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Dopamine D1/D5 receptors in the dorsal hippocampus are required for the acquisition and expression of a single trial cocaine-associated memory

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ABSTRACT

The role of the hippocampus in memory supporting associative learning between contexts and unconditioned stimuli is well documented. Hippocampal dopamine neurotransmission modulates synaptic plasticity and memory processing of fear-motivated and spatial learning tasks. Much less is known about the involvement of the hippocampus and its D1/D5 dopamine receptors in the acquisition, consolidation and expression of memories for drug-associated experiences, more particularly, in the processing of single pairing cocaine conditioned place preference (CPP) training. To determine the temporal dynamics of cocaine CPP memory formation, we trained rats in a one-pairing CPP paradigm and tested them at different time intervals after conditioning. The cocaine-associated memory lasted 24 h but not 72 h. Then, we bilaterally infused the dorsal hippocampus with the GABA A receptor agonist muscimol or the D1/D5 dopamine receptor antagonist SCH 23390 at different stages to evaluate the mechanisms involved in the acquisition, consolidation or expression of cocaine CPP memory. Blockade of D1/D5 dopamine receptors at the moment of training impaired the acquisition of cocaine CPP memories, without having any effect when administered immediately or 12 h after training. The expression of cocaine CPP memory was also affected by the administration of SCH 23390 at the moment of the test. Conversely, muscimol impaired the consolidation of cocaine CPP memory only when administered 12 h post conditioning. These findings suggests that dopaminergic inputs to the dorsal hippocampus are required for the acquisition and expression of one trial cocaine-associated memory while neural activity of this structure is required for the late consolidation of these types of memories.

1. Introduction

The role of the hippocampus in processing different types of memories is well documented (Dudai, 2004; McGaugh, 2000; Morris, 2006). Spatial learning, object recognition and aversively-motivated learning tasks, such as contextual fear conditioning and inhibitory avoidance, have been extensively employed to establish several of the modern concepts regarding the role of the hippocampus in memory processing (Izquierdo & Medina, 1997; Kim & Fanselow, 1992; Morris, 2006). The hippocampus underlies associative learning between a context and an unconditioned stimuli. If this learning is perceived as "novel", a signal is conveyed through polysynaptic pathways to the ventral tegmental area (VTA) dopamine (DA) neurons (Lisman & Grace, 2005; Luo, Tahsili-Fahadan, Wise, Lupica, & Aston-Jones, 2011), which are able to detect novelty signals and changes their firing pattern in response. VTA DA neurons innervate the hippocampus (Gasbarri, Sulli, & Packard, 1997), and hippocampal DA neurotransmission has been shown to modulate synaptic plasticity and memory (Bernabeu, Cammarota, Izquierdo, & Medina, 1997; Kramar, Chefer, Wise, Medina, & Barbano, 2014; Lemon & Manahan-Vaughan, 2006; Lisman & Grace, 2005; Rossato, Bevilaqua, Izquierdo, Medina, & Cammarota, 2009). However, much less is known about the involvement of the hippocampus in the acquisition, consolidation and expression of the memory for appetitive learning tasks and, in particular, drug-associated experiences.

One of the most commonly abused substances is cocaine, which is believed to have addictive properties because it reinforces drug-seeking habits by increasing ventral striatum DA levels (Thomas,

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Kalivas, & Shaham, 2008). Cocaine also elevates DA levels in the hippocampus (Kramar et al., 2014), a structure that has been shown to regulate the release of DA in the nucleus accumbens core and shell (Peleg-Raibstein & Feldon, 2006). In addition, cocaine enhances hippocampal long-term potentiation (LTP) (Thompson, Gosnell, & Wagner, 2002). On the other hand, the hippocampus is implicated in the reinstatement of cocaine-seeking behavior (Luo et al., 2011; Vorel, Liu, Hayes, Spector, & Gardner, 2001) and hippocampal D1/D5 DA receptors are up-regulated after a cocaine conditioned place preference (CPP) procedure (Tanaka, Kai, Kobayashi, Takano, & Hironaka, 2011).

Drug-paired environmental stimuli acquire incentive motivational valence through associative learning processes (Stewart, 1983). A classical animal model in which a context is paired with rewarding experiences, such as cocaine administration, is the CPP paradigm (Tzschentke, 2007). CPP can be conceived in terms of Pavlovian conditioning, associating a particular environment (conditioned stimulus; CS) with a reward (unconditioned stimulus; US) (Huston, Silva, Topic, & Müller, 2013). As the hippocampus plays a major role in the processing of contextual memories, we sought to determine whether this structure is implicated in regulating different stages of memory processing for this single trial association between cocaine and the context in which it was received. The interest of studying one-pairing cocaine CPP is that it is a rapidly acquired appetitive learning task in which the acquisition stage can be easily separated from the ensuing consolidation. It allows for a clear-cut distinction between different phases of memory processing –i.e. acquisition, consolidation, and expression – involved in the learning of a rewarding experience, as the animal learns the context-reward association in one single trial. Early and late phases of memory consolidation can be easily discriminated from each other as well (Bekinschtein et al., 2007).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (School of Veterinary, University of Buenos Aires, Argentina) were used. Groups of five rats (weighting around 200 g upon arrival at the laboratory) were housed in a vivarium maintained on a reversed 12-h light–dark cycle (lights off at 6:30 am) at a constant temperature of 23 °C. Animal care strictly followed institutional and international standards (National Research Council, 2011). Animals were habituated to the vivarium for at least one week before the start of any experimental procedure and were handled and weighted daily in order to minimize handling stress during experiments. Food and water were provided *ad libitum* except during experimental sessions. All the experiments performed during the dark phase of the diurnal cycle were conducted in dimly lit testing rooms equipped with white noise generators.

2.2. Drugs

Cocaine hydrochloride (Laboratorios Verardo y Cia., Argentina), SCH 23390 hydrochloride, muscimol (Sigma–Aldrich, St. Louis, MO) and eticlopride hydrochloride (Tocris Bioscience, U.K.) were all dissolved in sterile 0.9% physiological saline.

2.3. Surgical and intracerebral infusion procedures

Each rat was anesthetized with a mix of ketamine (85 mg/kg) and xylazine (10 mg/kg), and placed on a stereotaxic frame. The skull was exposed and leveled (flat skull, lambda and bregma at the same level) and 22-gauge guide cannulae for intracerebral infusions were bilaterally implanted, aimed at the CA1 region of the dorsal hippocampus. The stereotaxic coordinates used were as follows: AP: −3.9, ML: ±3.0, DV: −3.0 (Paxinos & Watson, 2004). Animals were given the analgesic meloxicam (0.2 mg/kg) to prevent post-surgical pain or discomfort and allowed 5–7 days of recovery before any experimental manipulation.

For intracerebral infusions, 30-gauge needles connected to Hamilton syringes were employed. The infusions were always bilateral, with infusions volume of 1 μl per side (injection rate: 1 μl/30 s). The needle was left in place for an additional minute after infusion to allow for diffusion and to prevent reflux. The doses employed of each compound (1.5 μg/μl for SCH 23390, 0.1 μg/μl for muscimol and 1.5 μg/μl for eticlopride hydrochloride) were proven to be effective by different studies (Izquierdo & Medina, 1997; Kramar et al., 2014; Lintas et al., 2011; Rossato et al., 2009). At the end of each experiment, cannula placement was verified by infusion of 1 μl of 4% methylene blue. Animals were killed by decapitation 20 min later and histological localization of the infusion sites was established, taking the extension of the dye as an indicator of the presumable diffusion of the vehicle or drug. The observed diffusion is similar to that found using ^{3}H-muscimol or fluorescent muscimol (0.5–1 μl) in different brain regions, which ranged from 0.5–1 mm to 2 mm (Allen et al., 2008; Martin & Ghez, 1999; see Fig. 2 for the corresponding schema), and is in agreement with published results from our group (Tomaiuolo, Gonzalez, Medina, & Piriz, 2014) in which rhodamine labeled α-bungarotoxin infusions match the schema obtained after the infusion of 1 ul methylene blue, shown here in Fig. 2. Only the behavioral data of animals with a correct placement of cannulae were included in the study.

2.4. Behavioral training and testing

Animals were trained and tested on a CPP box divided in two compartments (38 × 27 × 36 cm), separated by a central, smaller chamber (38 × 27 × 15 cm). Each compartment is connected to the central chamber by means of guillotine doors. The bigger compartments differed in several characteristics (color of walls: black or white, wall patterns: black stripes or white squares, type of

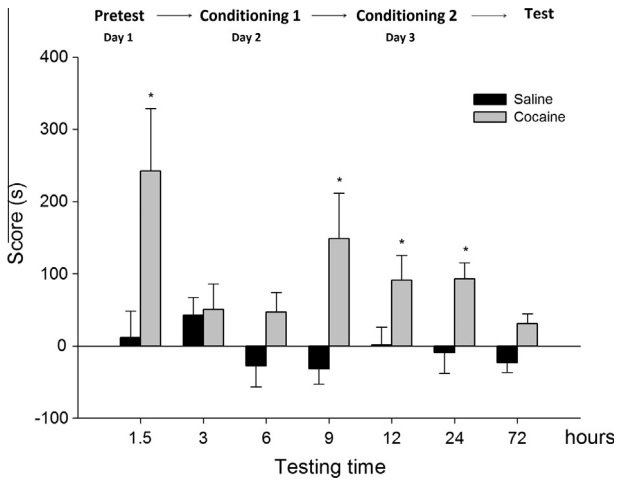

Fig. 1. Temporal dynamics of single trial cocaine CPP memory expression. Animals were trained using one-pairing cocaine CPP procedure. Tests were performed at different time points after cocaine (or saline in the case of controls) conditioning. Memory was evident at 1.5, 9, 12 and 24 h after the cocaine injection, but not at 3, 6 or 72 h. Asterisks indicate significant differences between cocaine injected animals and its corresponding saline controls. Independent groups of animals were tested at each time point and for this reason Student's *t*-tests were used to analyze these data. The results are combined and presented together in the same figure to decrease the number of displayed items. (n = 7–12/group. $^{*}p < 0.05$).

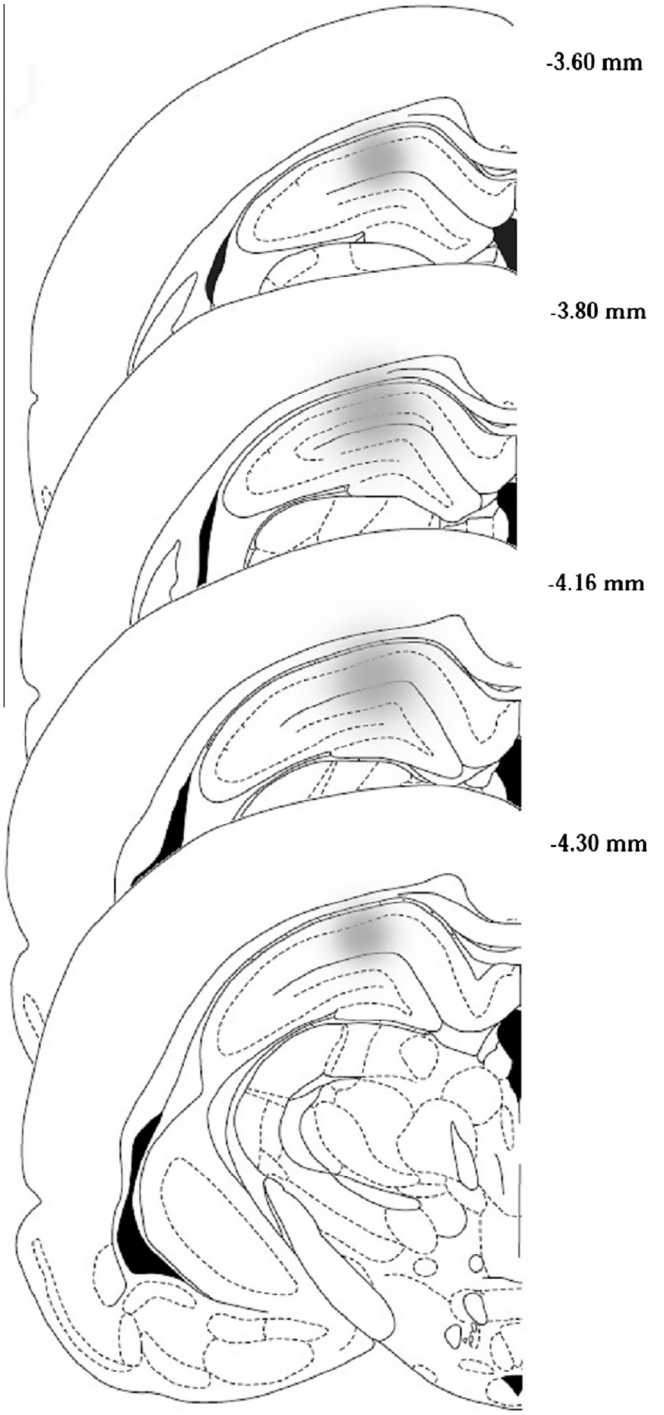

Fig. 2. Schema of the location and extension of the infusions performed on the dorsal hippocampus. The extension was verified at the end of each experiment by infusing 1 μl methylene blue per side. The drawings were adapted from Paxinos & Watson, 2004.

floor: grid or perforated). The central chamber was grey, did not have any special pattern on the walls and had plain floor. The experiments consisted of three phases: (1) a pretest phase in which the animals were allowed to explore the entire apparatus for 15 min and the preference for each compartment was determined; (2) a conditioning phase in which the animals were given an intraperitoneal (ip) saline injection prior to be confined in the initially preferred dark chamber for 30 min on the first conditioning day and an ip cocaine injection prior to be confined in the initially non-preferred white chamber for 30 min on the following day (saline ip injections were given in both compartments for control groups) for the one-pairing protocol; this procedure was repeated two more times in a three-pairing version to establish a stronger memory for the same association; and (3) a test phase, in which the animals were allowed to explore the entire apparatus again for 15 min. If during the pretest phase an animal failed to spend at least 90 s in each compartment it was excluded from the study (3 animals were excluded for this reason, less than 1%). A cocaine dose of 20 mg/kg was used for all the experiments (Kramar et al., 2014).

For the temporal dynamics experiments, animals were trained in a one-pairing CPP protocol, as explained above, and then tested at different time points post-conditioning (1.5, 3, 6, 9, 12, 24 and 72 h). An independent group of animals was used for each time point studied.

For the acquisition experiments, during the second day of the conditioning phase, SCH 23390, muscimol or vehicle were infused in the dorsal hippocampus and 15 min later the animals were conditioned in the white chamber with cocaine (or saline for control groups). Tests were performed 1.5 h later for short-term memory (STM), or 24 h later for long term memory (LTM).

For the postconditioning experiment, during the second day of the conditioning phase, animals received cocaine (or saline for control groups) in the white chamber and immediately after were infused in the dorsal hippocampus with SCH 23390 or its vehicle; test was performed 24 h later.

For late-phase consolidation experiments, during the second day of the conditioning phase, SCH 23390, muscimol or vehicle were infused in the dorsal hippocampus 12 h after cocaine administration (or saline for control groups) and test was performed 24 h later.

For the expression experiments, animals were conditioned as explained above in a one-pairing protocol. SCH 23390, muscimol or vehicle were infused in the dorsal hippocampus 15 min before testing LTM at 24 h. For the study of a stronger CPP memory, animals were trained in a three-pairing cocaine CPP protocol. SCH 23390, or vehicle were infused in the dorsal hippocampus 15 min before testing LTM at 10 days after the last conditioning session. Animals were tested again 24 h later in a drug-free state.

2.5. Statistical analyses

CPP data are presented as a score, in seconds: time spent in the drug-associated compartment during the test minus time spent in the to-be drug associated compartment during the pretest. Results are presented as mean ± SEM. Results were analyzed using a Student's *t*-test in the case where two groups were to be compared (temporal dynamics of cocaine CPP memory formation) and using a multifactorial analysis of variance (MANOVA) with drug (saline *versus* cocaine) and challenge (vehicle *versus* SCH 23390 or muscimol) as between-subject factors, in the case more than two groups were to be analyzed. For significant overall interactions, further analyses of partial interactions were carried out. Post hoc analyses were performed with Newman–Keuls test when the initial *p*-value was significant. A result was considered significant if $p < 0.05$. All data were analyzed using Statistica software (Statsoft Inc., France).

3. Results

We first determined the temporal dynamics of cocaine CPP memory formation by subjecting animals to one-pairing training sessions and then testing them at different time intervals after conditioning. As shown in Fig. 1, a clear-cut preference for the cocaine-*versus* saline-paired context was observed at 1.5 h after training

corresponding to what is generally ascribed to STM (Vianna et al., 2000). Memory for cocaine CPP was also expressed at 9, 12 and 24 h after training. No preference for the cocaine-associated context was evident at 3 or 6 h after conditioning. In addition, no CPP memory was expressed at 72 h (Fig. 1; 1.5 hs $t = -2.45$; 3 hs $t = -0.19$, n.s.; 6 hs $t = -1.86$, n.s.; 9 hs $t = -2.58$; 12 hs $t = -2.86$; 24 hs $t = -2.61$; 72 hs $t = -1.81$, n.s.) which is consistent with recent findings showing that long-lasting cocaine CPP LTM requires several training sessions (Kramar et al., 2014).

The reversible inactivation of the dorsal hippocampus by using bilateral microinfusions of the GABA A receptor agonist muscimol (see Fig. 2 to check for the location and extension of the infusions) 15 min before conditioning (Fig. 3a) did not affect cocaine CPP memory when tested 1.5 h or 24 h after training (Fig. 3b; main effect of drug: $F_{(1,35)} = 15.99$, $p < 0.001$; main effect of challenge: $F_{(1,35)} = 0.33$, $p = 0.57$, n.s.; drug × challenge: $F_{(1,35)} = 0.06$, $p = 0.81$, n.s., and Fig. 3c; main effect of drug: $F_{(1,32)} = 13.28$, $p < 0.001$; main effect of challenge: $F_{(1,32)} = 0.22$, $p = 0.64$, n.s.; drug × challenge: $F_{(1,32)} = 1.82$, $p = 0.19$, n.s). This suggest that neural activity in the dorsal hippocampus during or early after conditioning is not required for single trial cocaine CPP memory formation.

Cocaine enhances hippocampal LTP (Thompson et al., 2002), and presentation of an unexpected reward activates the firing of hippocampal neurons (Mizumori, Puryear, & Martig, 2009). Given that D1/D5 dopamine receptors are up-regulated after a cocaine CPP procedure (Tanaka et al., 2011), we next determined whether D1/D5 DA receptors in the dorsal hippocampus were involved in cocaine CPP memory processing. As shown in Fig. 3d and e, the preconditioning infusion of the specific D1/D5 DA receptor antagonist SCH 23390 into the CA1 region of the dorsal hippocampus impaired cocaine CPP STM and LTM retention (Fig. 3d; main effect of drug: $F_{(1,29)} = 7.09$, $p = 0.13$, n.s.; main effect of challenge: $F_{(1,29)} = 3.95$, $p = 0.05$; drug × challenge: $F_{(1,29)} = 5.28$, $p < 0.05$, and Fig. 3e; main effect of drug: $F_{(1,29)} = 7.82$, $p < 0.01$; main effect of challenge: $F_{(1,29)} = 1.70$, $p = 0.20$, n.s.; drug × challenge: $F_{(1,29)} = 5.10$, $p < 0.05$). To rule out an involvement of D2-like DA receptors in the acquisition of the one-pairing cocaine CPP memory, we employed the D2-like DA receptor antagonist eticlopride. The preconditioning infusion of this agent into the dorsal hippocampus did not affect cocaine CPP memory when tested 24 h after training (Sal: 7.7 ± 9.7 s, Coc/Veh: 72.2 ± 11.5 s, Coc/Eti: 100.2 ± 24.1 s; $F_{(2,14)} = 8,11$; $p < 0.01$, Coc/Veh *vs.* Coc/Eti, $p = 0.26$, n.s., Newman–Keuls test; $n = 5$–6/group).

To further investigate the role of D1/D5 DA receptors in cocaine-associated memory processing, we administered SCH 23390 in the dorsal hippocampus immediately or 12 h after

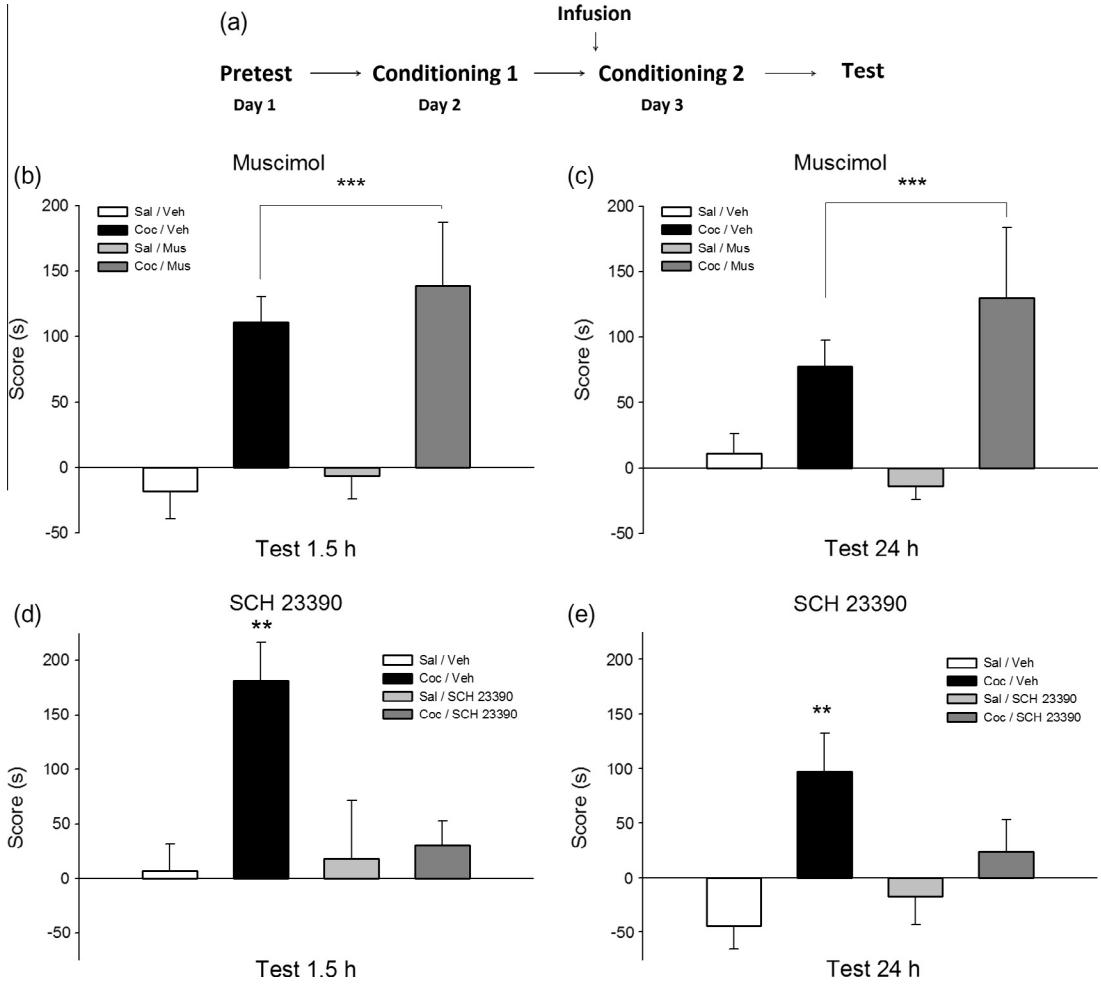

Fig. 3. D1/D5 antagonism in the CA1 region during acquisition, impairs short- and long-term cocaine CPP memory. The specific D1/D5 dopamine receptor antagonist SCH 23390, but not GABA A agonist muscimol, administered into the CA1 region of the dorsal hippocampus 15 min before conditioning (**a**) impaired cocaine CPP STM and LTM retention. The GABA A agonist muscimol had no effect on the 1.5 (**b**) or 24 h (**c**) tests for cocaine CPP memory established by one pairing training ($n = 7$–12/group). Treatment with the D1/D5 dopamine receptor antagonist SCH 23390 impaired cocaine CPP STM (**d**) and LTM (**e**) retention ($n = 7$–10/group). Post hoc analyses demonstrated that the groups conditioned with cocaine, infused with SCH 23390 15 min before the cocaine conditioning and tested at 1.5 or 24 h showed a lower score when compared with the other groups. Asterisks indicate a significant difference with Sal/Veh group (Newman–Keuls, $^{**}p < 0.01$). Asterisks upon brackets indicate a significant difference between saline- and cocaine-injected animals, collapsed across the factor challenge (Newman–Keuls, $^{***}p < 0.001$). Sal, saline; Coc, cocaine; Veh, vehicle; Mus, muscimol.

cocaine administration. In previous works (Kramar et al., 2014; Rossato et al., 2009), this 12-h period was determined to be fundamental for the storage of a long-lasting LTM tested at 7–14 days after training. In this case, we wanted to study the involvement of this late consolidation phase in the retention of cocaine CPP memory tested one day posttraining. Neither the immediate (Fig. 4a; main effect of drug: $F_{(1,22)} = 6.27$, $p < 0.05$; main effect of challenge: $F_{(1,22)} = 0.002$, $p = 0.96$, n.s.; drug × challenge: $F_{(1,22)} = 0.11$, $p = 0.74$, n.s) nor the late postconditioning administration of SCH 23390 (Fig. 4b; main effect of drug: $F_{(1,46)} = 26.10$, $p < 0.001$; main effect of challenge: $F_{(1,46)} = 2.59$, $p = 0.11$, n.s.; drug × challenge: $F_{(1,46)} = 0.32$, $p = 0.56$, n.s) altered memory retention for the association between cocaine and the context in which it was received. On the other hand, the infusion of muscimol into the CA1 region of the dorsal hippocampus 12 h after conditioning impaired CPP LTM consolidation (Fig. 5; main effect of drug: $F_{(1,26)} = 6.72$, $p < 0.05$; main effect of challenge: $F_{(1,26)} = 0.29$, $p = 0.59$, n.s.; drug × challenge: $F_{(1,26)} = 4.26$, $p < 0.05$).

Having established the participation of D1/D5 DA receptors in the acquisition of cocaine CPP memory, we next asked whether they were involved in the expression of cocaine CPP memory. There were no significant differences in memory expression between the distinct control groups (saline-conditioned) injected with vehicle, SCH 23390 or muscimol in the dorsal hippocampus, thus, the scores of all control groups were collapsed together (Fig. 6; saline groups: $F_{(2,6)} = 1.13$, $p = 0.38$, n.s.). The infusion of SCH 23390 15 min before a 24 h test completely blocked memory expression while the infusion of muscimol had no effect (Fig. 6; $F_{(3,31)} = 10.88$, $p < 0.001$), suggesting an involvement of the dopaminergic D1/D5 receptors of the dorsal hippocampus in the retrieval of a cocaine CPP LTM. Moreover, the infusion of SCH 23390 15 min before a test for a stronger cocaine-related memory conducted 10 days after the last conditioning session also disrupted the expression of this CPP memory (Fig. 7a, $F_{(2,22)} = 5.79$, $p < 0.01$). Nonetheless, the observed deficit was transient since a new test of the same animals carried out 24 h later showed a normal expression of the cocaine CPP memory in both Coc/SCH and Coc/Veh groups (Fig. 7b, $F_{(2,23)} = 7.32$, $p < 0.01$).

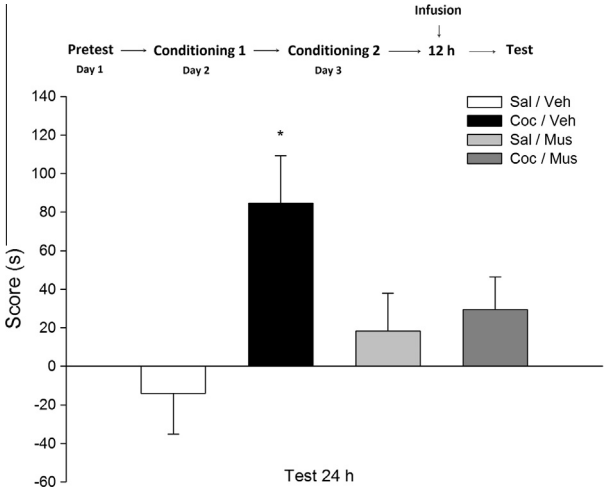

Fig. 5. Late postconditioning administration of the GABA A agonist muscimol impaired cocaine CPP memory retention. The infusion of muscimol into the CA1 region of the dorsal hippocampus 12 h after conditioning impaired cocaine CPP LTM consolidation when tested at 24 h ($n = 6$–9/group). Post hoc analyses demonstrated that the group conditioned with cocaine, infused with muscimol 12 h later and tested at 24 h showed a lower score when compared with the other groups. Asterisks indicate a significant difference with Sal/Veh group (Newman–Keuls, $^{*}p < 0.05$). Sal, saline; Coc, cocaine; Veh, vehicle; Mus, muscimol.

4. Discussion

The main finding of the present study is that the dorsal hippocampus and its dopaminergic inputs are required early and late after conditioning for memory processing of a one-pairing cocaine-associated contextual preference learning. We demonstrated for the first time that while general neural activity of the dorsal hippocampus appears to be necessary for the late-phase of cocaine CPP memory consolidation, functional D1/D5 DA receptors in this structure are important for the acquisition of the task and its recall.

We observed the presence of lapses in memory recall during the consolidation of a cocaine-associated memory. Sporadic reports of temporary lapses in recall have been published in the last 4 decades regarding invertebrates and vertebrates (Gerber & Menzel, 2000; Marra, O'Shea, Benjamin, & Kemenes, 2013; Riege & Cherkin, 1971). By using a single-trial associative conditioning of feeding in *Lymnaea*, Marra and coworkers (2013) showed that lapses in recall during memory formation correspond to transitions between different phases of memory processing requiring distinct molecular pathways. This phenomenon, known as the Kamin

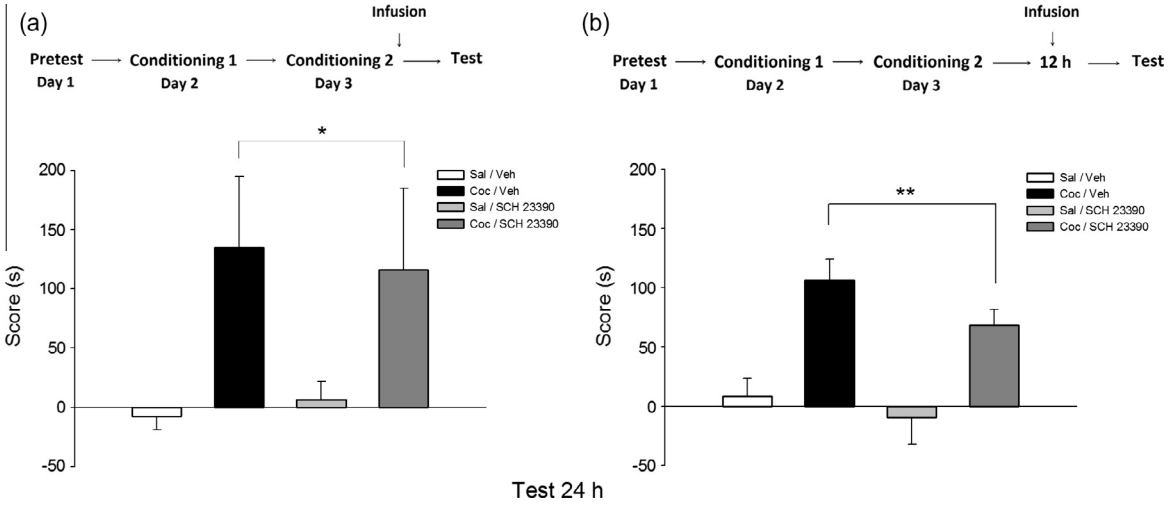

Fig. 4. Immediate or late postconditioning administration of the D1/D5 antagonist did not affect cocaine LTM CPP memory. The D1/D5 antagonist SCH 23390 had no effect on the 24 h test for cocaine CPP when infused immediately (**a**) ($n = 6$–7/group) or 12 h after cocaine administration (or saline for control groups) (**b**) ($n = 12$–13/group). Asterisks upon brackets indicate a significant difference between saline- and cocaine-injected animals, collapsed across the factor challenge (Newman–Keuls, $^{*}p < 0.05$, $^{**}p < 0.01$). Sal, saline; Coc, cocaine; Veh, vehicle.

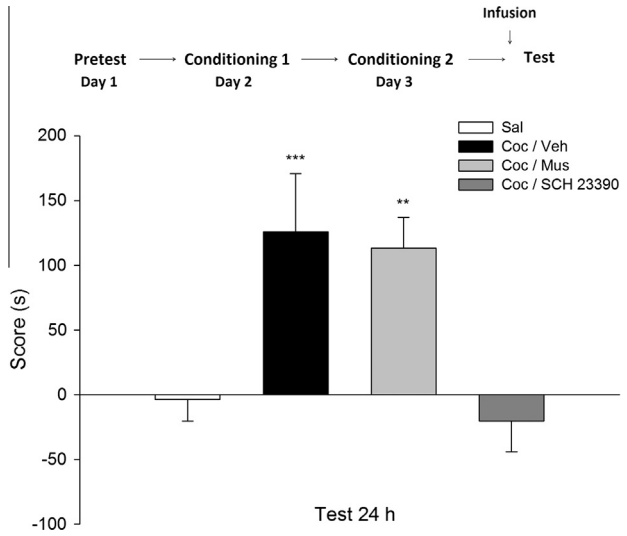

Fig. 6. Activation of the dopaminergic D1/D5 receptors in the dorsal hippocampus is necessary for the expression of cocaine CPP LTM. Animals were trained using one-pairing cocaine CPP procedure. The infusion of SCH 23390 15 min before a 24 h test impairs the expression of this type of memory while muscimol infusion did not affect the expression of cocaine CPP memory (n = 8–9/group). Saline groups are not statistically different from each other (p = 0.38) and, in consequence, their scores were grouped and presented together. Post hoc analyses demonstrated that the group conditioned with cocaine and infused with SCH 23390 15 min before test showed a score similar to the one observed in the saline group (p = 0.65 n.s.). Asterisks indicate a significant difference with the saline group (Newman–Keuls, $^{**}p < 0.01$; $^{***}p < 0.001$). Sal, saline; Coc, cocaine; Veh, vehicle; Mus, muscimol.

effect, where periods of memory retention are intercalated with periods when memory is not expressed (Kamin, 1957; Sutton & Carew, 2002) could be a likely explanation for the observed results but further experiments need to be performed to confirm this hypothesis. The lack of memory expression at 72 h post-conditioning is consistent with recent findings showing that long-lasting cocaine LTM requires more conditioning trials to persist in time (Kramar et al., 2014).

Our findings regarding the effects of SCH 23390 on the acquisition of cocaine CPP memory are consistent with those suggesting that activation of hippocampal D1/D5 receptors during encoding, but not thereafter, is necessary for the formation of LTM of a one-trial spatial memory (O'Carroll et al., 2006) and of an inhibitory avoidance task (Moncada, Ballarini, Martinez, Frey, & Viola, 2011). They also agree with those showing that the hippocampus is required early and late after training for memory processing of single trial aversively-motivated tasks (Katche, Cammarota, & Medina, 2013). Interestingly, consolidation of an opiate-reward memory also required differential molecular pathways at early and late post-conditioning phases in the amygdala and medial prefrontal cortex respectively (Gholizadeh et al., 2013). While these results suggests that dopamine in the hippocampus via activation of D1-like receptors is important for the acquisition of a non-persistent single-pairing cocaine CPP memory, recently results obtained when studying the persistence of appetitive memories showed that dopamine has a deleterious effect in maintaining the storage of multi-trial cocaine CPP memory via activation of D5 receptors (Kramar et al., 2014). Indeed, the acquisition process of the memory for a single-trial task learning may differ from the one involved in the case of multi-trial task learning.

Regarding the effects of preconditioning muscimol administration on cocaine CPP STM and LTM expression, our results suggest that inhibition of neural activity in the dorsal hippocampus during conditioning may not be required for the acquisition of this particular memory. Our findings partially agree with data from Holahan (2005) who, by employing a radial maze conditioned cue preference task in rats, did not find alterations in food CPP memory tested after 24 h in animals with a preconditioning muscimol-induced inactivation of the dorsal hippocampus. However, post-conditioning inactivation induced impairment in CPP memory (Holahan 2005). Recognized differences between the rewarding properties of food and drugs of abuse may account for the observed discrepancy (Hernandez & Hoebel, 1988). To entirely inactivate the hippocampus, further experiments using several intra-hippocampal infusions of muscimol alone or combined with a GABA B agonist (Fuchs, Evans, Parker, & See, 2004) should be conducted and this would give us definitive information concerning the role of

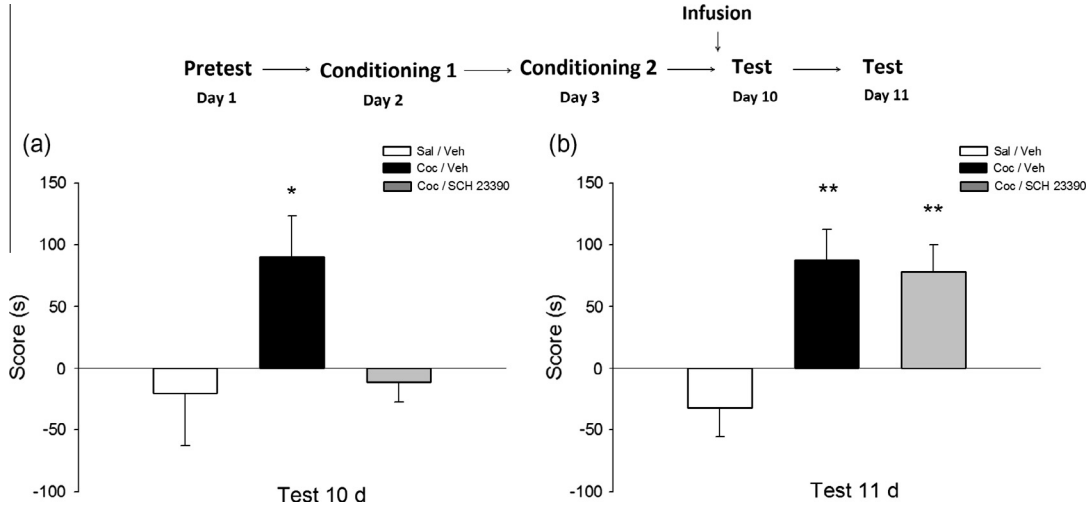

Fig. 7. The deficit observed in the expression of a CPP LTM caused by the infusion of the dopaminergic D1/D5 receptors antagonist in the dorsal hippocampus is transient. Animals were trained using three-pairing cocaine CPP procedure. The infusion of SCH 23390 15 min before a test conducted 10 days after the last conditioning session impaired the expression of this type of memory (**a**) (n = 8–9/group). Saline groups are not statistically different from each other (a, p = 0.81; b, p = 0.64) and, in consequence, their scores were grouped and presented together. Post hoc analyses demonstrated that the group conditioned with cocaine and infused with SCH 23390 15 min before test showed a score similar to the one observed in the saline group (**a**) (p = 0.85 n.s.). When the same animals were tested again 24 h later in a drug-free state, the group Coc/SCH showed a score similar to the one observed in the Coc/Veh group (**b**) (p = 0.79 n.s.) (n = 8–9/group). Asterisks indicate a significant difference with the saline group (Newman–Keuls, $^{*}p < 0.05$; $^{**}p < 0.01$). Sal, saline; Coc, cocaine; Veh, vehicle.

the hippocampus on the acquisition of a drug-associate learning task.

The reversible inactivation of the dorsal hippocampus by microinfusions of muscimol (Martin, 1991; Martin & Ghez, 1999) at 12 h after conditioning resulted in an impaired cocaine CPP LTM expression (Fig. 5), indicating that functional neuronal activity late after conditioning in the dorsal hippocampus participates in cocaine CPP memory consolidation. In addition, we found no alterations in cocaine CPP LTM recall after inactivation of the neural activity of the dorsal hippocampus (Fig. 6). We used a dose of muscimol that is similar to the one consistently found to be effective to block memory expression in other hippocampus-dependent learning tasks (Cohen et al., 2013; Gonzalez et al., 2013; Vianna et al., 2000). In contrast, using multi-trial cocaine CPP, Meyers, Zavala, Speer, and Neisewander (2006) showed that a high dose of muscimol (1 μg) infused in the dorsal hippocampus before testing hindered CPP memory retention. Differences in training procedures (multi- vs. single trial) and in muscimol concentrations might explain this discrepancy.

In marked contrast to what is known regarding the involvement of the ventral striatum on cocaine CPP processing (Li et al., 2011; Miller & Marshall, 2005; Ren et al., 2013; Rogge, Singh, Dang, & Wood, 2013; Thomas et al., 2008), few studies addressed the question of whether the hippocampus participates in different stages of cocaine CPP processing. Previous works that used multi-trial cocaine CPP training procedures found no support for the involvement of the dorsal hippocampus in the consolidation of CPP memory (Meyers et al., 2006). These authors showed that the dorsal hippocampus played a role in acquisition and expression, but not in consolidation, of cocaine CPP memory. Hernández-Rabaza et al. (2008) found that colchicine-induced lesions of the dentate gyrus impaired the establishment of cocaine CPP, suggesting that the dentate gyrus is important for a coherent representation of the context to which a rewarding experience is bound. However, this study did not discriminate about the role of the DG in acquisition, consolidation or expression of cocaine CPP. Using microinfusions of DNA methylation inhibitors into the dorsal hippocampus, Han et al. (2010) reported that the hippocampus contributed to the acquisition, but not the expression, of cocaine CPP. Interestingly, inactivation of the dorsal subiculum, a major output system of the dorsal hippocampus, impaired drug-seeking and drug-taking behavior during a cocaine self-administration protocol (Black, Green-Jordan, Eichenbaum, & Kantak, 2004) and acquisition of cocaine cue extinction learning (Szalay, Morin, & Kantak, 2011). Therefore, most of the previous studies that used multi-trial rewarding tasks showed that the hippocampal formation and closely related structures are involved in acquisition of multi-trial cocaine CPP processing. Our study, in contrast, focused on the acquisition, consolidation and expression of the memory for single trial cocaine-context association and is the first to demonstrate the implication of the dorsal hippocampus in these stages of memory processing. This distinction is very relevant since we are studying the earliest changes that occur in the hippocampus in order to encode the place-reward association after cocaine administration, a state that could set the bases for subsequent plasticity changes leading to drug dependence or addiction.

A major hypothesis in addiction research is that, even after a single administration, cocaine can induce neuroadaptations in mesocorticolimbic DA neurons in the VTA that are relevant to cocaine use and abuse (Lüscher & Bellone 2008; Thomas et al., 2008; Ungless, Whistler, Malenka, & Bonci, 2001). The presentation of an unexpected reward activates the firing of hippocampal neurons (Mizumori et al., 2009). It is also known that cocaine facilitates synaptic excitatory transmission in DA neurons (Engblom et al., 2008; Kauer & Malenka, 2007), resulting in increases in the release of DA in several regions including the medial prefrontal cortex, the nucleus accumbens, the amygdala and the hippocampus. In this context, during single trial cocaine CPP, two distinct surges of DA levels were found in the dorsal hippocampus: one directly related to cocaine administration that lasted for about 4–5 h, and another starting 13 h post conditioning, which appears to be involved in the persistence of LTM storage of cocaine CPP memory (Kramar et al., 2014). Based on our present results, we suggest that pre-conditioning blockade of D1/D5 DA receptors in the dorsal hippocampus impedes acquisition of CPP because it may block novelty detection (Barbosa, Pontes, Ribeiro, Ribeiro, & Silva, 2012; Lisman & Grace, 2005) and/or motivational salience-related signals (Bromberg-Martin, Matsumoto, & Hikosaka, 2010) conveyed by dopaminergic inputs at the time of training. If this were the case, early or late post-conditioning blockade of hippocampal D1/D5 receptors would not alter CPP memory consolidation. This prediction is supported by our current findings (Fig. 4a and b).

With regard to the role of the hippocampus in cocaine CPP memory recall, we found that cocaine CPP memory expression requires functional D1/D5 DA receptors in the dorsal hippocampus (Fig. 6). This modulatory action of D1/D5 receptors on memory recall is in disagreement with findings obtained using a paired-associated task (Bethus, Tse, & Morris, 2010) or using a fear-motivated inhibitory avoidance (Izquierdo et al., 1998). This could be explained by the fact that these two hippocampus-dependent tasks have different motivational valence compared to cocaine CPP. Indeed, our result are in accordance with those presented by Everitt's group. They showed an increase in DA release in structures associated with addicted-like behaviors, as the dorsal striatum or the nucleus accumbens core, after the presentation of a cocaine associated cues, in a cocaine-free state (Ito, Dalley, Howes, Robbins, & Everitt, 2000; Ito, Dalley, Robbins, & Everitt, 2002). The authors proposed this increment in DA to be related to a cocaine seeking behavior. Furthermore, dopamine transmission blockade by intracranial infusions of the α-flupenthixol in the posterior dorsomedial striatum, reduced performance of cue-controlled cocaine seeking at the early stage of self-administration (Murray, Belin, & Everitt, 2012). Recently, Otis, Fitzgerald, and Mueller (2014) have demonstrated that β-adrenergic receptor antagonism in the dorsal hippocampus before a multi-trial cocaine CPP test prevented CPP expression, inducing a persistent deficit in retrieval. As well, our results show that the antagonism of D1/D5 receptors at the moment of the test induces a deficit in the CPP expression of a one-pairing memory. However, when a stronger cocaine CPP memory was evaluated, we demonstrated that the observed deficit was transient in time. With our results, we cannot indisputably state that the deficit we observe concerns indeed memory retrieval. Because the distinction between memory expression and memory retrieval and the mechanisms underlying each phenomenon are still controversial issues, we choose to frame our results as an expression memory deficit, although some of them may indicate a retrieval deficit.

The concentration of SCH23390 used in the present study was chosen based on previous findings (Bethus et al., 2010; Kramar et al., 2014; Moncada et al., 2011; Rossato et al., 2009). Although we cannot totally exclude the possibility that SCH23390 exerts agonistic actions at 5-HT2a-c receptors at the concentration used here (Ramos, Goñi-Allo, & Aguirre, 2005), the fact that the activation of these receptors may facilitate hippocampus-dependent memory tasks (Harvey, 2003) weakens that assumption.

In conclusion, the dorsal hippocampus is an important and largely overlooked part of the neural circuit involved in encoding and maintaining cocaine-associated memories. Only recently, the attention has been drawn to investigate the role of this brain structure on the processing of reward-related experiences, specifically the ones associated with drugs of abuse (Kramar et al., 2014; Luo

et al., 2011). Further work needs to be undertaken to better understand to what extent the dorsal hippocampus is implicated in acquiring, maintaining and expressing drug-seeking and drug-taking behaviors.

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References

Allen, T. A., Narayanan, N. S., Kholodar-Smith, D. B., Zhao, Y., Laubach, M., & Brown, T. H. (2008). Imaging the spread of reversible brain inactivations using fluorescent muscimol. *Journal of Neuroscience Methods, 171*(1), 30–38.

Barbosa, F. F., Pontes, I. M., Ribeiro, S., Ribeiro, A. M., & Silva, R. H. (2012). Differential roles of the dorsal hippocampal regions in the acquisition of spatial and temporal aspects of episodic-like memory. *Behavioural Brain Research, 232*(1), 269–277.

Bekinschtein, P., Cammarota, M., Igaz, L. M., Bevilaqua, L. R., Izquierdo, I., & Medina, J. H. (2007). Persistence of long-term memory storage requires a late protein synthesis- and BDNF-dependent phase in the hippocampus. *Neuron, 53*(2), 261–277.

Bernabeu, R., Cammarota, M., Izquierdo, I., & Medina, J. H. (1997). Involvement of hippocampal AMPA glutamate receptor changes and the cAMP/protein kinase A/CREB-P signalling pathway in memory consolidation of an avoidance task in rats. *Brazilian Journal of Medical and Biological Research, 30*(8), 961–965.

Bethus, I., Tse, D., & Morris, R. G. (2010). Dopamine and memory: Modulation of the persistence of memory for novel hippocampal NMDA receptor-dependent paired associates. *Journal of Neuroscience, 30*(5), 1610–1618.

Black, Y. D., Green-Jordan, K., Eichenbaum, H. B., & Kantak, K. M. (2004). Hippocampal memory system function and the regulation of cocaine self-administration behavior in rats. *Behavioural Brain Research, 151*(1–2), 225–238.

Bromberg-Martin, E. S., Matsumoto, M., & Hikosaka, O. (2010). Dopamine in motivational control: Rewarding, aversive, and alerting. *Neuron, 68*(5), 815–834.

Cohen, S. J., Munchow, A. H., Rios, L. M., Zhang, G., Asgeirsdóttir, H. N., & Stackman, R. W. Jr., (2013). The rodent hippocampus is essential for nonspatial object memory. *Current Biology, 23*(17), 1685–1690.

Dudai, Y. (2004). The neurobiology of consolidations, or, how stable is the engram? *Annual Review of Psychology, 55*, 51–86.

Engblom, D., Bilbao, A., Sanchis-Segura, C., Dahan, L., Perreau-Lenz, S., Balland, B., et al. (2008). Glutamate receptors on dopamine neurons control the persistence of cocaine seeking. *Neuron, 59*(3), 497–508.

Fuchs, R. A., Evans, K. A., Parker, M. C., & See, R. E. (2004). Differential involvement of the core and shell subregions of the nucleus accumbens in conditioned cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology (Berl), 176*(3–4), 459–465.

Gasbarri, A., Sulli, A., & Packard, M. G. (1997). The dopaminergic mesencephalic projections to the hippocampal formation in the rat. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 21*(1), 1–22.

Gerber, B., & Menzel, R. (2000). Contextual modulation of memory consolidation. *Learning & Memory, 7*(3), 151–158.

Gholizadeh, S., Sun, N., De Jaeger, X., Bechard, M., Coolen, L., & Laviolette, S. R. (2013). Early versus late-phase consolidation of opiate reward memories requires distinct molecular and temporal mechanisms in the amygdala-prefrontal cortical pathway. *PLoS ONE, 8*(5), e63612.

Gonzalez, C., Kramar, C., Garagoli, F., Rossato, J. I., Weisstaub, N., Cammarota, M., et al. (2013). Medial prefrontal cortex is a crucial node of a rapid learning system that retrieves recent and remote memories. *Neurobiology of Learning and Memory, 103*, 19–25.

Han, J., Li, Y., Wang, D., Wei, C., Yang, X., & Sui, N. (2010). Effect of 5-aza-2-deoxycytidine microinjecting into hippocampus and prelimbic cortex on acquisition and retrieval of cocaine-induced place preference in C57BL/6 mice. *European Journal of Pharmacology, 642*(1–3), 93–98.

Harvey, J. A. (2003). Role of the serotonin 5-HT(2A) receptor in learning. *Learning & Memory, 10*(5), 355–362.

Hernández-Rabaza, V., Hontecillas-Prieto, L., Velázquez-Sánchez, C., Ferragud, A., Pérez-Villaba, A., Arcusa, A., et al. (2008). The hippocampal dentate gyrus is essential for generating contextual memories of fear and drug-induced reward. *Neurobiology of Learning and Memory, 90*(3), 553–559.

Hernandez, L., & Hoebel, B. G. (1988). Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. *Life Sciences, 42*(18), 1705–1712.

Holahan, M. R. (2005). Complementary roles for the amygdala and hippocampus during different phases of appetitive information processing. *Neurobiology of Learning and Memory, 84*(2), 124–131.

Huston, J. P., Silva, M. A., Topic, B., & Müller, C. P. (2013). What's conditioned in conditioned place preference? *Trends in Pharmacological Sciences, 34*(3), 162–166.

Ito, R., Dalley, J. W., Howes, S. R., Robbins, T. W., & Everitt, B. J. (2000). Dissociation in conditioned dopamine release in the nucleus accumbens core and shell in response to cocaine cues and during cocaine-seeking behavior in rats. *Journal of Neuroscience, 20*(19), 7489–7495.

Ito, R., Dalley, J. W., Robbins, T. W., & Everitt, B. J. (2002). Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. *Journal of Neuroscience, 22*(14), 6247–6253.

Izquierdo, I., Medina, J. H., Izquierdo, L. A., Barros, D. M., de Souza, M. M., & Mello e Souza, T. (1998). Short- and long-term memory are differentially regulated by monoaminergic systems in the rat brain. *Neurobiology of Learning and Memory, 69*(3), 219–224.

Izquierdo, I., & Medina, J. H. (1997). Memory formation: the sequence of biochemical events in the hippocampus and its connection to activity in other brain structures. *Neurobiology of Learning and Memory, 68*(3), 285–316.

Kamin, L. J. (1957). The retention of an incompletely learned avoidance response. *J. Comp. Physiol. Psychol., 50*(5), 457–460.

Katche, C., Cammarota, M., & Medina, J. H. (2013). Molecular signatures and mechanisms of long-lasting memory consolidation and storage. *Neurobiology of Learning and Memory, 106*, 40–47.

Kauer, J. A., & Malenka, R. C. (2007). Synaptic plasticity and addiction. *Nature Reviews Neuroscience, 8*(11), 844–858.

Kim, J. J., & Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science, 256*(5057), 675–677.

Kramar, C. P., Chefer, V. I., Wise, R. A., Medina, J. H., & Barbano, M. F. (2014). Dopamine in the dorsal hippocampus impairs the late consolidation of cocaine-associated memory. *Neuropsychopharmacology, 39*(7), 1645–1653.

Lemon, N., & Manahan-Vaughan, D. (2006). Dopamine D1/D5 receptors gate the acquisition of novel information through hippocampal long-term potentiation and long-term depression. *Journal of Neuroscience, 26*(29), 7723–7729.

Li, Y. Q., Xue, Y. X., He, Y. Y., Li, F. Q., Xue, L. F., Xu, C. M., et al. (2011). Inhibition of PKMzeta in nucleus accumbens core abolishes long-term drug reward memory. *Journal of Neuroscience, 31*(14), 5436–5446.

Lintas, A., Chi, N., Lauzon, N. M., Bishop, S. F., Gholizadeh, S., Sun, N., et al. (2011). Identification of a dopamine receptor-mediated opiate reward memory switch in the basolateral amygdala-nucleus accumbens circuit. *Journal of Neuroscience, 31*(31), 11172–11183.

Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA loop: Controlling the entry of information into long-term memory. *Neuron, 46*(5), 703–713.

Luo, A. H., Tahsili-Fahadan, P., Wise, R. A., Lupica, C. R., & Aston-Jones, G. (2011). Linking context with reward: A functional circuit from hippocampal CA3 to ventral tegmental area. *Science, 333*(6040), 353–357.

Lüscher, C., & Bellone, C. (2008). Cocaine-evoked synaptic plasticity: A key to addiction? *Nature Neuroscience, 11*(7), 737–738.

Marra, V., O'Shea, M., Benjamin, P. R., & Kemenes, I. (2013). Susceptibility of memory consolidation during lapses in recall. *Nature Communications, 4*, 1578.

Martin, J. H. (1991). Autoradiographic estimation of the extent of reversible inactivation produced by microinjection of lidocaine and muscimol in the rat. *Neuroscience Letters, 127*(2), 160–164.

Martin, J. H., & Ghez, C. (1999). Pharmacological inactivation in the analysis of the central control of movement. *Journal of Neuroscience Methods, 86*(2), 145–159.

McGaugh, J. L. (2000). Memory – A century of consolidation. *Science, 287*(5451), 248–251.

Meyers, R. A., Zavala, A. R., Speer, C. M., & Neisewander, J. L. (2006). Dorsal hippocampus inhibition disrupts acquisition and expression, but not consolidation, of cocaine conditioned place preference. *Behavioral Neuroscience, 120*(2), 401–412.

Miller, C. A., & Marshall, J. F. (2005). Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. *Neuron, 47*(6), 873–884.

Mizumori, S. J., Puryear, C. B., & Martig, A. K. (2009). Basal ganglia contributions to adaptive navigation. *Behavioural Brain Research, 199*(1), 32–42.

Moncada, D., Ballarini, F., Martinez, M. C., Frey, J. U., & Viola, H. (2011). Identification of transmitter systems and learning tag molecules involved in behavioral tagging during memory formation. *Proceedings of the National Academy of Sciences of the United States of America, 108*(31), 12931–12936.

Morris, R. G. (2006). Elements of a neurobiological theory of hippocampal function: The role of synaptic plasticity, synaptic tagging and schemas. *European Journal of Neuroscience, 23*(11), 2829–2846.

Murray, J. E., Belin, D., & Everitt, B. J. (2012). Double dissociation of the dorsomedial and dorsolateral striatal control over the acquisition and performance of cocaine seeking. *Neuropsychopharmacology, 37*(11), 2456–2466.

National Research Council (2011). *Guide for the care and use of laboratory animals* (8th ed.). Washington, DC: The National Academies Press.

O'Carroll, C. M., Martin, S. J., Sandin, J., Frenguelli, B., & Morris, R. G. (2006). Dopaminergic modulation of the persistence of one-trial hippocampus-dependent memory. *Learning & Memory, 13*(6), 760–769.

Otis, J. M., Fitzgerald, M. K., & Mueller, D. (2014). Inhibition of hippocampal β-adrenergic receptors impairs retrieval but not reconsolidation of

cocaine-associated memory and prevents subsequent reinstatement. *Neuropsychopharmacology, 39*(2), 303–310.
Paxinos, G., & Watson, C. (2004). *The rat brain in stereotaxic coordinates* (5th ed.). San Diego, USA: Elsevier Academic Press.
Peleg-Raibstein, D., & Feldon, J. (2006). Effects of dorsal and ventral hippocampal NMDA stimulation on nucleus accumbens core and shell dopamine release. *Neuropharmacology, 51*(5), 947–957.
Ramos, M., Goñi-Allo, B., & Aguirre, N. (2005). Administration of SCH 23390 into the medial prefrontal cortex blocks the expression of MDMA-induced behavioral sensitization in rats: An effect mediated by 5-HT2C receptor stimulation and not by D1 receptor blockade. *Neuropsychopharmacology, 30*(12), 2180–2191.
Ren, Z. Y., Liu, M. M., Xue, Y. X., Ding, Z. B., Xue, L. F., Zhai, S. D., et al. (2013). A critical role for protein degradation in the nucleus accumbens core in cocaine reward memory. *Neuropsychopharmacology, 38*(5), 778–790.
Riege, W. H., & Cherkin, A. (1971). One-trial learning and biphasic time course of performance in the goldfish. *Science, 172*(3986), 966–968.
Rogge, G. A., Singh, H., Dang, R., & Wood, M. A. (2013). HDAC3 is a negative regulator of cocaine-context-associated memory formation. *Journal of Neuroscience, 33*(15), 6623–6632.
Rossato, J. I., Bevilaqua, L. R., Izquierdo, I., Medina, J. H., & Cammarota, M. (2009). Dopamine controls persistence of long-term memory storage. *Science, 325*(5943), 1017–1020.
Stewart, J. (1983). Conditioned and unconditioned drug effects in relapse to opiate and stimulant drug self-adminstration. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 7*(4–6), 591–597.
Sutton, M. A., & Carew, T. J. (2002). Behavioral, cellular, and molecular analysis of memory in Aplysia I: Intermediate-term memory. *Integrative and Comparative Biology, 42*(4), 725–735.
Szalay, J. J., Morin, N. D., & Kantak, K. M. (2011). Involvement of the dorsal subiculum and rostral basolateral amygdala in cocaine cue extinction learning in rats. *European Journal of Neuroscience, 33*(7), 1299–1307.
Tanaka, T., Kai, N., Kobayashi, K., Takano, Y., & Hironaka, N. (2011). Up-regulation of dopamine D1 receptor in the hippocampus after establishment of conditioned place preference by cocaine. *Neuropharmacology, 61*(4), 842–848.
Thomas, M. J., Kalivas, P. W., & Shaham, Y. (2008). Neuroplasticity in the mesolimbic dopamine system and cocaine addiction. *British Journal of Pharmacology, 154*(2), 327–342.
Thompson, A. M., Gosnell, B. A., & Wagner, J. J. (2002). Enhancement of long-term potentiation in the rat hippocampus following cocaine exposure. *Neuropharmacology, 42*(8), 1039–1042.
Tomaiuolo, M., Gonzalez, C., Medina, J. H., & Piriz, J. (2014). Lateral Habenula determines long-term storage of aversive memories. *Frontiers in Behavioral Neuroscience, 8*, 170.
Tzschentke, T. M. (2007). Measuring reward with the conditioned place preference (CPP) paradigm: Update of the last decade. *Addiction Biology, 12*(3–4), 227–462.
Ungless, M. A., Whistler, J. L., Malenka, R. C., & Bonci, A. (2001). Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature, 411*(6837), 583–587.
Vianna, M. R., Alonso, M., Viola, H., Quevedo, J., de Paris, F., Furman, M., et al. (2000). Role of hippocampal signaling pathways in long-term memory formation of a nonassociative learning task in the rat. *Learning & Memory, 7*(5), 333–340.
Vorel, S. R., Liu, X., Hayes, R. J., Spector, J. A., & Gardner, E. L. (2001). Relapse to cocaine-seeking after hippocampal theta burst stimulation. *Science, 292*(5519), 1175–1178.