

Compensation in the neural circuitry of fear conditioning awakens learning circuits in the bed nuclei of the stria terminalis

Andrew M. Poulos^a, Ravikumar Ponnusamy^a, Hong-Wei Dong^b, and Michael S. Fanselow^{a,1}

^aDepartment of Psychology, Brain Research Institute, and ^bDepartment of Neurology, Laboratory of Neuro Imaging, University of California, Los Angeles, CA 90095-1563

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The basolateral amygdala (BLA) is thought to be essential for fear learning. However, extensive training can overcome the loss of conditional fear evident following lesions and inactivation of the BLA. Such results suggest the existence of a primary BLA-dependent and a compensatory BLA-independent neural circuit. We tested the hypothesis that the bed nuclei of the stria terminalis (BST) provides this compensatory plasticity. Using extensive context-fear conditioning, we demonstrate that combined BLA and BST lesions prevented fear acquisition and expression. Additionally, protein synthesis in the BST was critical only for consolidation of BLA-independent but not BLA-dependent fear. Moreover, fear acquired after BLA lesions resulted in greater activation of BST regions that receive hippocampal efferents. These results suggest that the BST is capable of functioning as a compensatory site in the acquisition and consolidation of context-fear memories. Unlocking such neural compensation holds promise for understanding situations when brain damage impairs normal function or failure to regulate compensatory sites leads to anxiety disorders.

amygdala | basolateral amygdala | context | plasticity | bed nucleus of the stria terminalis

A largely supported view in the neuroscience of associative memory is the existence of essential neural circuits that have the capacity to learn, retain, and retrieve specific classes of experience (1–7). For example, in reflexive motor learning or Pavlovian eyeblink-conditioning, the integration of sensory stimuli within the cerebellar interpositus nuclei are required for the acquisition, retention, and retrieval conditional responses (8). Similarly, the striatum is considered critical for habit learning (9, 10) and the hippocampus essential for spatial learning (11). In fear-conditioning, a circuit centered around the basolateral amygdala complex (BLA; consisting of the lateral amygdala, basomedial, basolateral, and posterior nuclei) is viewed essential for the acquisition and expression of fear memories (12–16). The importance of the BLA for fear memory has been supported by numerous studies showing that disruption of protein synthesis, NMDA receptor function, neuronal activity, synaptic transmission, and plasticity all prevent the establishment of fear memories (14–18).

Context fear learning normally occurs when hippocampal context information, which exits the subiculum, converges with aversive information in the BLA (15). In turn, when the contextual information activates the BLA, this information is relayed to the central nucleus of the amygdala (CEA), whose efferents to the ventral periaqueductal gray (vPAG) trigger the expression of fear as indexed by conditional freezing (conditional response) (19). Lesions or inactivations of the CEA can disrupt contextual fear (20, 21; but see 22). Of particular relevance in this study is that pretraining lesions or inactivations of the BLA have been shown to strongly impair the acquisition of fear (23–25). However, with extensive overtraining (~75 trials), the loss of conditional fear evident following lesions or inactivations of the BLA can be overcome (25–27). These findings suggest that under some cir-

cumstances, alternate neural pathways can acquire fear. Certainly, the enormous interconnectivity of the brain affords such potential (28) in that there are multiple routes from information sources to adaptive behaviors. Indeed, plasticity in multiple brain regions outside of the BLA is important for the acquisition of fear (20, 29, 30). This interconnectivity and availability of alternate pathways capable of undergoing plasticity does not protect against future damage, as posttraining lesions of the BLA eliminate fear even when previously intact rats are overtrained (26).

To address such findings, we proposed a dynamic-systems view of memory where the most efficient neural pathway between information and action dominates processing. However, if information flow is precluded in such a neural pathway, plasticity in alternate regions is capable of compensating, albeit with less efficiency (27, 31). This theory is evident, as animals that learn fear in the absence of the primary pathway require significant overtraining (>50 trials) and begin to display significant forgetting after 7 d (25, 32). Thus, although plasticity in the BLA normally supports contextual fear-conditioning, without the BLA, some alternate regions must compensate.

The alternate or compensatory regions for BLA function are currently unknown. Therefore, the goal of the following experiments was to identify this compensatory region. A likely candidate would be a group of neurons that interconnects the hippocampal formation (HPF), which processes contextual information, and vPAG, which generates several fear-related behaviors. To support fear-learning, this compensatory network would also need to be capable of undergoing long-term plasticity. The bed nuclei of the stria terminalis (BST) is such a structure composed of two main divisions: the posterior and the anterior division, with the latter composed of the lateral and medial groups. Recent studies have shown that the BST is capable of undergoing experience-dependent plasticity (33, 34). Like the BLA, the anteromedial group of the BST receives direct projections from the ventral HPF and sends information to the vPAG (35, 36). Such neural connectivity provides a route by which contextual information encoded by the HPF could bypass the BLA and activate the vPAG to generate freezing. Conversely, the BST is capable of receiving noxious information (i.e., footshock) both directly and indirectly (37, 38). Consistent with this hypothesis, lesions or inactivations of the BST result in a wide range of fear- and anxiety-related deficits (39–42). In addition, the anterolateral group of the BST—perhaps through its interconnections with the posterior BLA (BLAp), the only

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¹To whom correspondence should be addressed. E-mail: mfanselow@gmail.com.

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This attenuation of freezing by pretraining BST lesions complements a previous study by Sullivan et al. (44), which showed that posttraining electrolytic lesions of the BST attenuated the expression of freezing during a test of contextual-fear memory. Freezing was lowest in the combined-lesioned rats in comparison with all other groups. The low level of freezing in the combined-lesion group is consistent with the idea that the BST compensates for damage to the BLA.

Role of Protein Synthesis in the BST in Overtrained Fear (Experiment 2).

Permanent lesions of the BST do not allow us to distinguish between contributions of the BST to learning of context fear from expression of context fear. If learning-related plasticity in the BST compensates for the loss of the BLA, then protein synthesis in the BST should be especially important for the consolidation of contextual conditioning when the BLA is lesioned. Therefore, we overtrained rats with sham or pretraining lesions of the BLA and, immediately after training, infused the protein synthesis inhibitor anisomycin (ANISO) or vehicle into the BST. Because no drug is present during training or testing, this procedure isolates the drug to an influence on posttraining consolidation. Lesion and cannula placements are shown in Fig. 3.

Fig. 4 shows that during the test session 24 h later, animals overtrained with BLA lesions showed normal levels of fear retention compared with sham overtrained rats. In intact animals, ANISO infusions into BST failed to disrupt fear retention. However, BLA-lesioned animals infused with ANISO failed to show any evidence of a fear memory. These impressions were confirmed by a two-way ANOVA, which revealed a main effect of Lesion [$F(1, 22) = 19.92, P < 0.001$] and Drug [$F(1, 22) = 4.49, P < 0.05$], as well as a significant interaction between Lesion and Drug (Fig. 4) [$F(1, 22) = 12.79, P < 0.01$]. Planned comparison indicated that vehicle-infused BLA-lesioned animals froze similarly to BLA intact rats infused with vehicle (VEH) or ANISO. The BLA+ANISO group showed the least amount of freezing compared with BLA+VEH, SHAM+VEH, or SHAM+VEH (all P values < 0.001).

If ANISO caused permanent damage to the BST, it would have produced similar results to combined BLA+BST lesion animals in exp. 1. Therefore, we reovertrained the BLA+ANISO group and found that these animals acquired fear-conditioning similar to intact, BLA-lesioned, and ANISO-treated alone animals. To exam-

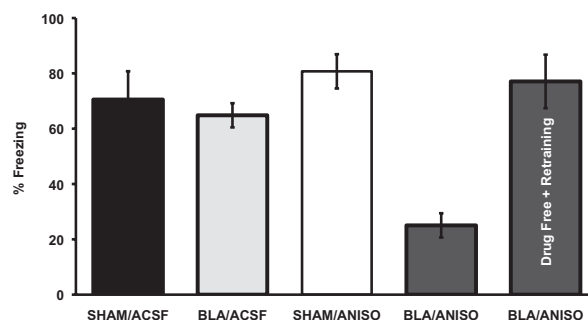


Fig. 4. Behavioral measurement of context-fear memory in rats with combined: (i) Sham lesion and BST ACSF infusion (black), (ii) sham lesion and BST ANISO infusion (light gray), (iii) BLA lesion and BST ACSF infusion (white), (iv) BLA lesion and BST ANISO infusion (medium gray), and (v) retraining (76 trials in a novel context) in previously trained and tested BLA lesion and BST ANISO-infused animals (medium gray with description). Total mean (\pm SEM) percentage of observations spent freezing during an 8-min test session for conditional fear.

ine whether infusions spread to regions of the BST, which receive input from the ventral HPF, the retrograde neural tracer Fluoro-Gold was infused through the cannula previously used to infuse VEH or ANISO. Fig. 5 shows that Fluoro-Gold infusions spread to a large extent of the BST, and retrogradely labeled soma within the HPF, BLA, CEA, and prefrontal cortex (PFC).

Expression of an Immediate Early Gene in the BST During the Retrieval of Overtrained Fear (Experiment 3).

Animals that acquired contextual-fear conditioning independent of the BLA failed to establish a long-term memory when protein synthesis was blocked within BST, suggesting protein synthesis was required for the consolidation of BLA-independent fear memories. Prior anatomical studies have shown that HPF efferents project mainly to the anteromedial group of the BST. We hypothesized that this region is activated during the retrieval of BLA-independent fear, and thus quantified the expression of the immediate early gene *C-fos* following tests of contextual fear. Animals were overtrained or not (training context minus any shocks) with pretraining sham or excitotoxic lesions of the BLA, and tested for fear 24 h later. Then, 1 h and 20 min

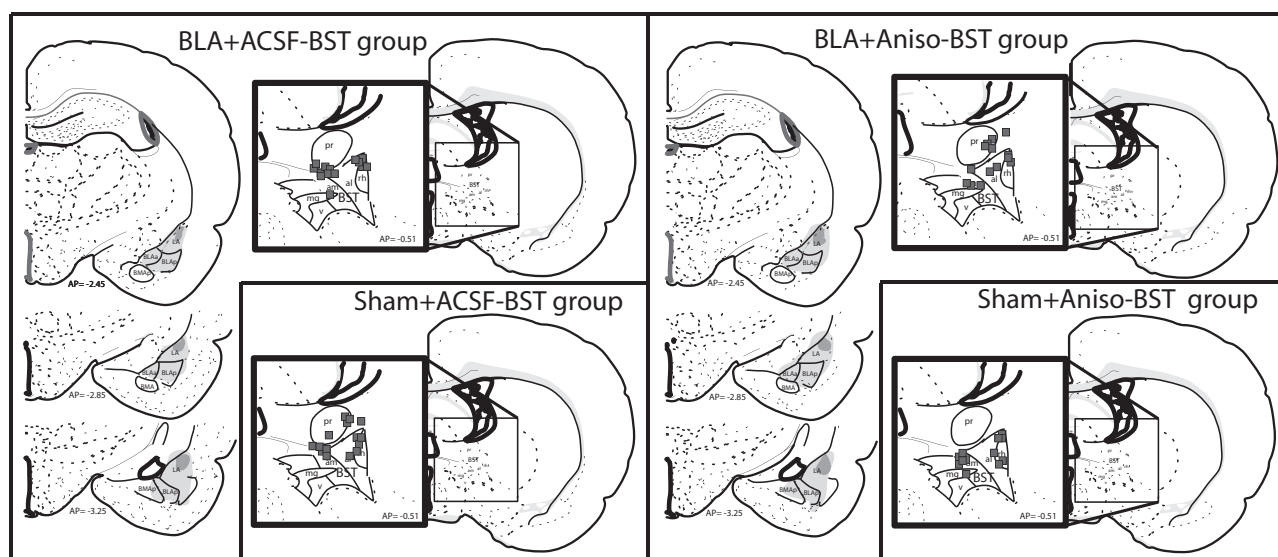


Fig. 3. Histological analysis of BLA lesion and BST cannula placements for exp. 2. Reconstruction of the minimal (dark gray) and maximal (light gray) excitotoxic lesion in the region of the BLA (AP 2.6–3.3 mm) and cannula tip placement within the BST (square). Coronal section images taken and adapted from Swanson (52). The largest extent of any given BLA lesion included LA, BLAa, BLAp, and BMAP; the smallest lesion only included damage to the LA.

enhanced trace eyeblink-conditioning (49) are disrupted by BST lesions. Perhaps the most well-studied functional role of the BST is in relation to models of anxiety. Walker and Davis have shown elegantly that disrupting BST function can attenuate the potentiated startle triggered during exposure to bright light or corticotrophin releasing hormone, whereas the same response to discrete cues previously paired with footshock remained unaffected (41). In Pavlovian fear-conditioning as measured by freezing and corticosteroid release, posttraining BST lesions selectively abolish the expression of context, but not cued conditional-fear responses (44). This finding has led to models of fear-conditioning that now incorporate the anterolateral group of the BST as part of the conditional-response expression pathway for context fear (44, 50). The results in exp. 1 that rats with only BST lesions showed less of a deficit than rats with combined lesions suggests that in intact rats, context-fear expression is only partly mediated by the BST. Normally, a BLA→CEA→PAG pathway likely mediates some fear expression. More importantly, the present results indicate that posttraining protein synthesis is necessary under conditions where fear-learning occurs without the BLA. When the BLA is functioning normally, BST plasticity is down-regulated but this plasticity is revealed when BLA function is lost. Although the mechanisms of this down-regulation of BST plasticity are not known, it likely plays a role in keeping fear appropriate to the degree of threat (31). Loss of this down-regulation could lead to excessive fear, resulting from additional plasticity (or memory) in parallel pathways. Such excessive fear may contribute to anxiety disorders.

The diversity of BST function as described above is likely reflected in the numerous subdivisions that comprise the BST, which receive a diverse set of afferents, such as those related to cognition (PFC), spatial information (HPF), and fear (BLAp and CEA), and in turn project to heterogeneous neural regions responsible for the generation of stress responses (paraventricular nucleus) and the expression of defensive behaviors (vPAG) (35).

The collective literature (described earlier) indicates that either, HPF→BLA→CEA→BST→vPAG (39, 41, 46, 47) or HPF→BLAp→BST→vPAG (22) is the primary route by which context fear is normally acquired, retained, and expressed (Fig. S2). However, like the BLA, the anteromedial group of the BST also receives direct projections from the HPF and information from nociceptive-related input (37, 51). These nuclei are well-situated anatomically to provide a compensatory site of fear-related plasticity.

In a prior study, we found that learning normally down-regulates learning in other potential yet unidentified circuits (27). Here we found that protein synthesis-dependent plasticity in the BST is not necessary for fear conditioning when the BLA is intact, but is sufficient to compensate for loss of the BLA. This theory suggests that this plasticity in the BST is not driven when the BLA learns. Therefore, when the BLA is undergoing fear-related learning, it down-regulates plasticity in the BST. Thus, with the BLA intact, no significant learning occurs in the proposed alternate pathway (27). The present study provides strong evidence that competition between faster (BLA-dependent) and slower learning circuits exist, and that under specific circumstances, the balance between these systems can be tilted to reveal a compensatory learning circuit within the brain.

Materials and Methods

Exp. 1: Single and Combined Lesions of the BLA and BST and Extensive Overtraining. Subjects were male Long-Evans hooded rats weighing 300 to 340 g, obtained from a commercial supplier (Harlan). Rats were housed individually in standard stainless-steel cages on a 12-h light/12-h dark cycle and were provided ad libitum access to food and water. After being housed, the rats were handled daily (~60 s per rat) for 5 d to acclimate them to the experimenter. All procedures were approved by the University of California Los Angeles Animal Research Committee.

Surgery. A detailed description of lesion surgeries can be found in *SI Materials and Methods*. Coordinates for excitotoxic lesions were as follows: BLA: AP, 2.6 and 3.3 mm posterior; ML, 5.1 mm lateral; and DV, 8.2 and 8.4 mm ventral to bregma. BST: AP, 0.8 mm posterior; ML, 1.1 and 2.0 mm; and DV, 6.2 and 7.0 mm.

Conditioning apparatus. The conditioning apparatus consisted of aluminum (side walls) and plexiglas (front, back, and top) chambers (28 × 21 × 22 cm; Lafayette Instruments). The floor of each chamber had 18 stainless-steel rods (4-mm diameter, 1.5 cm apart) connected to a shock scrambler and generator (which, along with internal ventilation fans, supplied background noise of 70 dB, A scale). The chambers were cleaned with 5% ammonium hydroxide solution and scented with 0.1% benzaldehyde in 100% ethanol. These computer-controlled (Med-Associates) chambers were in a well-lit room separate from the experimenter.

Behavioral procedures. The overtraining procedure was as follows: After a 2-min exposure to the chamber, rats were given 76 unsignaled shocks (1 mA, 2 s) with a 64-s ITI. Two minutes after the final shock, rats were removed from the chamber and returned to the home cage. The day after training, the rats were tested in the original training context.

Freezing behavior was defined as the absence of any visible movement (including the vibrissae), except that required for respiration. Freezing behavior was scored by a blind observer according to an instantaneous time-sampling procedure in which each animal was observed every 8 s. For each minute (defined as eight samples or 64 s), the number of observations scored as freezing were summed and converted to a percentage (number of freezing observations/total number of observations × 100). Previous study indicates that this measure conforms to the requirements of parametric analysis. During overtraining, freezing was measured after the 1st, 10th, 15th, 20th, 30th, 40th, 50th, 60th, 70th, and 76th shocks. During the test, freezing was measured for the entire 8 min.

Histology. At the completion of behavioral testing (for exp. 1, 2, and 3), all rats were overdosed with sodium pentobarbital and perfused intracardially with 0.9% saline, followed by 4% buffered formalin. The brains were removed and stored in 10% formalin for at least 2 wk before slicing. These brains were cryoprotected in 30% sucrose-PBS mixture for 48 h and were sectioned in a cryostat. Coronal sections (50 μm) were taken through the extent of the BLA and BST, mounted on gelatinized slides, and stained with thionin or prepared for NeuN immunohistochemistry.

Neu-N immunohistochemistry. For complete details of Neu-N immunohistochemistry, see *SI Materials and Methods*. Briefly, tissue sections were washed and rinsed before being transferred to blocking solution and incubated overnight in Neu-N antibody (1:4,000) solution. Next, tissue sections were incubated in mouse antibody IgG (1.25 h), followed by Avidin-Biotin-Peroxidase complex (ABC), then 3 to 3' diaminobenzidine tetrahydrochloride (DAB, Sigma). Lesions were verified by reconstructing the damage on stereotaxic atlas templates (52) (for complete details, see *SI Materials and Methods*).

Statistical analyses. All experiments were analyzed by appropriate ANOVA's. Thereafter, Fisher's planned comparisons were computed with significance set at *P* value < 0.05.

Exp. 2: BLA Lesion, BST Cannulation, Infusion, and Overtraining. Rats received sham or bilateral lesions of the BLA (see Exp. 1, *Surgery*) and bilateral cannulae implantation within the BST (see *SI Materials and Methods*). Overtraining and memory tests were performed exactly as described in exp. 1 (*Behavioral procedures*). Immediately following overtraining, ACSF or ANISO were infused into the BST (for infusion procedures, see *SI Materials and Methods*). Following memory tests, ANISO-infused rats were once again overtrained (same context) and retested for fear memory. After the cessation of behavioral testing, a small number of ANISO-infused rats were infused with the retrograde neural-tracer Fluoro-Gold (conjugated) to estimate the spread of ANISO and identify BST afferents that were likely affected by the protein synthesis inhibitor.

Histology. Following the final drug infusion, Fluoro-Gold-infused rats remained in their home cage for an additional 2 wk before being perfused, whereas non-Fluoro-Gold rats were perfused 1 to 2 d later (see exp. 1, *Histology*). Brains of non-Fluoro-Gold-infused rats were prepared for thionin staining (see Exp. 1, *Histology*). Brains sections of Fluoro-Gold-infused rats were mounted on slides, coverslipped, and allowed to dry. The next day, Fluoro-Gold slides were photographed with a light microscope (Zeiss) with fluorescent capabilities to determine if labeling was present in BST, BLA, CEA, HPF, and medial prefrontal cortex.

Exp. 3: BLA Lesion, Overtraining, and Fear-Retrieval Related C-fos Expression. Rats received sham or bilateral lesions of the BLA (see Exp. 1, *Surgery*). Rats

were overtrained or not (placed in the training context without receiving footshocks) and memory tests were performed exactly as described in Exp. 1 (*Behavioral procedures*). Ninety minutes following context memory, tests rats were overdosed and brains were prepared for thionin staining (see Exp. 1, *Histology*) and C-fos immunohistochemistry. Regions of the BST that have been previously shown to receive projections from the ventral HPF were analyzed for C-fos expression (35).

C-fos immunohistochemistry. For complete details of C-fos immunohistochemistry, see *SI Materials and Methods*. Briefly, tissue sections were washed and

rinsed before being transferred to blocking solution and incubated overnight in C-fos antibody (1:1,000) solution. Next, tissue sections were incubated in rabbit antibody IgG (1 h), followed by ABC, then DAB. After the final rinse, tissue was mounted on microscope slides, dried, dehydrated, and coverslipped to quantify C-fos expression. For details of C-fos quantification, see *SI Materials and Methods*.

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