant main effect of Drug [$F(2,22) = 8.09$, $P = < 0.01$]. Multiple comparisons of marginal means indicated that the discrimination ratio was only significantly higher in the choice phase when rats were injected with 1 mg/kg heroin post-sample. The choice discrimination ratio was significantly higher than the sample discrimination ratios when rats were injected with 5 or 10 mg/kg PRO post-training and evaluated using a 24-h retention interval (Table 1).

Injections of 1 mg/kg heroin during conditioning had a bi-phasic effect on locomotion. Fig. 2B represents mean (SEM) distance moved by the same rats during the first CS- & 0 mg/kg heroin and CS+ & 1 mg/kg heroin pairings. In pairing 1, the ANOVA revealed a significant interaction between Dose and Time [$F(11, 121) = 7.53$, $P < 0.01$], as well as a significant main effect of Time [$F(11, 121) = 13.16$, $P < 0.01$]. The post-hoc analysis further indicated that, after receiving 1 mg/kg heroin, the animals moved significantly less in the first 20 min and significantly more during the remaining 70–120 min of the session. In pairing 5, the ANOVA revealed a significant interaction between Dose and Time [$F(11, 121) = 9.91$, $P < 0.01$], as well as a significant main effect of Time [$F(11, 121) = 3.80$, $P < 0.01$] and Dose [$F(1, 121) = 5.22$, $P < 0.05$]. The post-hoc analysis further indicated that, after receiving 1 mg/kg heroin, the animals moved significantly less in the first 10 min and significantly more during the remaining 50–110 min of the session.

Propranolol (10 mg/kg) blocked hyperactivity in the CS+ previously paired with 1 mg/kg heroin. Fig. 3C represents mean (SEM) total distance moved by the same rats confined to the CS- and the CS+ compartments. The ANOVA revealed a significant interaction between CS and Dose [$F(1, 11) = 5.70$, $P < 0.05$], as well as a significant main effect of CS [$F(1, 11) = 15.91$, $P < 0.01$].

Finally, propranolol (10 mg/kg) blocked the effects of the CS+ previously paired with 1 mg/kg heroin on OR choice DRs. Fig. 2D represents mean (±SEM) discrimination ratio produced during the sample and choice phase of OR following post-training injections of 0 mg/kg PRO or 10 mg/kg PRO prior to confinement into CS compartments previously paired with 0 (CS-) and 1 mg/kg heroin (CS+). The ANOVA revealed a significant interaction between Drug and CS [$F(1,11) = 5.65$, $P = < 0.05$], as well as a significant main effect of Drug [$F(1,11) = 9.49$, $P < 0.05$]. Multiple comparisons further indicated that the choice discrimination ratio was only significantly higher when animals were injected with 0 mg/kg PRO prior to confinement into the CS+. The analysis of total object exploration was non-significant (data not shown).

4. Discussion

Cocaine, nicotine, and their conditioned stimuli (Wolter et al., 2019) have the ability to enhance memory consolidation and consequently improve learning of some tasks. The present study compared the effects of post-training heroin and a heroin contextual conditioned stimulus (CS+) on object recognition memory and investigated the role of opioid and beta-adrenergic receptors in heroin/CS+ memory modulation by co-administering the respective antagonist's naltrexone (NTX) and propranolol (PRO). It was found that immediate, but not delayed post-sample exposure to heroin, or to the heroin CS+ enhanced object memory. Interestingly, these effects were not altered by NTX, but they were both blocked by PRO. Taken together, these data suggest that a context paired with heroin shares the memory enhancing effect of heroin itself and that these unconditioned and conditioned drug stimuli may modulate memory through the activation of beta-noradrenergic receptors.

Using the object recognition task, Experiment 1 revealed a dose dependent increase of test discrimination ratios (Fig. 1A) only when 1 mg/kg heroin was administered immediately following the sample phase (Table 1). This observation suggests that post-sample administration of heroin enhanced the memory of the objects explored during the sample phase and rules out possible effects of the drug on other stages of memory processing or on other cognitive functions (Nader et al., 2000; Dudai, 2004; Roozendaal and McGaugh, 2012). It is interesting to note, however, that although this conclusion is consistent with other demonstrations of heroin- or morphine-induced memory enhancements (Mondadori and Waser, 1979; Castellano, 1980; Stäubli and Huston, 1980; Levy et al., 2009; Leri et al., 2013), there is also substantial evidence that the same drugs can impair memory when administered post-training (Castellano and Oliverio, 1975; Introini et al., 1985; Castellano et al., 1994) and that opioid antagonists such as naloxone or naltrexone enhance consolidation (Fulginiti and Cancela, 1983; Introini et al., 1985; Introini-Collison and Baratti, 1986; Introini-Collison et al., 1989). To this point, it is important to note that post-sample

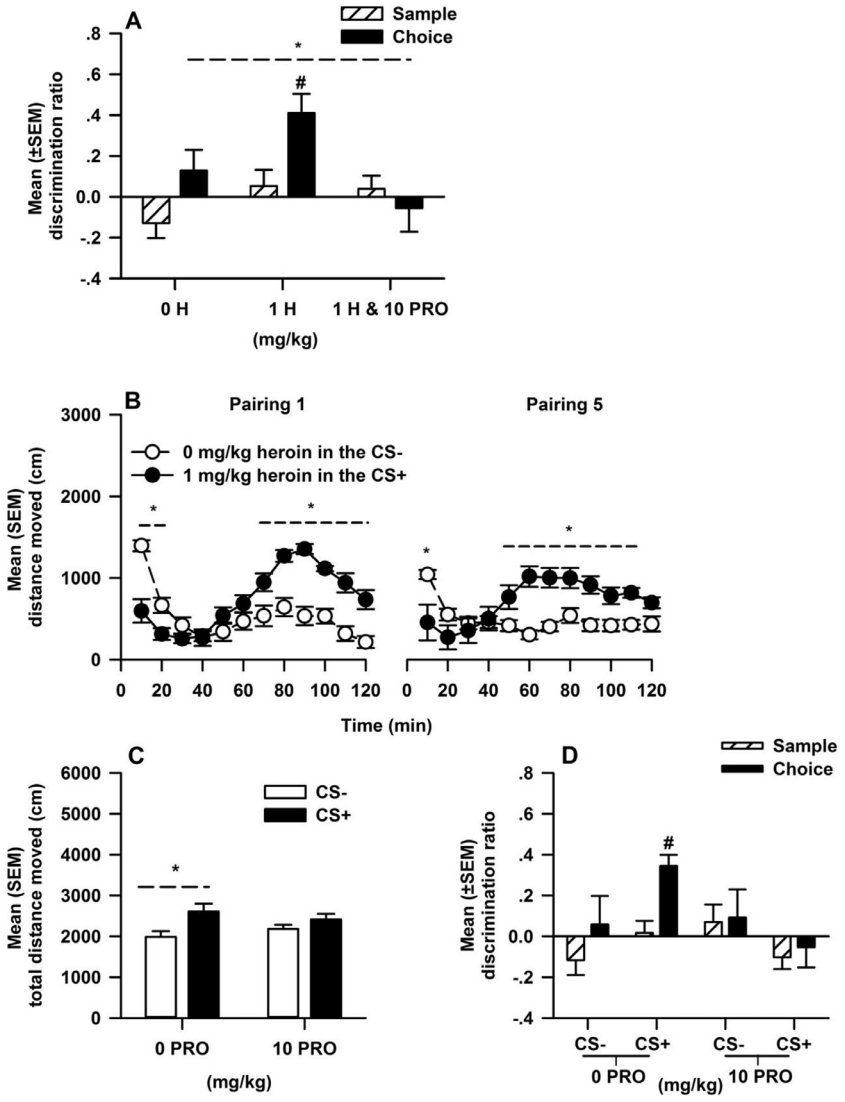

Fig. 3 **(A):** Mean (±SEM) discrimination ratios from sample and choice phases by the same rats ($n = 12$) following post-sample injections of 0 mg/kg heroin, 1 mg/kg heroin or 1 mg/kg heroin & 10 mg/kg PRO. The * denotes a significant difference compared to 0 mg/kg H choice phase discrimination ratio. The # denotes a significant difference compared to sample discrimination ratio within dose. **(B):** Mean (SEM) distance moved by the same rats ($n = 12$) in compartments paired with injections of 0 mg/kg heroin (CS-) and 1 mg/kg heroin (CS+) during the first and last set of pairings. **(C):** Mean (SEM) total distance moved following 30 min of confinement into the CS- and CS+ of rats pre-treated with either 0 mg/kg PRO or 10 mg/kg PRO. The * denotes a significant difference between compartments. **(D):** Mean (±SEM) discrimination ratios during sample and choice phases of OR displayed by the same rats ($n = 12$) following injections of 0 mg/kg PRO or 10 mg/kg PRO prior to confinement into CS- and the CS+. The # denotes a significant difference compared to the sample phase DR.

injections of 1 and 3 mg/kg naltrexone in Experiment 2 did not alter test discrimination ratios. This observation strongly suggests that the nature of the memory task is a critical determinant of the direction of post-training effects of opioid agonists and antagonists. This conclusion is substantiated by our previous observation that post-training cocaine impaired performance in a win-stay task motivated by sucrose (Cloke et al., 2014) despite enhancing object recognition memory (Rkieh et al., 2014). Clearly, this intriguing possibility should be explored directly using a variety of tasks motivated by incentive and aversive stimuli and various drug reinforcers.

The current study also explored the effects of immediate and delayed post-sample exposure to a heroin contextual CS on object memory. In the same animals, it was found that post-sample confinement into the heroin CS+, but not into the vehicle-paired CS-, significantly increased test discrimination ratio (Fig. 1D). Importantly, when exposure to the heroin CS+ was delayed by 6 h following the sample phase, there was no evidence of object memory facilitation (Table 1), a finding confirming that exposure to the heroin CS+ facilitated OR by a selective action on memory consolidation. It is important to point out that this is not the only conditioned effect of the heroin-paired CS observed in

this study. In fact, in Experiments 1-3, rats displayed the expected bi-phasic locomotor response (Leri et al., 2013) to heroin during conditioning (Figs. 1B-3B), as well as a substantial conditioned hyperlocomotion in the CS+ where they were confined in a drug free-state (Figs. 1C-3C). Presumably, the animals would have also displayed a significant "preference" for the CS+ over the CS-, but this was not tested in Experiments 1-3 because our (Leri and Rizos, 2005) and many other (Galaj et al., 2016; Paniccia et al., 2018) laboratories have already shown this, and the finding that opiate agonists produce place preference in rodents is not disputed (For review see, Tzschentke, 2007; Tomek and Olive, 2018). At a more general level, therefore, using conditioning parameters similar to those employed in traditional place conditioning studies, it is observed that a heroin-paired context not only has incentive properties and stimulates motor activity, but also enhances memory consolidation.

The second experiment explored the role of opioid receptors in the memory enhancing actions of post-sample heroin and the post-sample contextual heroin CS+ by administering 3 mg/kg naltrexone just prior to 1 mg/kg heroin, or just prior to confinement in the CS+ compartment. Unexpectedly, this dose of naltrexone, which effectively blocked analgesia induced by 1 mg/kg heroin (Experiment 2), did not change the memory enhancing action of post-sample heroin (Fig. 2A). Similarly, although 3 mg/kg naltrexone blocked the conditioned hyperactivity displayed in the CS+ compartment (Fig. 2C), it failed to alter the effect of confinement in the heroin CS+ on object memory modulation and it had no effect when administered during confinement in the CS- (Fig. 2D). This latter finding rules out any effect of post-training naltrexone on object memory due to an interaction with a history of exposure to heroin and seems to suggest that opioid receptors are not involved in memory consolidation processes promoted by opioid agonists or opioid conditioned stimuli. It should be noted, however, that naltrexone is a relatively weak antagonist at delta opioid receptors (Raynor et al., 1994), and that these receptors may play a key role in these memory effects. In fact, subanalgesic doses of the selective delta agonist rubiscolin-6 enhances memory (Pavone et al., 1990), and these effects are blocked by the delta opioid antagonist naltrindole (Yang et al., 2003). Clearly, it would be interesting to ascertain whether naltrindole could block the enhancement of object memory induced by post-sample heroin or heroin CS.

The final experiment explored the role of the *beta*-noradrenergic system in the memory enhancing actions of post-sample heroin, and the post-sample contextual heroin CS+, by administering 10 mg/kg propranolol just prior to 1 mg/kg heroin, or just prior to confinement in the CS+ compartment. Post-sample injections of PRO blocked the memory enhancing effect heroin (Fig. 3A), as well as conditioned hyperactivity (Fig. 3C) and CS+ enhancement of OR discrimination (Fig. 3D). A control study revealed that propranolol (5 or 10 mg/kg) injected post-training during a 24 h retention interval had no effect on object recognition (Table 1), suggesting that PRO could not alter OR when tested with the selected experimental parameters. Here it should be acknowledged that this PRO effect could have been different had the animals been tested in a different apparatus (Winters et al., 2004; Roozendaal et al., 2008).

Although it is not surprising that an adrenoreceptor antagonist would block the memory enhancing action of heroin and heroin CS+ (Introini-Collison and Baratti, 1986, 1992; Introini-Collison et al., 1989; Cahill et al., 1994; Zhao et al., 2011; Goode et al., 2016), the finding is nevertheless notable for two main reasons. First, it provides additional evidence that the post-training effects of heroin and post-training exposure to the heroin CS+ act through established mechanisms of memory consolidation that are dependent on noradrenergic activity. Second, this finding indicates that the post-training effects of heroin and the heroin CS+ can be pharmacologically manipulated. It would be very interesting to test the involvement of other known modulators of memory consolidation because administration of heroin, or exposure to a heroin CS, are both likely to generate a "novelty signal" (Redondo and Morris, 2011; Duszkiewicz et al., 2019) dependent on dopamine activity. Moreover, it would be interesting to explore whether both heroin and heroin CSs exert their effect on memory consolidation by similar activation of stress hormones (McGaugh, 2002; Roozendaal et al., 2002), by involving similar patterns of noradrenergic and cholinergic activity in the basolateral amygdala (Castellano et al., 1996; McGaugh et al., 1996; Roozendaal and McGaugh, 1997; Vazdarjanova and McGaugh, 1999; Power et al., 2003; Roozendaal et al., 2009), or by modulating the same molecular mechanisms of long-term potentiation (Pourmotabbed et al., 1998; Ito et al., 2001; Bao et al., 2007).

In conclusion, this study extends the hypothesis of White (1996) indicating that addictive substances such as heroin can impart their memory enhancing properties onto Pavlovian conditioned stimuli to facilitate memory consolidation. This study also shows that heroin and a contextual conditioned stimulus paired with heroin enhance memory consolidation through the activation of beta-noradrenergic receptors.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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Contributors

Michael Wolter and Francesco Leri designed the study and wrote the protocol. Michael Wolter, Ethan Huff, Nana Baidoo, Kristen Jardine and Zoey Pulles were involved in the data collection. Michael Wolter managed the literature searches and analyses. Michael Wolter, Francesco Leri and Boyer Winters undertook the statistical analysis, and Michael Wolter and Francesco Leri wrote the first draft of

the manuscript. All authors contributed to and have approved the final manuscript.

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