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Enhancement of striatum-dependent memory by conditioned fear is mediated by beta-adrenergic receptors in the basolateral amygdala

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ABSTRACT

Emotional arousal can have a profound impact on various learning and memory processes. For example, unconditioned emotional stimuli (e.g., predator odor or anxiogenic drugs) enhance dorsolateral striatum (DLS)-dependent habit memory. These effects critically depend on a modulatory role of the basolateral complex of the amygdala (BLA). Recent work indicates that, like unconditioned emotional stimuli, exposure to an aversive conditioned stimulus (CS) (i.e., a tone previously paired with shock) can also enhance consolidation of DLS-dependent habit memory. The present experiments examined whether noradrenergic activity, particularly within the BLA, is required for a fear CS to enhance habit memory consolidation. First, rats underwent a fear conditioning procedure in which a tone CS was paired with an aversive unconditioned stimulus. Over the course of the next five days, rats received training in a DLS-dependent water plus-maze task, in which rats were reinforced to make a consistent body-turn response to reach a hidden escape platform. Immediately after training on days 1–3, rats received post-training systemic (Experiment 1) or intra-BLA (Experiment 2) administration of the β-adrenoreceptor antagonist, propranolol. Immediately after drug administration, half of the rats were re-exposed to the tone CS in the conditioning context (without shock). Post-training CS exposure enhanced consolidation of habit memory in vehicle-treated rats, and this effect was blocked by peripheral (Experiment 1) or intra-BLA (Experiment 2) propranolol administration. The present findings reveal that noradrenergic activity within the BLA is critical for the enhancement of DLS-dependent habit memory as a result of exposure to conditioned emotional stimuli.

1. Introduction

Mammalian memory is organized into dissociable neural systems that differ in terms of the type(s) of memory they mediate (White and McDonald, 2002; Squire, 2004; White et al., 2013). Extensive evidence indicates that among these memory systems is a stimulus-response/habit system principally dependent on the integrity of the dorsolateral striatum (DLS) (Packard et al., 1989; Packard and McGaugh, 1996; Packard and Knowlton, 2002; Yin et al., 2004; Goodman and Packard, in press). DLS-dependent memory processes have been implicated in a variety of learning and memory tasks including response learning in the plus-maze, whereby animals acquire an egocentric turning response at the maze choice-point to receive reinforcement (Packard and McGaugh, 1996; Chang and Gold, 2004; Yin and Knowlton, 2004). Memory in DLS-dependent maze tasks may be considered an exemplar of habit memory, given that the learned behavior in these tasks remains insensitive to reward devaluation (Sage and Knowlton, 2000; Lin and Liao, 2003; De Leonibus et al., 2011; Smith et al., 2012; Smith and Graybiel, 2013).

Stress influences a wide variety of learning and memory processes, and whether stress enhances or impairs memory partly depends on the type of memory being investigated (Kim and Diamond, 2002; McGaugh, 2004; Sandi and Pinelo-Nava, 2007; Packard, 2009; Roozendaal et al., 2009; Sandi, 2013; Arnsten, 2015). Converging evidence indicates that DLS-dependent habit memory in the plus-maze may be facilitated by the induction of emotional arousal through the exposure of animals to aversive unconditioned stimuli (Packard, 2009; Packard and Goodman, 2012, 2013; Sandi, 2013; Schwabe, 2013). For example, DLS-dependent habit memory may be facilitated following chronic restraint stress, tail shock,

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exposure to predator odor, or administration of anxiogenic drugs (Kim et al., 2001; Packard and Wingard, 2004; Wingard and Packard, 2008; Elliott and Packard, 2008; Schwabe et al., 2010c; Packard and Gabriele, 2009; Leong et al., 2012; Leong and Packard, 2014; Taylor et al., 2014; Goodman et al., 2015). Furthermore, some evidence suggests that, as observed with unconditioned emotional stimuli, exposure to emotionally arousing conditioned stimuli also modulates memory (Holahan and White, 2002, 2004; Hawley et al., 2013; Leong et al., 2015). In particular, recent work from our laboratory revealed that exposing rats to shock-associated stimuli (i.e., a tone and context previously paired with footshock—hereafter termed 'CS exposure') enhanced DLS-dependent habit memory and biased animals toward the use of a response learning strategy in the plus-maze (Leong et al., 2015). The neural mechanisms underlying this behavioral effect have yet to be fully characterized.

Noradrenergic activity, particularly within the basolateral complex of the amygdala (BLA), plays a critical role in regulating emotional arousal and the emotional modulation of memory (McGaugh, 2004; Roozendaal et al., 2009). Additionally, the BLA is required for the acquisition and expression of Pavlovian fear conditioning (Campeau and Davis, 1995; Maren et al., 1996; LeDoux, 2000, 2003; Maren, 2001a, 2001b). Studies have found that noradrenaline administered directly into the BLA modulates memory consolidation, whereas administration of a β-adrenoceptor antagonist blocks the emotional modulation of memory (Liang et al., 1990; Hatfield and McGaugh, 1999). In addition, the memory modulatory effects of systemically administered adrenaline are also blocked after intra-BLA administration of the β-adrenoceptor antagonist, propranolol, across a range of learning and memory tasks (Liang et al., 1986; for review, see Roozendaal et al., 2009). Evidence from our laboratory indicates that similar neural mechanisms underlie the emotional enhancement of DLS-dependent habit memory in the plus-maze. For example, administration of anxiogenic drugs directly into the BLA is sufficient to enhance DLS-dependent habit memory and the enhancement of habit memory produced by exposure to predator odor or systemic administration of anxiogenic drugs is blocked by neural inactivation of the BLA (Elliott and Packard, 2008; Wingard and Packard, 2008; Packard and Gabriele, 2009; Leong and Packard, 2014).

In view of this evidence, we hypothesized that the enhancement of DLS-dependent habit memory consolidation after exposure to an aversive CS (Leong et al., 2015) may also be dependent on noradrenergic activity, particularly within the BLA. In order to test this hypothesis, rats were first subjected to a standard fear conditioning paradigm (i.e., repeated tone-shock pairings). Rats were then trained in a response learning task in the water plus-maze that requires the use of DLS-dependent habit memory. Following training sessions, rats were given systemic (Experiment 1) or intra-BLA (Experiment 2) administration of propranolol immediately before CS exposure.

2. Materials and methods

2.1. Subjects

Subjects were experimentally naïve adult male Long Evans (Blue Spruce) rats, obtained from Harlan Laboratories (Indianapolis, IN), and weighing 275–375 g at the time of training. Subjects were individually housed in clear plastic cages with sawdust bedding in a climate-controlled vivarium. Standard rodent chow and water were accessible *ad libitum*. Experimenters handled rats for 1 min per day for five days prior to the start of behavioral training or surgeries. For Experiment 1, rats experienced a 12:12 light–dark cycle (lights on at 7:00 a.m. and off at 7:00 p.m.). Experiment 2 utilized a 14:10 light–dark schedule (lights on at 7:00 a.m. and off at 9:00 p.m.). All phases of behavioral training occurred during the light phase of the cycles. The Institutional Animal Care and Use Committee at Texas A&M University approved all experimental procedures.

2.2. Apparatus

For Experiment 1 and 2, fear conditioning occurred within 8 identical rodent conditioning chambers (MED Associates). These chambers were housed within external sound-attenuating cabinets in an isolated room. The chambers (30 cm × 24 cm × 21 cm) are comprised of aluminum (side walls) and Plexiglas (real wall, front door, and ceiling). The floor of each chamber consisted of 19 stainless steel rods (4 mm in diameter) spaced center to center at 1.5 cm apart. Footshock (2 s, 1 mA; unconditioned stimulus, US) was delivered via a shock source and solid-state grid scrambler (MED Associates). A speaker attached to each individual chamber provided the auditory conditioned stimulus (2 kHz, 20 s, 80 dB). Small fans in each cabinet provided background noise (70 dB). Cameras mounted above the Plexiglas ceiling of the chambers remotely recorded each animal's behavior. For the conditioning context, a small volume of 1.5% acetic acid odor was poured into the metal pan beneath the grid floor, the testing room lights remained on, and the cabinet doors were left open. Each chamber was cleaned with water and acetic acid before and after conditioning. The same contextual cues were used for both conditioning and CS exposure sessions. A load-cell platform beneath each chamber recorded chamber displacement (−10 V to +10 V) as a result of each animal's movement. Load-cell activity values were acquired and digitized at 5 Hz with Threshold Activity software (Med Associates). Activity values were transformed offline into absolute values ranging from 0 to 100 (with lower values indicating less displacement of the chamber); rats were scored as freezing if absolute values were $\leq$10 for 1 s or more. Freezing was analyzed as a percentage of total time across each trial as described below.

The water maze consisted of a clear Plexiglas plus-maze (43 cm in height; each arm is 27 cm wide and 60 cm in length) that was inserted in a black circular tub (180 cm in diameter; 45 cm in height; see Leong et al., 2012; Goodman and Packard, 2014; Leong and Packard, 2014; Leong et al., 2015). For Experiment 1 and 2, the maze was filled with water to a level of ~21 cm; water temperature was 25 °C (i.e., room temperature). A submerged clear plastic platform (15 cm × 14 cm × 20 cm) served as the hidden escape platform; the platform was about ~1 cm below the water level throughout maze training. A movable piece of Plexiglas (43 cm in height; 27 cm wide) blocked entry into the arm opposite to the start arm for each trial, creating a T-maze as necessary for the response learning task described below. The maze room contained multiple extra-maze cues.

2.3. Surgery

Prior to behavioral training in Experiment 2, rats were anesthetized with isoflurane and treated with atropine nitrate (0.4 mg/kg, i.p.). Each rat was secured in a stereotaxic frame (David Kopf Instruments) and a small incision was made in the tissue above the skull; bregma and lambda of the skull were leveled on an even plane. Jeweler's screws were affixed to the skull. Small holes were drilled in the skull and guide cannulae (10 mm, 26 gauge; Small Parts) were lowered to the following coordinates: −2.2 posterior to bregma; ±5.0 medial/lateral to the midline; −6.0 ventral to dura (targeting the BLA). Dental cement was used to anchor the guide cannulae to the screws in the skull. Stainless steel dummy cannulae (11 mm, 30 gauge) were inserted into the guide cannulae (extending 1 mm beyond the end of the guide cannulae into the

BLA). Dummy cannulae were replaced once before fear conditioning and again after each infusion session. Rats were allowed 7 days of recovery from surgery before the start of behavioral training.

2.4. Fear conditioning

Freezing behavior served as the index of fear for conditioning and during exposure to the conditioned fear stimuli. On the first day of behavioral training, rats (in squads of eight; counterbalanced by group assignments) were transported in black plastic containers from their homecages in the vivarium to the fear conditioning chambers in the laboratory. 3 min after being placed in the conditioning chambers, rats received three tone (2 kHz, 20 s, 80 dB)-footshock (2 s, 1 mA) pairings; the tone and shock co-terminated. Tone-footshock pairings were separated by 1-min interstimulus intervals; rats remained in the conditioning chambers for 1 min after the final tone-footshock pairing. Rats were immediately returned to the vivarium after conditioning.

2.5. Response learning task

For Experiment 1 and 2, training procedures for the response learning task were identical to the procedures employed in our previous studies (Leong et al., 2012; Goodman and Packard, 2014; Leong et al., 2015; Wingard et al., 2015). Twenty-four hrs after fear conditioning, rats were individually transported from the vivarium to the room containing the water plus-maze. Rats were transported to the maze in white plastic containers. Rats were trained in the water maze across five consecutive days with six trials per day. For each trial, the subject was removed from the white transport container and gently placed into the water maze (facing the maze wall) in either the north (N) or south (S) arm; rats were allotted 1 min to swim to a hidden platform at the end of another arm (east or west). The arm opposite to the start arm would be blocked with the removable plastic wall. The location of the hidden platform was consistently in the arm in which a right body turn at the maze's choice point (i.e., at the middle of the maze) would lead to finding the platform. For instance, if a rat started in the north arm, the hidden escape platform would be in the west arm; if the rat started in the south arm, the hidden platform would be in the east arm. On the first, third, and fifth day of training (odd days), the sequence of the start arm was NSSNNS. On even days, the sequence of the start arm was SNNSSN. If the rat did not locate the escape platform within 1 min, the experimenter would manually guide the rat to the escape platform. Once the rat climbed onto the platform, the rat would remain on the escape platform for 10 s before being returned to the white plastic container for a 30 s intertrial interval. If the subject made a full-body entry into the arm containing the hidden platform, then this response was scored as correct. If the rat made a full-body entry into the adjacent arm that did not contain the hidden platform, then this response was scored as incorrect. If the rat exited the start arm and made a full-body entry back into the start arm, then this was also scored as incorrect. Performance in the maze was analyzed as a percentage of correct responses for each day as described below.

2.6. Behavioral procedures: experiment 1

An overview of the designs for each experiment is depicted in Fig. 1. For Experiment 1 (prior to behavioral training), rats were randomly assigned to drug (propranolol [PROP] or vehicle [VEH]) and exposure (FEAR or NEUTRAL) conditions, yielding the following groups: PROP-FEAR ($n = 8$), PROP-NEUTRAL ($n = 8$), VEH-FEAR ($n = 8$), VEH-NEUTRAL ($n = 8$). For Experiment 1, PROP and VEH rats received systemic (i.p.) administration of propranolol (3.0 mg/kg) or vehicle (respectively) immediately following maze training on the first three days. This dose of propranolol was selected based on previous evidence that this dose blocks the memory modulatory properties of glucocorticoid administration (Roozendaal et al., 2006b). Propranolol (Sigma–Aldrich) was dissolved in saline and prepared fresh for each day's use. Systemic injection of propranolol was administered at a volume of 1 ml/kg.

Immediately following propranolol or vehicle administration (on the first three days of training in the maze), rats were exposed to either the CS in the original conditioning chambers (FEAR rats) or to a clean blue plastic container enclosed in a separate room (NEUTRAL rats) for an equal duration. FEAR rats received three non-reinforced conditioned tone presentations in the conditioning chambers (separated by 1 min interstimulus intervals in the chamber, with 3 min of baseline and 1 min following the final tone-alone presentation). FEAR rats were transported to and from the fear conditioned chambers in the same black transport boxes used during conditioning. NEUTRAL rats were transported in the white plastic containers used throughout their training in the maze.

2.7. Behavioral procedures: experiment 2

In Experiment 2, rats were randomly assigned to drug (PROP or VEH) and exposure (FEAR or NEUTRAL) conditions, yielding the following groups: PROP-FEAR ($n = 6$), PROP-NEUTRAL ($n = 9$), VEH-FEAR ($n = 9$), VEH-NEUTRAL ($n = 7$). All apparatuses and procedures were identical to those in Experiment 1, except that drugs were administered directly into the BLA. For each infusion, propranolol (Sigma–Aldrich) was dissolved in distilled water to a concentration of 1.0 μg/μl. Physiological saline was used for VEH animals. Gas-tight syringes (Hamilton Co.) were secured to an automated syringe pump (KD Scientific). Polyethylene tubing (PE-20; Braintree Scientific) was inserted over the gas-tight syringes. Internal injection needles (11 mm, 33 gauge; Small Parts) were fitted to the opposite end of the tubing. The stainless steel dummy cannulae were removed from within the guide cannulae and the injectors were inserted into the guides. PROP rats received bilateral infusions of propranolol at a rate of 0.5 μL/min for 1 min, yielding a dose of 0.5 μg of propranolol per hemisphere (VEH rats received an equal volume of saline at an equal rate of infusion). This dose of propranolol was selected based on previous evidence that intra-BLA infusions at this dose block the memory modulatory properties of glucocorticoid administration (Roozendaal et al., 2006b). Injectors remained in the guide cannulae for 1 min after infusion before being removed; clean dummy cannulae were inserted into the guides after these procedures. Rats remained in a clean white 5-gallon bucket during the infusion process.

2.8. Histology

Rats from Experiment 2 were overdosed on pentobarbital (0.5 ml, i.p.) and intracardially perfused with physiological saline and 10% formalin. Brains were extracted and stored in 10% formalin for twenty-four hrs then switched to a sucrose-formalin solution until sectioning. Brains were flash frozen and sectioned at 40 μm on a cryostat. Every third slice was wet-mounted to a gel-subbed microscope slide. Sections were stained with 0.25% thionin. Photomicrographs of brain slices were generated for each rat using a Leica MZFLIII microscope. Only rats with injector tips localized within the BLA (bilaterally) were included in the final analyses.

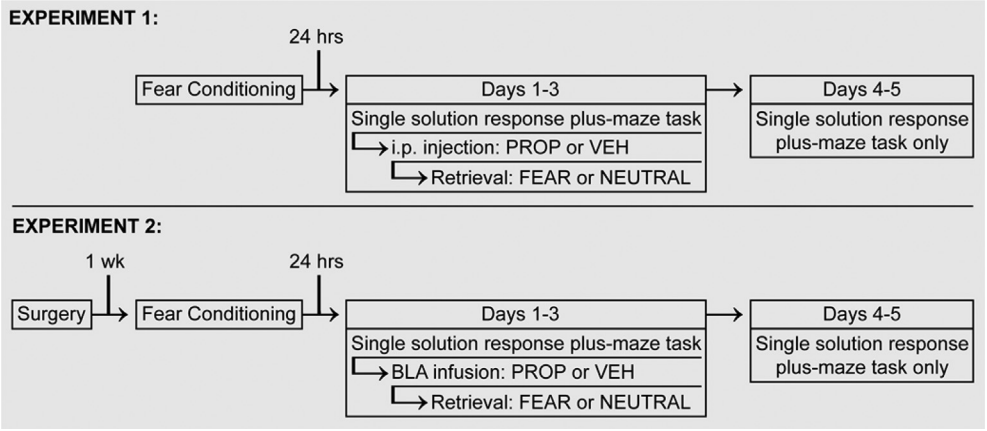

Fig. 1. An overview of the experimental designs.

3. Results

3.1. Systemic propranolol prevents fear-enhanced consolidation of habit memory (experiment 1)

Twenty-four hrs prior to training in the response learning task, rats reliably conditioned to the auditory tone (Fig. 2A). Repeated measures ANOVA revealed a main effect of trial [$F_{(1,28)} = 161.998$; $p < 0.0001$] such that rats significantly increased in freezing from baseline to the final tone at conditioning. As expected, rats did not differ based on drug or exposure assignments across conditioning trials [$Fs < 2$]. After maze training, CS exposure in the conditioning context reliably induced freezing behavior in FEAR rats (Fig. 2A). Collapsed across the three days of CS exposure, a main effect of trial revealed that rats significantly increased in mean freezing following the onset of the CS [$F_{(1,14)} = 30.194$; $p < 0.0001$], indicating robust CS-evoked fear. Peripheral administration of propranolol did not significantly alter freezing, as rats exposed to fear conditioned stimuli did not significantly differ across drug assignments during the retrieval phase [$Fs < 1$].

Water maze performance for Experiment 1 is depicted in Fig. 2B. As illustrated, systemic propranolol administration prevented the memory enhancement produced by post-training exposure to the fear CS. This was confirmed in the ANOVA by a significant drug × exposure interaction for responding in the maze across days 2–5 of training [$F_{(1,28)} = 6.599$; $p < 0.05$]. Post hoc analyses revealed that VEH-FEAR rats exhibited significantly more correct responses (%) across days 2–5 as compared to PROP-FEAR [$p < 0.01$] or VEH-NEUTRAL [$p < 0.05$] rats, whereas PROP-FEAR, PROP-NEUTRAL, and VEH-NEUTRAL rats did not significantly differ from one another across training. A main effect of day indicated that performance in the maze improved for all groups across days 2–5 [$F_{(3,84)} = 13.733$; $p < 0.0001$]. Factorial ANOVA of group performance on Day 1 revealed no significant group differences [$Fs < 2$]. A trending but nonsignificant main effect of propranolol was detected across days 2–5 [$F < 3$]. No other significant comparisons were detected [$Fs < 1$]. In sum, the data from Experiment 1 reveal that post-training peripheral antagonism of β-adrenoreceptors is sufficient to blunt the enhancement of habit memory as a result of exposure to fear CSs.

3.2. Intra-BLA propranolol infusions prevent fear-enhanced consolidation of habit memory (experiment 2)

Intra-BLA cannula placements are illustrated in Fig. 3. As in Experiment 1, conditioning in Experiment 2 was robust for all groups (Fig. 4A). A main effect of trial indicated that rats significantly increased in freezing from baseline to the final tone at conditioning [$F_{(1,27)} = 48.746$; $p < 0.0001$]. Groups did not significantly differ from baseline to the final conditioning trial [$Fs < 2$]. During post-maze fear exposure, the CS reliably induced freezing (Fig. 4A). Collapsed across the three days of CS exposure, a main effect of trial revealed that rats significantly increased in mean freezing following the onset of the CS [$F_{(1,13)} = 13.930$; $p < 0.005$]. PROP-FEAR and VEH-FEAR rats did not significantly differ in their levels of freezing across the three days of fear CS exposure [$Fs < 2$] (similar to Experiment 1).

In contrast to experiment 1, ANOVA of maze performance on the first day of maze training revealed a significant drug × exposure interaction [$F_{(1,27)} = 5.395$; $p < 0.05$], indicating that the groups differed in baseline memory performance. This was unexpected, because all groups were treated equally before and during Day 1 maze training. Drug administration and fear CS exposure did not occur until immediately after maze training on Day 1. Nevertheless, post hoc analyses revealed that VEH-FEAR rats exhibited significantly fewer correct responses on the first day of maze training as compared to PROP-FEAR rats [$p < 0.05$]. On days 2–5, a main effect of day was observed [$F_{(3,81)} = 10.247$; $p < 0.0001$], but no other significant main effects or interactions were detected for % correct responses [$Fs < 1.5$]. Given that, in contrast to experiment 1, groups in experiment 2 displayed differences in Day 1 baseline memory performance and that significant differences on the first day of training may influence differences in future performance, we normalized the responding of each rat in the maze to each rat's relative performance for the first day. Specifically, the percentages of correct responses of each rat for each day (2–5) were divided by the rat's percentage correct on day 1 (i.e., a value of 1 indicates an equal amount of correct responses as compared to day 1, a value of 2 indicates twice as many correct responses as compared to day 1, and so on). As such, we analyzed the relative rate of increase in habit memory expression in the maze as compared to the first day of training (i.e., before drugs were administered). These results are shown in Fig. 4B. ANOVA of percentage correct responses across training days 2–5 revealed a significant drug × exposure interaction [$F_{(1,27)} = 5.413$; $p < 0.05$]. Additionally, a significant day × drug × exposure interaction was revealed [$F_{(1,27)} = 2.855$; $p < 0.05$]. A main effect of PROP was trending, but not significant [$F < 2.5$]. Post hoc tests revealed that VEH-FEAR rats increased their performance in the maze at a faster rate as compared to PROP-FEAR [$p < 0.05$] and VEH-NEUTRAL [$p < 0.05$] rats. Conversely, PROP-FEAR, PROP-NEUTRAL, and VEH-NEUTRAL rats did not significantly differ across days 2–5 of maze training. A main effect of day

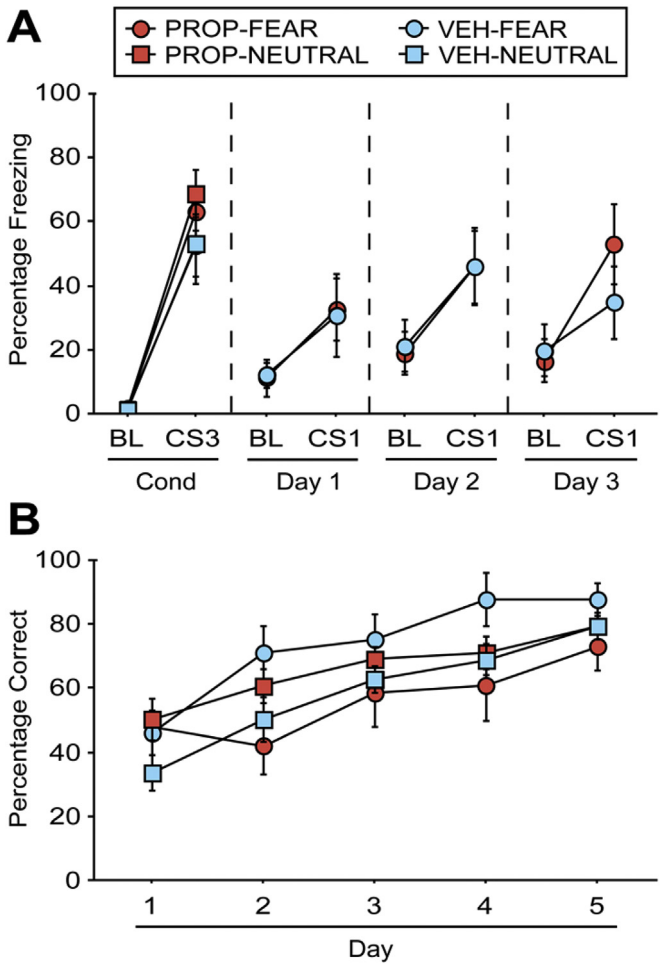

Fig. 2. Post-training i.p. injections of propranolol prevent the enhanced consolidation of response learning in the water plus-maze task as a result of exposure to fear conditioned stimuli. **A**, Freezing (mean %; ±SEM) across the course of conditioning ('Cond') and across days 1–3 of post-maze fear retrieval in Experiment 1. 'BL' depicts freezing across 3 min of acclimation to the conditioning chamber for each day. 'CS3' depicts freezing during the final 20-sec CS at conditioning. 'CS1' depicts freezing during the first 20-sec CS of each day of fear retrieval. **B**, Mean % correct (±SEM) for each day of training in the water plus-maze. Rats receiving systemic propranolol (3.0 mg/kg) prior to exposure to fear conditioned stimuli (PROP-FEAR) exhibited significantly less % correct responses over the course of training as compared to vehicle-treated controls (VEH-FEAR) [$p < 0.05$]. Rats receiving injections of propranolol or vehicle but not re-exposed to fear conditioned stimuli (PROP-NEUTRAL and VEH-NEUTRAL) did not significantly differ across training nor did they significantly differ from PROP-FEAR rats.

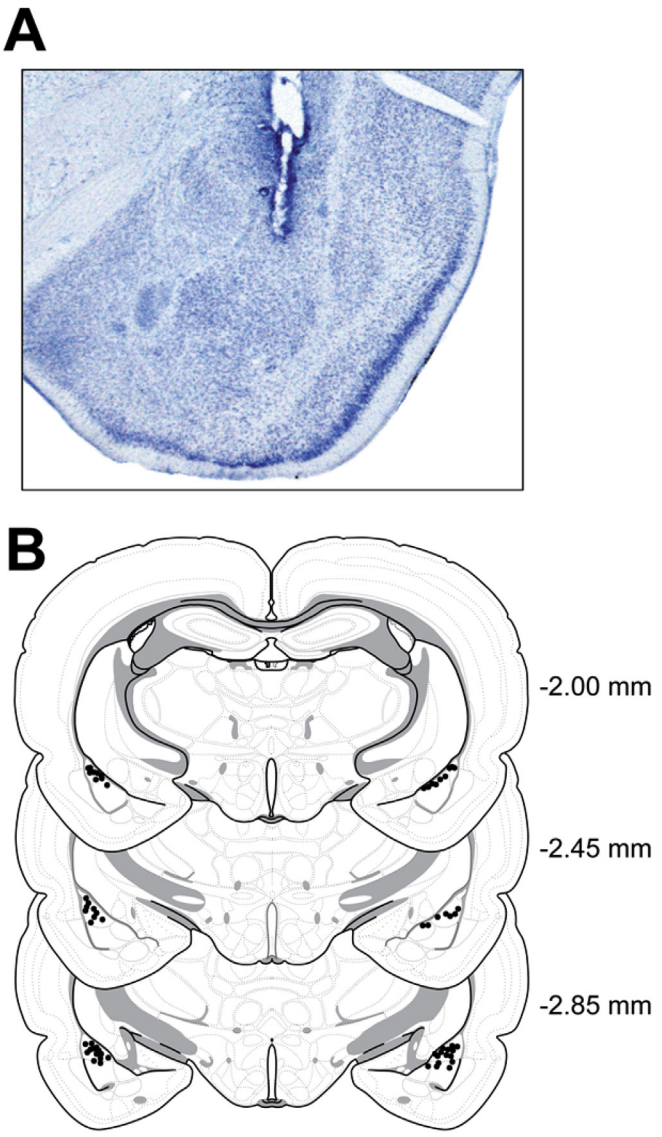

Fig. 3. **A**, Representative photomicrograph depicting an injector tip terminating in the basolateral amygdala (40 μm thionin-stained coronal section). **B**, Illustration of overlapping injection sites (black filled-in circles) in the basolateral complex of the amygdala. Placements are representative of all rats included in the final analyses for Experiment 2. Adapted from Swanson (2002). Distances are relative to bregma.

was observed [$F_{(3,81)} = 9.642$; $p < 0.0001$], indicating that rats in general significantly increased in their performance in the maze across days. No other main effects or interactions were detected [$Fs < 1$]. In sum, intra-BLA infusions of propranolol prevented the relative increase in performance in the response learning water plus-maze task after exposure of rats to conditioned fear cues.

4. Discussion

The present findings indicate that the enhancement of DLS-dependent habit memory produced by exposure of rats to fear CSs is blocked by systemic (Experiment 1) or intra-BLA (Experiment 2) antagonism of β-adrenoreceptors. The finding that post-training exposure to fear CSs, relative to exposure to neutral stimuli, enhanced habit memory is consistent with previous research from our laboratory (Leong et al., 2015). Given previous evidence indicating that *delayed* post-training CS exposure does not influence habit memory in the plus-maze (Leong et al., 2015), we assume that CS exposure influences maze performance by augmenting the initial consolidation phase of habit memory. In addition, previous evidence indicates that animals not given fear conditioning or animals given fear conditioning but no post-training CS exposure do not display enhanced habit memory in the plus-maze (Leong et al., 2015). This suggests that the enhancement of habit memory in the present study is specifically attributed to CS exposure (as opposed to the fear conditioning that transpired twenty-four hrs prior to maze training). Also, given the present finding that CS exposure was associated with conditioned freezing, it is plausible that post-training CS exposure enhanced habit memory by eliciting emotional arousal (i.e., fear).

Attributing the present habit memory enhancement to emotional arousal concords with extensive previous evidence indicating that high emotional arousal produced by unconditioned

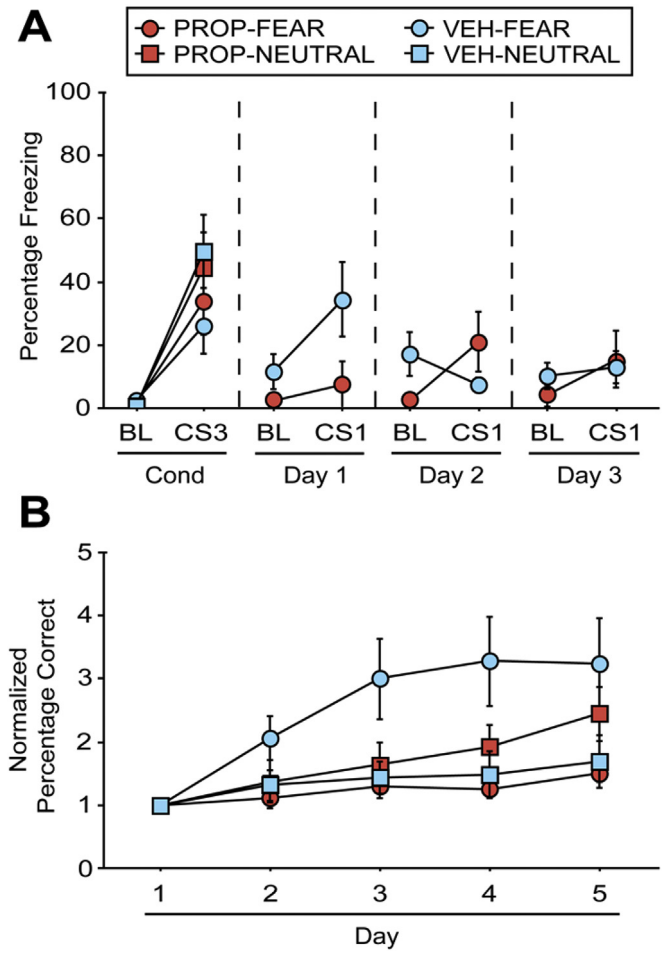

Fig. 4. Post-training intra-basolateral amygdala (BLA) infusions of propranolol prevent the enhanced consolidation of response learning in the water plus-maze task as a result of exposure to fear conditioned stimuli. **A**, Freezing (mean %; ±SEM) across the course of conditioning ('Cond') and across days 1–3 of post-maze fear retrieval in Experiment 2. 'BL' depicts freezing across 3 min of acclimation to the conditioning chamber for each day. 'CS3' depicts freezing during the final 20-sec CS at conditioning. 'CS1' depicts freezing during the first 20-sec CS of each day of fear retrieval. **B**, Y-axis shows mean % correct for each day as normalized to the mean % correct from day 1 (±SEM). Rats receiving intra-BLA propranolol (0.5 μg per hemisphere) prior to exposure to fear conditioned stimuli (PROP-FEAR) exhibited a slower rate of increase in the relative % correct responses over the course training (days 2–5) as compared to vehicle-treated controls (VEH-FEAR) [$p < 0.05$]. Rats receiving injections of propranolol or vehicle but not exposed to fear conditioned stimuli (PROP-NEUTRAL and VEH-NEUTRAL) did not significantly differ in their rate of learning across training nor did they significantly differ from PROP-FEAR rats.

stimuli enhances DLS-dependent memory processes (Packard, 2009; Packard and Goodman, 2012; Schwabe, 2013). For example, systemic infusion of anxiogenic drugs such as α-2-adrenoreceptor antagonists yohimbine or RS 79948-197 similarly enhances DLS-dependent habit memory in the water plus-maze task (Wingard and Packard, 2008; Packard and Gabriele, 2009; Leong et al., 2012) and leads to the preferential use of DLS-dependent learning in tasks that can be solved adequately using alternative strategies (Packard and Wingard, 2004; Elliott and Packard, 2008). Enhancements of DLS-dependent habit memory are also observed after exposure to behavioral or ecologically valid stressors, such as chronic restraint, tail shock, or predator odor (Kim et al., 2001; Schwabe et al., 2008; Leong and Packard, 2014; Taylor et al., 2014). Notably, the stress/anxiety-induced enhancement of habit memory originally demonstrated in rodents (Packard and Wingard, 2004) has also been demonstrated in humans following administration of anxiogenic drugs (e.g., hydrocortisone) or exposure to psychological stressors (Schwabe et al., 2007, 2008, 2010b, 2013; Schwabe and Wolf, 2009, 2010; Guenzel et al., 2014).

The influence of emotional arousal on memory systems may involve the release of stress hormones and subsequent activation of glucocorticoid, mineralocorticoid, and adrenergic receptors in the brain (McGaugh, 2004). Consistent with this suggestion, drug treatments increasing the activation of these receptors mimic the mnemonic effects of emotional arousal, whereas decreasing activation of these receptors through the use of selective antagonists prevents the effects of emotional arousal on memory (McGaugh, 2004; Roozendaal and McGaugh, 2011). For example, administration of the β-adrenoreceptor antagonist propranolol blocks the emotional enhancement of DLS-dependent habit memory in humans (Schwabe et al., 2011b), and a similar blockade may be observed following administration of mineralocorticoid receptor antagonists in mice and humans (Schwabe et al., 2010a, 2013). In addition, propranolol administration blocked the fear CS-enhancement of habit memory in the present study, consistent with the hypothesis that noradrenergic activity also underlies the mnemonic benefit of exposure to aversive CSs.

A modulatory role of the BLA has also been implicated in the emotional enhancement of DLS-dependent habit memory (Packard, 2009; Packard and Goodman, 2012). Direct administration of anxiogenic drugs into the BLA mimics the enhancement of habit memory produced by systemic administration of these drugs (Elliott and Packard, 2008; Wingard and Packard, 2008). In addition, the enhancement of habit memory after systemic administration of anxiogenic drugs or exposure to predator odor is blocked by reversible inactivation of the BLA (Packard and Gabriele, 2009; Leong and Packard, 2014). The present finding that administration of the β-adrenoreceptor antagonist propranolol directly into the BLA blocks the fear-enhancement of habit memory suggests that the mnemonic effects of *conditioned* emotional stimuli might similarly depend on both the noradrenergic system and a modulatory role of the BLA. Interestingly, this present finding suggests for the first time that noradrenergic activity specifically *within* the BLA is required for emotional arousal to influence DLS-dependent memory. Moreover, prior evidence indicates that increasing noradrenergic activity in the BLA is *sufficient* to enhance memory in a task identical to the one employed in the present study (Wingard and Packard, 2008), and the present results suggests that this effect is likely mediated through β-adrenergic receptors. Prior research indicates that exposure to fear CSs increases norepinephrine release in the amygdala (Tanaka et al., 2000; Zhou et al., 2015) and this increase in amygdala norepinephrine release may be responsible for the enhancement of habit memory observed in the present study. Future studies are necessary to examine whether increasing BLA noradrenergic activity augments the enhancement of habit memory by fear CSs and whether BLA norepinephrine levels correlates with these memory enhancements.

Although we only analyzed data for rats having injectors within the BLA, it is possible that drug had spread to other regions of the amygdala (e.g., the central nucleus [CeA]). While previous evidence suggests that the BLA, not CeA, mediates the memory modulating capacity of the amygdala (see Roozendaal and McGaugh, 1996; Quirarte et al., 1997; Roozendaal and McGaugh, 1997; Akirav and Richter-Levin, 2002), it is possible that the enhancement of habit memory in the present study may have been partially influenced by blockade of β-adrenoreceptors in the CeA. The CeA may influence habit memory through an indirect CeA-dorsal striatum pathway (Ferreira et al., 2008; Lingawi and Balleine, 2012). Whether the role of the CeA in habit memory depends on β-adrenoreceptor activity has yet to be examined.

An additional consideration regarding the fear CS enhancement

of habit memory is how the physiological processes during emotional arousal (e.g., stress hormone activity and BLA function) lead to the enhancement of DLS-dependent memory processes. One possibility is that stress hormones *directly* increase activation of the DLS. Indeed, previous evidence indicates that systemic or direct administration of corticosterone into the dorsal striatum enhances memory consolidation in both the cued water maze and inhibitory avoidance task (Medina et al., 2007; Quirarte et al., 2009; Goodman et al., 2015). Thus, fear CS exposure may be associated with the release of stress hormones such as corticosterone that *directly* increase activity of the DLS and consequently enhance habit memory consolidation in the plus-maze. Aside from this "direct" mechanism of enhancement, it is also reasonable to hypothesize that fear CS exposure may have enhanced habit memory *indirectly* through modulation of other brain regions. Extensive evidence indicates that in some learning situations, DLS-dependent memory processes may be facilitated by lesion or inactivation of the hippocampal formation (Packard et al., 1989; McDonald and White, 1993; Schroeder et al., 2002; for review, see Poldrack and Packard, 2003). Given that stress/anxiety is frequently associated with impaired hippocampus-dependent memory function (Diamond et al., 1996; de Quervain et al., 1998; Conrad et al., 2004; Sandi et al., 2005; Park et al., 2008; Wingard and Packard, 2008; for review, see Sandi and Pinelo-Nava, 2007), CS exposure may have similarly impaired hippocampal function in the present study, thus indirectly enhancing DLS-dependent habit memory. Consistent with this suggestion, previous evidence from our laboratory indicates that anxiogenic drug doses that impair hippocampus-dependent place learning also enhance DLS-dependent response learning, and that these enhancing and impairing effects of anxiogenic drug administration critically depend on BLA function (Wingard and Packard, 2008; Packard and Gabriele, 2009). Taking this "indirect" hypothesis a step further, it is tempting to speculate that propranolol administration in the present study might have blocked the CS enhancement of habit memory *indirectly* by preventing an impairment of hippocampal function. This hypothesis is consistent with some evidence indicating that propranolol might rescue the impairment of hippocampus-dependent memory produced by glucocorticoid administration (Roozendaal et al., 2004; de Quervain et al., 2007).

In addition to memory impairments, previous evidence indicates that memory *enhancements* following corticosterone administration are also blocked by concurrent infusions of propranolol (Quirarte et al., 1997; Roozendaal et al., 2006a). Notably, we have recently demonstrated that the corticosterone-induced enhancement of DLS-dependent habit memory may also be blocked by concurrent propranolol administration (Goodman et al., 2015). Thus, consistent with the view that glucocorticoid and noradrenergic mechanisms might interact to produce the emotional enhancement of habit memory, CS exposure in the present study would be expected to increase the release of glucocorticoids (Goldstein et al., 1996; Cordero et al., 1998; Hagewoud et al., 2011), whereas administration of propranolol might prevent glucocorticoids from enhancing habit memory (Goodman et al., 2015).

Another possible mechanism underlying the current results is that propranolol administration may have reduced fear expression (Rodriguez-Romaguera et al., 2009; Fitzgerald et al., 2014, 2015; Giustino et al., 2016). However, in the current study, CS-evoked levels of freezing across retrieval were not significantly different between propranolol- and vehicle-treated animals in either experiment. Similarly, Cain and colleagues (2004) reported no significant differences between mice treated (i.p.) with propranolol or vehicle in the early phases of massed auditory CS extinction or across a 60-min extinction session in a conditioned context (also, see Fitzgerald et al., 2015; Zhou et al., 2015). However, it is possible that floor effects might have competed with propranolol's effects on freezing in the current study. A higher dose of propranolol may also be required to significantly impact fear expression during post-maze CS exposure. Regardless, CS-evoked fear in the current study was sufficient to modulate performance in the maze for vehicle-treated animals.

Finally, numerous investigators have suggested that enhancement of the dorsal striatum-dependent memory system might in part underlie the development of some neuropsychiatric disorders, in particular disorders with prominent habit-like behavioral features (White, 1996; Everitt and Robbins, 2005; Schwabe et al., 2011a; Berner and Marsh, 2014; Gillan and Robbins, 2014; Goodman et al., 2014; Goodman and Packard, 2016). For instance, post-traumatic stress disorder (PTSD) is partly characterized by intractable avoidance behaviors that occur in response to trauma-related cues, and some investigators suggest that such avoidance symptoms may be a manifestation of enhanced DLS-dependent habit memory following very high levels of emotional arousal (i.e., trauma; Packard, 2009; Schwabe et al., 2010c; Goodman et al., 2012). The fear CS enhancement of habit memory observed in the present study may be considered a putative animal model of this proposed mechanism, whereby the conditioned emotional stimuli represent the trauma-related cues that enhance dorsal striatum-dependent memory processes and lead to the development or expression of behavioral avoidance symptoms in PTSD. Clinical evidence indicates that β-adrenoreceptor antagonists such as propranolol, when administered shortly after trauma or after PTSD has already developed, may be useful in treating some PTSD symptoms (Famularo et al., 1988; Pitman et al., 2002; Vaiva et al., 2003; Brunet et al., 2008; Krauseneck et al., 2010; Giustino et al., 2016). Considering that propranolol blocked the fear CS enhancement of habit memory, propranolol administered in the acute aftermath of trauma may similarly reduce the development of habit-like symptoms in PTSD.

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