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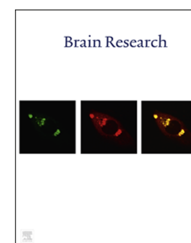

Research Report

Fear conditioning alters neuron-specific hippocampal place field stability via the basolateral amygdala

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ABSTRACT

It is well established that physical changes to an environment result in plasticity of hippocampal place cell activity, while in the absence of changes, place fields are remarkably stable. Manipulations of a rat's perception of the environment without physically changing the environment also result in plasticity of place cell firing. Here, we tested the hypothesis that a rat's perception of an environment could be changed by introducing an auditory fear-conditioned stimulus (CS) to a previously neutral environment, inducing plasticity of hippocampal place fields. First, stable place fields were isolated for rats exploring a radial-arm maze in one environment, and then the rats were fear-conditioned to an auditory CS in a completely separate environment. Later, the CS was specifically paired once with a location in the previously neutral radial-arm maze, either within the given neuron's place field (in-field) or an area outside of the place field (out-of-field). A single, paired presentation of the CS with a location in-field for a specific place cell disrupted the stability of that neuron's place field, whereas pairing the CS with a location out-of-field did not affect place field stability. We further showed that this place field disruption for a CS presented in-field was mediated by inputs from the basolateral amygdala (BLA). Temporarily inactivating the BLA immediately post-CS re-exposure attenuated the CS-induced place field destabilization. Our results show neuron-specific conditional plasticity for actively firing hippocampal place cells, and that the BLA mediates this plasticity when an emotionally arousing or fear-related CS is used.

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1. Introduction

Many pyramidal neurons in the rat hippocampus fire preferentially when a rat enters a specific location in an environment and are known as place cells (O'Keefe and Dostrovsky, 1971). The specific place in which the cell fires at a high frequency, its place field, is established very rapidly (Wilson and McNaughton, 1993) and can remain stable in a stable environment for at least several months (Muller et al., 1987; Thompson and Best, 1990). While only a fraction of CA1 pyramidal cells have place fields in a given environment (Thompson and Best, 1989), the ensemble firing of place cells form cognitive maps of all encountered environments. Each distinct place map generated for different environments is unrelated to the map of dissimilar environments (Bostock et al., 1991; Guzowski et al., 1999; Lever et al., 2002; Muller and Kubie, 1987; O'Keefe and Conway, 1978; Sharp, 1997; Thompson and Best, 1989; Wilson and McNaughton, 1993).

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A number of studies have demonstrated the importance of local and distal sensory cues on place field formation and stability (Hetherington and Shapiro, 1997; Miller and Best, 1980; Muller and Kubie, 1987; O'Keefe and Conway, 1978; Olton et al., 1978; Shapiro et al., 1997; Thompson and Best, 1989). Without the presence of specific sensory cues, rats use path integration or idiothetic cues for navigation (Fuhs et al., 2005; McNaughton et al., 1996; Sharp et al., 2001; Taube, 1998, 1995; Taube et al., 1990). In a study by O'Keefe and Speakman (1987), rats were trained to find a goal location using a set of distal cues. If the cues were removed before the rat returned to this environment, the firing of place cells matched the rat's behavior independent of the rat correctly finding the goal, as in place cell firings predicted that the rat had found the goal.

Changing the environment can cause partial remapping or total disruption of place fields (Bostock et al., 1991; Muller and Kubie, 1987). These physical changes include movement or removal of specific sensory cues or changes in the shape of the contextual environment. Keeping the environment stable, but changing the rat's perception of the environment also disrupts place fields (Quirk et al., 1990; Skaggs and McNaughton, 1998). Skaggs and McNaughton showed that rats developed distinct hippocampal place maps for two identical boxes (box N and box S) linked by a corridor. If rats were consistently placed in N and allowed to explore both boxes, then instead were placed in S, the hippocampal place map of box S initially represented N, but with more exploration shifted to firing patterns consistent with S. This study indicates that place cells do not fire simply in response to physical sensory inputs, but rather an internal representation of the environment.

The exact mechanism for place field formation is unknown. Since a large number of brain structures project directly or indirectly to the hippocampus and the hippocampus responds to sensory information in multiple modalities (Best and Thompson, 1989; Brankack and Buzsáki, 1986; Ranck, 1973), it is possible that hippocampal place fields represent the integration of neuronal inputs converging onto pyramidal neurons from these brain regions. One brain region likely to be involved in place field formation is the basolateral complex of the amygdala (BLA). The encoding of the emotional salience of an event in an environment occurs through activation of the amygdala (Cousens and Otto, 1998; Flavell and Lee, 2012; Goosens and Maren, 2001; Maren et al., 1996; Phillips and LeDoux, 1992) which drives plasticity in regions outside of the amygdala thereby "tagging" and enhancing specific salient environmental information (Bergado et al., 2011; Richter-Levin and Akirav, 2003). Anatomically, the BLA has been shown to be directly connected to the dorsal hippocampus (Strien et al., 2009). Functionally, Roozendaal and McGaugh (1997) showed that BLA lesions block the memory enhancing effects of hippocampal activation. Post-training injections of a glucocorticoid receptor agonist enhanced retention of an inhibitory avoidance task. When the BLA was lesioned, the glucocorticoid receptor agonist no longer affected retention.

In spatial learning, bilateral lesions of BLA or of the stria terminalis (ST), an output tract of the amygdala, blocked the memory enhancing effects of an adrenalectomy combined with a glucocorticoid receptor agonist on a water maze task (Roozendaal et al., 1996; Roozendaal and McGaugh, 1996). On a win-shift radial-arm maze task, a hippocampal infusion of glutamate enhanced memory but this memory enhancement was impaired when combined with an amygdalar infusion of lidocaine (Packard and Chen, 1999). Several studies have shown a modulatory role of the amygdala in hippocampal plasticity (Ikegaya et al., 1995, 1996, 1997; Li and Richter-Levin, 2012; McIntyre et al., 2005; Nakao et al., 2004). Stress has been shown to impair memory on a Morris water maze task and this stress effect can be blocked by lesioning the amygdala (Kim et al., 2001). Animals that were stressed showed reduced long-term potentiation (LTP) in the hippocampus that was blocked by an electrolytic lesion of the amygdala demonstrating the importance of plasticity between the amygdala and hippocampus in fear related memories. Twenty-four h after acquisition of an inhibitory avoidance task, post-burst afterhyperpolarizations (AHPs) were reduced in dorsal CA1, a memory consolidation mechanism exhibited in multiple other tasks (Moyer et al., 1986; Thompson et al., 1996) and these learning-dependent AHP reductions were ablated by temporary inactivation of the BLA immediately pre- or post-inhibitory avoidance training (Farmer and Thompson, 2012). Together this suggests that BLA lesions block memory enhancing effects of hippocampal activation during spatial as well as other forms of learning and that the BLA plays a modulatory role in hippocampal memory.

Although it is clear that the amygdala modulates plasticity in the hippocampus and the hippocampus is associated with spatial representation, it is not clear exactly how this plasticity relates to encoding of a fearful event into place cell activity. It is known that BLA neurons increase firing rates during and post presentation of a fearful stimulus to both unconditioned or conditioned stimuli (Chang et al., 2005; Kim et al., 2010; Maren, 2000; Pelletier et al., 2005). During fear memory retrieval 24 h post conditioning, the hippocampus and amygdala exhibit theta rhythm synchronization suggesting an ongoing communication between the amygdala and hippocampus during the retrieval phase (Narayanan et al., 2007; Pape et al., 2005; Seidenbecher et al., 2003). It is possible that CS-induced increases in BLA firing in synchrony with hippocampal place cell firing represents a perceived change in the environment and can therefore alter place cell firing.

In this study, we examined the effects of a fear-conditioned auditory CS on plasticity of the internal representation of an environment (i.e. altering the stability of individual place cell's place fields) and the role of the BLA in this plasticity. We paired an auditory CS and a footshock US in a conditioning environment completely separate from the spatial place cell recording environment, enabling later specific pairing of the CS with a location in the neutral environment either in- or out-of-field for specific place cells. BLA modulation of place cell plasticity was also assessed by temporarily inactivating the BLA immediately post-CS re-exposure.

2. Results

2.1. *Auditory fear conditioning: freezing responses elicited by CS re-exposure in the maze environment*

Pairing auditory CSs with footshock USs in one environment produced generalized freezing responses when retested later

in a separate spatial environment. Pairing three 5 kHz CSs with 0.5 mA footshock USs greatly increased freezing in conditioned rats when comparing a 180 s post-pairing testing period to a 180 s baseline period (Fig. 2B), while pseudoconditioned unpaired tones and footshocks did not significantly increase time spent freezing between the testing period and the baseline period. A repeated measures ANOVA showed a significant main effect of conditioning group, $F(1,8)=19.042$, $p<0.01$ (Fig. 2B). Percent freezing during the baseline period was not different between the pseudoconditioned and conditioned group, $F(1,8)=1.642$, $p=0.2359$, but the conditioned group froze significantly more during the testing period compared to the pseudoconditioned group, $F(1,8)=8.463$, $p<0.05$ (Fig. 2B).

2.2. *Stability of place field locations post-CS presentation compared to previous session's location*

Consistent with the standard characteristics of place cells, the neurons analyzed in this experiment fired significantly more action potential spikes while the rat was in-field than when the rat was out-of-field, $t(40)=3.603$, $p<0.001$ (Fig. 1B), while the area encompassed by the place field was significantly less than the area out-of-field $t(228)=-396.668$, $p<0.001$ (Fig. 1C). Although quantification of freezing behavior was not possible without interfering with place field recording, a period of freezing was also verified by independent observations of each rat's behavior immediately after single CS re-exposure on the radial-arm maze, indicating that a fear association with the CS had occurred. The stability of place fields over the course of the experiment was measured as a correlation of a place field map from each session to the place field map from the previous session. These correlations values are represented as percent of baseline such that a value less than 100% indicates a decrease in place field stability between those two time points compared to the stability in the baseline recording sessions. A repeated measures ANOVA revealed a significant effect of subject group on place field stability, $F(2,286)=9.414$, $p<0.01$ and a significant interaction of subject group and time on place field stability, $F(2,286)=5.629$, $p<0.05$ (Figs. 3 and 5). Overall, place field stability was significantly different over time when the CS was re-exposed in-field with an intact BLA compared to CS re-exposure out-of-field with an intact BLA ($p<0.01$). There were no time points after CS re-exposure with a place field stability value significantly different from baseline stability values in animals where the CS was re-exposed out-of-field with an intact BLA as determined by a pairwise comparison (Figs. 3 and 5A). However, there was a significant decrease in place cell stability from 0.5 h to 1.5 h post-CS re-exposure ($p<0.05$) when the CS was re-exposed in-field with an intact BLA (Figs. 3 and 5B). Correspondingly, there was a significant difference in place field stability when the CS was re-exposed in-field with an intact BLA compared to CS re-exposure out-of-field with an intact BLA between 0.5 and 1 h and 1 and 1.5 h post-CS re-exposure ($p<0.05$ and $p<0.01$ respectively; Fig. 3).

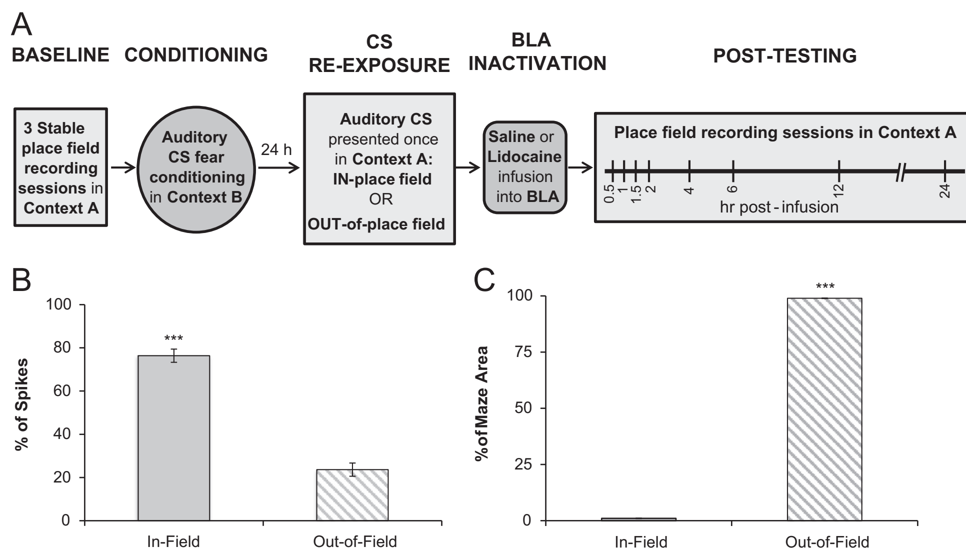

Fig. 1 – (A) Procedure for measuring neuron-specific changes in place cell stability after CS re-exposure. Rats were trained to explore an 8 arm radial-arm maze (Context A) until stable place fields were quantified for 3 sessions (BASELINE). Rats were then taken to a completely distinct and separate environmental context (Context B) and received 3 pairings of a 5 kHz, 5 s, 70 dB CS and a 1 s, 0.5 mA footshock US (CONDITIONING). 24 h later, rats were brought back to the radial-arm maze (Context A) and the CS was presented either while they were exploring an area within a neuron's place field (in-field) or an area well outside of the place field (out-of-field) (CS RE-EXPOSURE). Immediately post-CS re-exposure, saline or lidocaine was infused into the BLA (BLA INACTIVATION). The stability of place fields were then measured 0.5, 1, 1.5, 2, 4, 6, 12, and 24 h post-CS presentation to examine time-dependent expression of plasticity (POST-TESTING). (B) Percent of spikes that occurred while the rat was within the place field (in-field) versus all other regions on the maze (out-of-field). Bars represent mean ± S.E. ($n=29$), with significantly more spikes occurring while the rat was in-field (*$p<0.0001$). (C) Percent of the maze area that was included in-field versus out-of-field. Bars represent mean ± S.E. ($n=29$), with significantly less of the maze included in-field (***$p<0.0001$).**

2.3. Stability of place field locations post-CS re-exposure compared to baseline locations

Although intersession place field location correlations were not significantly different from baseline intersession stability values from 1.5 to 24 h after CS re-exposure in-field with an intact BLA (Fig. 3), clearly the location of the place fields had undergone plasticity from their locations during the baseline sessions for this group (Fig. 5B). Therefore, place field maps from rats who received CS re-exposure in-field with an intact BLA were correlated back to the place field maps during the baseline recording sessions, and a significant difference in correlation values were observed at all time points post-CS re-exposure compared to correlations between baseline recording session, $F(10,283)=3.040$, $p>0.01$ (Figs. 4 and 5B) indicating that the place field re-stabilized in a new location post-CS re-exposure.

2.4. Interaction of BLA and place cell activity

Temporary inactivation of the BLA immediately post-CS re-exposure in-field attenuated or eliminated changes in place field location stability (Figs. 3 and 5C). As discussed in Section 2.2, a repeated measures ANOVA revealed a significant interaction between subject group and time recorded on place field stability, $F(2,286)=5.629$, $p<0.05$, and a Fisher *post hoc* analysis revealed a significant difference between CS re-exposure in-field with an intact BLA and CS re-exposure in-field with an inactivated BLA ($p<0.05$; Fig. 3). A pairwise comparison revealed a significant difference in the place field stability after CS was presented in-field with an intact BLA and CS re-exposure in-field with an inactivated BLA between 0.5 and 1 h and 1 and 2 h post-CS re-exposure ($p<0.05$ and $p<0.01$ respectively; Fig. 3). However, the place field stability was not significantly different when the CS was presented out-of-field with an intact BLA compared to CS re-exposure in-field with an inactivated BLA ($p=0.552$; Figs. 3 and 5), and a pairwise comparison showed no significant differences in place field stability between any particular time point after CS re-exposure in-field with an inactivated BLA compared to baseline place field stability (Fig. 3).

3. Discussion

Together these results indicate that adding a fearful component (an auditory CS) to an environment is sufficient to induce plasticity of place cell location-specific firing activity, with this fear-induced plasticity specific to the particular location in an environment where the place cell was actively firing during CS re-exposure. This plasticity was induced by a single re-exposure of the CS in a previously neutral environment, and was neuron-specific (place cells that were inactive during CS presentation did not exhibit this plasticity). This hippocampal plasticity was dependent upon the BLA, since inactivation of the BLA with lidocaine attenuated or eliminated the plasticity from occurring. The current findings are novel, in that the conditioning did not occur in the spatial maze environment, but the plasticity was readily induced by only a single re-exposure of the CS within the spatial maze environment after conditioning was established in a separate environment. The neuron-specificity for only actively firing place cells is much more specific than has been previously shown.

Fear induced changes in hippocampal place cell activity have been reported by other research groups. Contextual fear conditioning with coyote urine decreases place field stability 1 h after exposure and increases stability 24 h and up to 5 days post urine exposure (Wang et al., 2012), indicating establishment of new stable place fields. Furthermore, Moita et al. (2003) paired an auditory CS with electrical stimulation to the eyelid while rats explored an environment. One hour after conditioning, the rats were allowed to explore the environment while the CS was presented at random intervals, and CA1 place cell activity was recorded. Place cells were more likely to exhibit the CS-evoked response when the CS was presented in the cell's field than when it was presented out-of-field. Accordingly, contextual fear conditioning (associating fear with an entire context) caused a more pronounced partial remapping of place cells than cued fear conditioning (Moita et al., 2004). Alternatively, when rats explored a maze in a forced goal-directed manner and received a footshock preceded by a CS in the same location on the maze, CS presentation resulted in very little place field remapping (Oler et al., 2008). In each of these studies, the place cell plasticity occurred in the same environment in which the conditioning occurred; it is, therefore, impossible to determine if the plasticity was due to changes in the context or to the CS alone. In the present study, rats were conditioned in an environment distinct from our recording environment, enabling precise pairing of the CS with a specific location in the recording environment, either while the place cell was firing at a high rate (in-field) or when the cell was essentially silent (out-of-field) (Thompson and Best, 1989).

Consistent with Wang et al. (2012), in the current study an initial decrease in place field stability was followed by an increase in stability. Because the physical maze environment remained constant throughout the recording sessions, it is reasonable to hypothesize that this change in the hippocampal representation of the environment represents a change in the rat's perception of the environment. Conceivably, the intervals at which place field stability differed most from previous sessions could denote the consolidation period for associating the previously acquired fear memory (associated with the CS, and presented only once in the maze environment) with the neutral context. After being consolidated, this new fear association and the change in perception of the environment then became stable, represented by an increased stability of now altered location-specific place cell activity, i.e. uncorrelated with its previous location.

A potential mechanism of fear induced plasticity in hippocampal place cells is increased synchrony between the amygdala and hippocampus. Emotional arousal elicits theta activity in the amygdala (Paré and Collins, 2000; Paré et al., 2002) and hippocampus (Moita et al., 2003). Furthermore, amygdala and hippocampal theta activity synchronize after emotional arousal (Narayanan et al., 2007; Pape et al., 2005; Seidenbecher et al., 2003) and this synchrony is implicated in learning (Lesting et al., 2011). It is possible that synchrony between the BLA and hippocampus enables the BLA to modulate activity in the hippocampus (for review: Pelletier and Paré, 2004).

Our results are consistent with Hebbian theory, and indicate that pairing the CS with an active place field results in remapping of that specific place field, but not of other fields, and that this plasticity is modulated by BLA activity. BLA modulation of hippocampal place cell activity during an emotionally arousing event is supported by Kim et al. (2007) who demonstrated a decrease in place field stability after exposure to an audiogenic stress treatment. More recently, (Kim et al., 2012) decreased place cell stability by directly stimulating the BLA.

Several studies indicate that the BLA modulates synaptic plasticity and memory in the hippocampus (for review: McGaugh, 2004), including modulation of LTP in the hippocampus (Ikegaya et al., 1995, 1996, 1997; Li and Richter-Levin, 2012; Nakao et al., 2004) and AHP plasticity in the hippocampus (Farmer and Thompson, 2012). A potential mechanism of BLA modulated synaptic plasticity is through modulation of intracellular protein activation in the hippocampus. Activity regulated cytoskeletal (Arc) protein is known to be involved in synaptic plasticity and is essential for memory consolidation (for review: Korb and Finkbeiner, 2011). Infusions of a β-adrenoceptor agonist, clenbuterol, into the BLA increases Arc protein expression in the hippocampus, and temporary inactivation of the BLA by lidocaine reduces Arc protein expression in the hippocampus (McIntyre et al., 2005) suggesting regulation of hippocampal Arc protein expression as a potential intracellular mechanism of BLA induced place field plasticity. Stress has also been shown to increase GTP-bound Ras and Raf, MEK1/2, and ERK1/2, and JNK1/2, and CaMKII phosphorylation, proteins involved in the MAPK pathway (Cammarota et al., 2008; Yang et al., 2004; Zheng et al., 2008). BLA lesions attenuate the stress induced increases in phospho-ERK in the hippocampus (Jeon et al., 2012) indicating a role of the BLA in stress-induced activation of the MAPK pathway in the hippocampus. The MAPK pathway is known to be involved in the induction of LTP in the hippocampus and is specifically necessary for learning of emotionally arousing tasks (for review: Giovannini, 2006; Sweatt, 2001). Taken together, these findings suggest that the BLA modulates synaptic or other forms of neural plasticity in the hippocampus involved in the formation of hippocampal dependent memory.

In summary, our data is the first direct evidence of a modulatory role of the BLA on the activity of specific hippocampal place cells. This BLA induced hippocampal plasticity results in an initial destabilization of place fields followed by place cell stability in a new location which might represent a change in the rat's perception of the environment. This plasticity is Hebbian, since only active neurons (exhibiting place field firing) underwent remapping of their location-specific firing. These results provide valuable insight into the underlying association between fear memories and contextual representation in the hippocampus.

4. Experimental procedure

4.1. *Subjects*

A total of 8 male Long Evans rats (250–350 g) were used for recording studies and 10 for behavioral assessment and were cared for following the guidelines of the Institutional Animal Care and Use Committee (University of Texas at Dallas). They were housed individually with food and water available ad libitum and maintained on a 12 h light/dark cycle.

4.2. *Surgery and electrode preparation*

Recording electrodes consisted of four drivable tetrode bundles emerging from the base of a chronically implanted microdrive. Tetrodes were individually fed through 4 cannulae, each attached to a separate microdrive screw such that each tetrode bundle could be advanced separately for optimal electrode placement and single-unit isolation. The cannulae were encased in a 1 cm diameter plastic housing (Vulintus, LLC; Richardson, TX) for protection against damage and debris, and attached to an external connector with ground and reference connections attached to an active headstage for recordings. Rats were anesthetized with isoflurane, and the tetrodes were stereotaxically implanted into CA1 of the hippocampus (from bregma: −4.0 mm AP, 2.5 mm ML, −2.5 DV). A 27 ga. stainless steel guide cannula for lidocaine or saline infusion were implanted into the ipsilateral basolateral complex of the amygdala (from bregma: −2.7 mm AP, 5.2 mm ML, 6.4 mm DV). Rats were given 72 h to recover from the surgery, with 1 mg/kg of antibiotic injected post-surgery. At the end of experiments, electrode placement was verified histologically post-mortem within CA1 as described by Goble et al. (2009). The location of the injection site for the cannulae was verified histologically within the basolateral amygdala, as described by Farmer and Thompson (2012). Methyl green was infused into the cannula for histological verification of cannula placement within the BLA using light microscopy. Data was excluded if microelectrode placement was not within CA1, or if dye placement was not within the BLA.

4.3. *Data acquisition and analysis of stable place fields*

Single-unit activity was acquired for 29 cells from 8 rats and analyzed as described in Goble et al. (2009). In brief, tetrodes were lowered up to 40 μm at a time and allowed 2–3 h to settle until stable location-specific unit activity was obtained using a Plexon MAP system. Typically, stable location-specific unit activity was isolated within 1–4 weeks after implantation. The rat's spatial location was tracked via LEDs atop the active head-stage in real time. Three consecutive baseline recording sessions (10 min long with at least 10 min between sessions) of a given place cell firing in the same location on the maze were required to define a stable place field for that neuron. During each session, each rat was required to visit each arm of the radial-arm maze at least once. The maze was divided into 18×24 bins and the firing rate of each individual cell was calculated for each bin. Place fields for individual CA1 neurons consisted of regions on the maze with a firing rate of at least 2 standard deviations above the average firing rate across the entire maze. Place cell stability was measured by correlating the place field location of each session on a bin-by-bin basis to the previous recording session or to the baseline recording sessions. Only single-units with stable place fields (i.e. having stable amplitude and other waveform characteristics and stable location-specificity across all baseline recordings) were used.

4.4. *Spatial testing procedures and baseline data collection*

All spatial testing procedures took place in a rectangular (2.2 m × 2.9 m) room surrounded by black curtains. An 8-arm radial-arm maze (1.3 m diameter, elevated 1.22 m from the floor) was placed in the center of the room with 2 fixed visual cues under dim lighting conditions to encourage exploratory behaviors. Rats were handled 5 min/d for 3 d and trained to explore all 8 arms of the maze for small appetitive rewards in 10 min sessions, which allowed time for re-exploration of all of the arms in most sessions. The maze environment was cleaned with a mild detergent solution between each session. Each rat was given a minimum of 10 min resting time between each recording session, during which the rat was returned to his home cage located outside of the testing room. Prior to each session, rats were carried from their home cage through the same trajectory to a fixed resting cage inside the testing environment for 5 min before beginning the recording session, so that stable environmental spatial cues were familiar throughout the experiment. All 8 arms were baited with 1 ml of chocolate milk in a 2 cm^2 black weigh boat at the ends of the arms (so that rewards were not visible until reached). Each rat was placed on the radial-arm maze at the same entry site and orientation, and allowed to explore until each arm of the maze was visited at least once. On average, during a 10 min recording session, rats spent ~30 s in a given cell's place field. When place fields were reliably located, a total of 3 baseline sessions of place cell activity were collected from each rat for specific neurons, at intervals of approximately 15 min between sessions. These baseline recording sessions were used for assessment of stability of the fields prior to and after fear conditioning, CS re-exposure, BLA infusions, and subsequent retesting. A timeline detailing the sequence of these procedures is shown in Fig. 1A.

4.4.1. *Auditory fear conditioning*

Rats were placed in a Plexiglas conditioning box consisting of a trough shaped-alleyway (60 cm long, 15 cm deep, 20 cm wide at top, 6.4 cm wide at bottom) with 2 metal floor plates, located in an entirely different laboratory and room from the radial-arm maze used for place field recording. Rats were given 3 min to acclimate to this conditioning context, followed by 3 paired conditioning trials of a 5 s duration, 5 kHz tone CS (delivered via a speaker (MCM Audio Select) @ 70 dB SPL measured from the center of the box) immediately followed by a 1 s, 0.5 mA footshock US, with an ITI of 4 min ± 30 s. Rats remained in the conditioning box an additional 4 min after these three auditory fear conditioning trials before being returned to their home cages for at least 24 h.

4.4.1.1. *Behavioral assay of auditory fear conditioning*. To quantify fear responses, two additional groups of 5 rats each underwent auditory fear conditioning as detailed in Section 4.4.1 above. The conditioned group underwent paired CS-US auditory fear conditioning. They were then given 3 min to acclimate to the radial-arm maze, followed by a 3 min baseline period of exploration without CS presentations, and a 3 min testing period with 3 tone CS presentations (5 kHz, 5 s, 70 dB), ITI 60 s ± 10 s. The pseudoconditioned group received the same number of CS tones and footshocks as the conditioned group, but the tones and footshocks were not paired together during the conditioning session. Fear responses were measured as the percent time spent freezing during the 3 min baseline and testing sessions for the pseudoconditioned ($n=5$) and the conditioned ($n=5$) group. See Fig. 2A for a summary of this procedure.

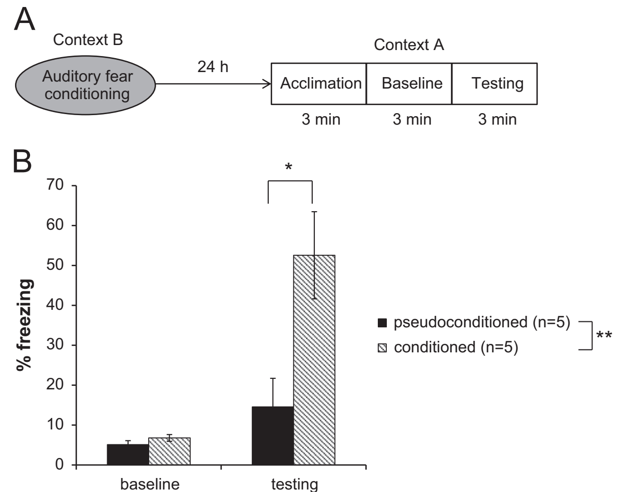

Fig. 2 – Conditioning produced fear associated with the auditory CS. (A) Procedure for measuring freezing behavior due to auditory fear conditioning: Rats were placed in a conditioning apparatus (Context B) and given 3 tones (5 kHz, 5 s, 70 dB) and 3 footshocks (1 s, 0.5 mA) either unpaired (pseudoconditioned) or paired (conditioned). Twenty-four hr later, rats were placed on a radial-arm maze (Context A) and given 3 min to acclimate. Baseline freezing was measured for the next 3 min. During the testing phase, freezing was measured while 3 tones were randomly presented during a 3 min period. (B) Percent freezing during the baseline session and testing session for both the pseudoconditioned and conditioned groups. A 100% freezing value would represent a rat freezing continuously for 180 s. Bars represent mean ± S.E. ($n=5$ for both groups). There was a significant main effect of conditioning group on freezing ($p<0.01$), with significantly more freezing for the conditioned group during the testing session (*$p<0.05$) but not during the baseline session.**

4.4.2. *CS re-exposure*

Twenty-four hr after auditory fear conditioning, each of the 8 chronically implanted rats were placed back on the radial-arm maze and stability of established place field activity was assessed under conditions identical to the baseline recording sessions for a single place field recording session. An MCM Audio Select speaker was located in the maze room (hidden from the rats' view, 1 m from the center of the maze). As the rat explored the maze, the CS was presented for 5 s either while the rat was located within the place field of a given single-unit (while the unit exhibited a high firing rate) or while the rat was exploring an area of the maze well outside of the place field (while it exhibited a low firing rate). The rat was thus explicitly re-exposed to the CS for a single time in the previously neutral radial-arm maze environment, in a

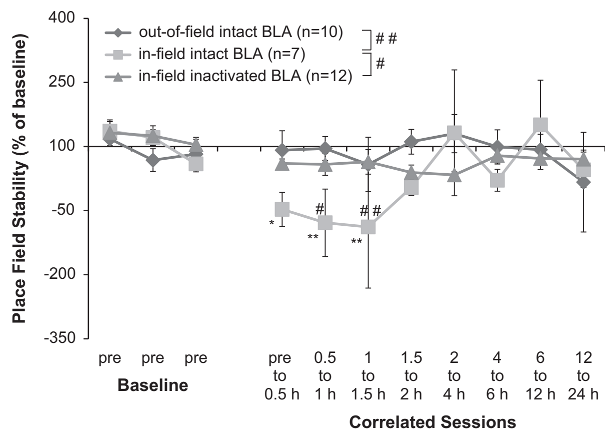

Fig. 3 – Place field stability assessed by comparing place cell firing locations from one recording session to the previous recording session. Percent of baseline average correlation values of place field locations session to session at intervals before and after the CS re-exposure either out-of-field with an intact BLA ($n=10$), in-field with an intact BLA ($n=7$), or in-field with an inactivated BLA ($n=12$). A place field stability value of less than 100% indicates a decrease in stability between 2 time points compared to stability between the baseline recording sessions. Each point represents a percent of the mean baseline correlation value ± S.E. The X-axis shows the two recording intervals correlated, with baseline to 0.5 h representing a correlation of the last baseline firing rate map to the firing rate map 0.5 h post-CS re-exposure. "pre" represents the comparison of a baseline firing rate map to the previous baseline firing map. # indicates $p<0.05$ for a repeated measures ANOVA between the experimental groups. ## indicates $p<0.01$ for a repeated measures ANOVA between the experimental groups. * indicates $p<0.05$ for a *post hoc* Fisher test for those given correlation values to baseline. ** indicates $p<0.01$ for a *post hoc* Fisher test for those given correlation values to baseline.

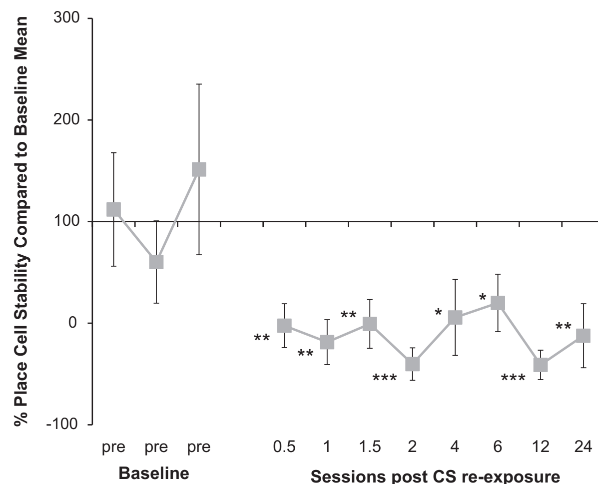

Fig. 4 – Place field plasticity induced by CS re-exposure in-field in rats with intact BLA, assessed by comparing place cell firing locations from each session to the average location of stable baseline firing. Percent of baseline average correlation values for place field locations at different intervals were compared to baseline recording sessions when CS was presented in-field with an intact BLA ($n=7$). A place cell stability value of less than 100% indicates a decrease in place field stability at that time point compared to place field stability between the baseline recording sessions. Each point represents a percent of the mean baseline correlation values ± S.E. * indicates $p<0.05$, ** indicates $p<0.01$, and * indicates $p<0.0001$ for a *post hoc* Fisher test.**

neuron-specific fashion, with the CS specifically paired either to in-field ($n=7$) or out-of-field place field activity ($n=10$).

4.4.3. *Effects of transient BLA inactivation on place field plasticity*

Immediately post-CS re-exposure, the BLA was infused with 0.35 μl of either 2.0% lidocaine or physiological saline over a duration of 1 min. This concentration and timing of lidocaine infusions was used in previous studies to attenuate BLA mediated memory enhancements and BLA mediated plasticity in other brain regions, including the hippocampal CA1 region (Farmer and Thompson, 2012; Goshadrou and Ronaghi, 2012; Holloway-Erickson et al., 2012; LaLumiere and McGaugh, 2005; McIntyre et al., 2005). Consistent with these previous studies, lidocaine was infused during the consolidation phase to attenuate consolidation of CS association with context A. Following this infusion into the BLA, place cell activity was recorded for a total of 8 sessions per neuron (10 min recording sessions) at intervals 0.5, 1, 1.5, 2, 4, 6, 12, 24 h after the CS re-exposure to permit a full description of the time course of all place field plasticity observed (see Fig. 1 for a summary of this procedure).

A total of 12 units were included in the CS in-field inactivated BLA group, and 7 single-units were included in the CS in-field intact BLA group. A total of 10 single-units were included in the CS out-of-field intact BLA group.

4.5. *Statistical analyses*

4.5.1. *Spatial correlations*

Autocorrelations of each single-unit (total of 29 units) were compared session by session or session to baseline across conditions, to assess changes in burst firing modes in response to the different independent variables detailed above. Only neurons that fired throughout all recording sessions were included in the correlational analysis. Notably, signals from one neuron each from both the out-of-field intact BLA group and the in-field intact BLA group were lost after auditory fear conditioning, very likely due to displacement of the electrode, and were therefore removed from the analysis. All other neurophysiological waveforms remained stable across all 12 individual recording sessions for each rat. Session by session correlations consisted of pixel-to-pixel autocorrelations of the location of the current place field compared to the previous place field location. Session to baseline analyses consisted of pixel-to-pixel autocorrelations of a given session's place field location to each of the baseline place field locations and averaged for each time point. All correlation values are shown

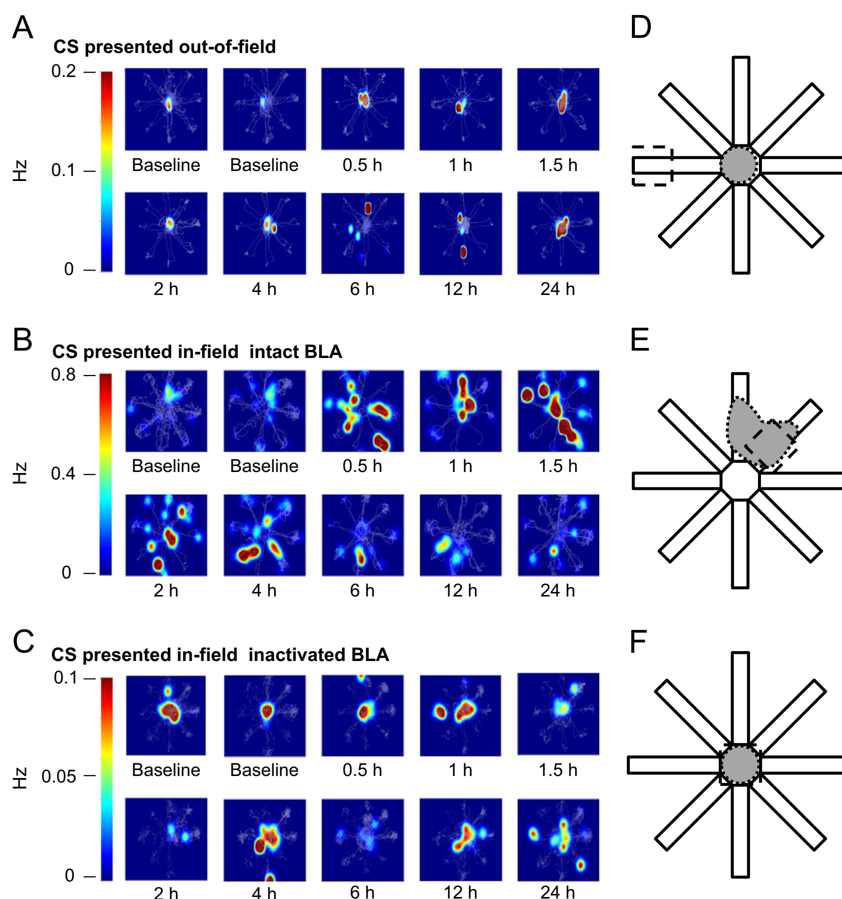

Fig. 5 – Place cell firing rate maps (firing intensity in Hz) before conditioning and after CS re-exposure for representative individual place cells. Areas in dark blue had a firing rate of 0 Hz, while the red color indicates the locations with the highest firing rate. The first 2 recording sessions shown are the final 2 baseline recording sessions before auditory fear conditioning. All other recording sessions for each neuron are at the intervals shown post-CS re-exposure on the radial-arm maze. The gray traces indicate the path traveled by the rat through the radial-arm maze. (A) A place cell for which the CS was re-exposed out-of-field, with little or no plasticity of its place field location. (B) A place cell for which the CS was re-exposed in-field with an intact BLA, and subsequent plasticity in its place field. (C) A place cell for which the CS was re-exposed in-field with an inactivated BLA, with an attenuation of the plasticity observed in (B). (D–F) Diagrams of the radial-arm maze with the dotted gray areas indicating the baseline place field location and the dotted square indicating the specific location on the maze the rat occupied when the CS re-exposure occurred. (D) Diagram of the place field location and the CS re-exposure out-of-field. The stable place field was located in the center of the maze and the CS was re-exposed while the rat was at the end of the left-most arm. (E) Diagram of place field location and CS re-exposure in-field with an intact BLA. The stable place field was in the upper-right portion of the maze and the tone was re-exposed when the rat was exploring within this place field. (F) Diagram of place field location and CS re-exposure in-field with an inactivated BLA. The stable place field was in the center of the maze and the CS was re-exposed while the rat was exploring the center of the maze.

as percent baseline. A value less than 100% indicates a decrease in place cell stability compared to the stability during the baseline recording session. A repeated measures ANOVA was used to compare place cell stability before and after CS presentation on the radial-arm maze across in-field intact BLA, in-field inactivated BLA, and out-of-field groups with a *post hoc* Fisher test.

4.5.2. *Analysis of freezing response after auditory fear conditioning*

Fear responses to CS-tone presentation were determined by using a repeated measures ANOVA to compare percent freezing during the baseline session to the testing session in the pseudoconditioned and conditioned group with a *post hoc* Fisher test. A t-test was used to compare the percent freezing response during a CS presentation to that during a pseudo-conditioned stimulus presentation.

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