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Current Biology

Maladaptive Properties of Context-Impoverished Memories

Highlights

- Contextually poor fear memories overgeneralize and resist extinction
- Poor contextual memories can be improved or distorted by updating post-recall
- Post-recall memory alterations depend on memory reconsolidation
- A neurocomputational model helps explain these findings based on uncertainty

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In Brief

The context in which fearful events occur can be poorly encoded into memory, but the consequences are unclear. Zinn et al. show that contextually poor fear memories maladaptively overgeneralize and resist extinction. However, these memories are subject to a context-updating mechanism during recall that can both correct and severely distort them.

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Maladaptive Properties of Context-Impoverished Memories

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SUMMARY

The context in which sudden fearful events occur can be poorly encoded into memory. Yet, the consequences of the resulting context-impoverished memories remain unknown. We demonstrate that restricting the time available for context encoding during contextual fear conditioning causes maladaptively overgeneralized and inextinguishable fear. However, post-conditioning context exposure enables further context encoding through hippocampal reconsolidation-dependent memory updating. Updating in the conditioning context alleviates overgeneralization and restores capacity for extinction. However, updating in a similar safe context erroneously shifts fear from the dangerous to the safe context. We argue that these phenomena can be explained by uncertainty about where events occurred. Moreover, we show that a hippocampal-neocortical neurocomputational model based on this assumption successfully simulates and explains our observations. These findings reveal that context-impoverished memories are maladaptive and can be improved or distorted after recall, with implications for basic memory theory, memory distortion, and treatment of disorders like post-traumatic stress disorder.

INTRODUCTION

Traumatic events, such as roadside bombs or violent crimes, can occur with little time to process the situation or context in which they occurred. Such circumstances have the potential to leave sufferers with memories of events that are highly impoverished in contextual detail. Yet, the consequences of such poor context encoding remain unclear. It has recently been proposed, although never directly shown, that poor contextualization may underlie the symptomatology of disorders like post-traumatic stress disorder (PTSD) [1–4]. It has also been proposed that poorly encoded memories may be susceptible to alteration by post-event manipulations like suggestion or interrogation [5–8]. However, whether poor context encoding can underlie maladaptive fear responses or post-event memory alterations remains unknown.

The consequences of poor context encoding are also unclear in fundamental learning paradigms, including contextual fear conditioning, that are routinely used to study the neural basis of complex fear learning [9–20]. Contextual fear conditioning is a conserved form of Pavlovian conditioning in which an aversive event (unconditional stimulus; US) is paired to the environmental context in which it occurred (conditional stimulus; CS) [21–23]. It is well known that context fear conditioning does not occur when the US happens soon after exposure to a novel context. Rather, some period of exploration is required for context-dependent fear to be learned [21–23]. This is thought to occur because time is needed to notice and learn enough about the attributes of a context to construct a hippocampal representation that can become associated with fear in the amygdala [14, 21, 22, 24, 25]. Expanding on this, we recently found that the biochemical activity thought to reflect context acquisition continues to increase as the learning session extends beyond the minimal time required for conditioning [23]. This suggests that robust conditioning does not require comprehensive context learning, and that many strong contextual fear memories might be deficient in contextual detail. Nonetheless, the consequences of such deficient context learning remain unknown.

The present work investigated the significance of this extended period of hippocampal activity and putative context encoding. Given that contextual memories are thought to form the basis upon which contexts are recognized in the future [26], we hypothesized that poor context encoding would produce confusion about where events occurred. Such confusion might in turn lead to inappropriate and intractable fear,

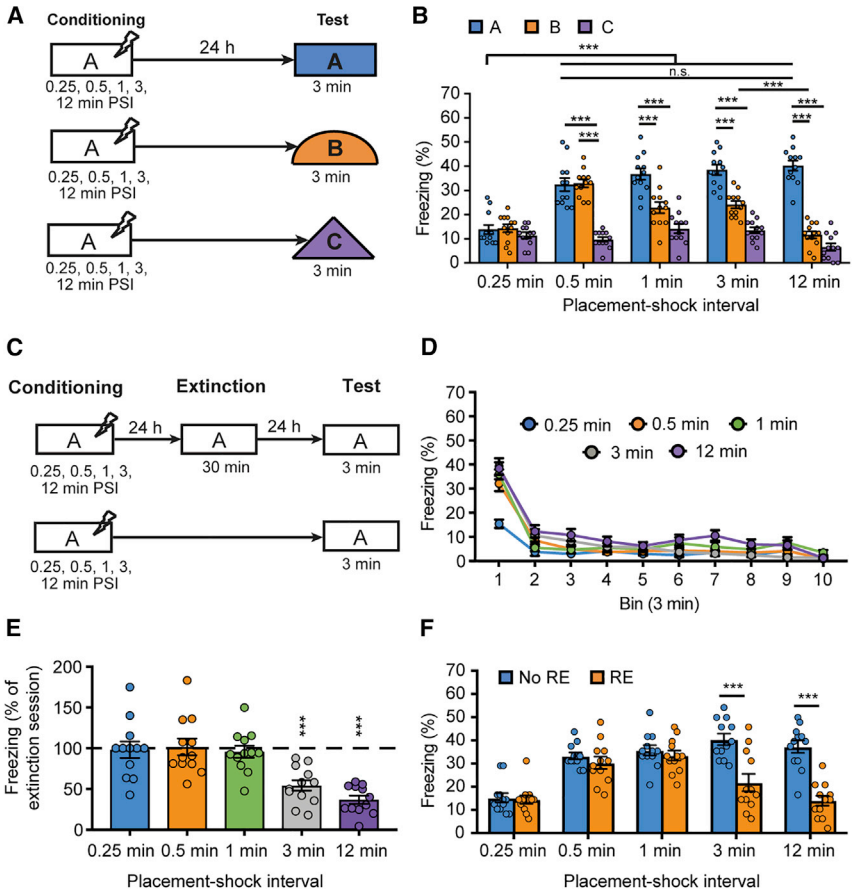

Figure 1. The Extent of Initial Context Learning Determines Conditioning, Generalization, and Extinction

(A and B) Effect of PSI on conditioning and generalization.

(A) Experimental design.

(B) Fear strength and generalization worsen as PSI shortens.

(C–F) Effect of PSI on extinction.

(C) Experimental design.

(E) Within-subjects analysis performed by converting test freezing to a percentage of the first 3 min of the extinction session reveals that long-term extinction only occurs at ≥3-min PSIs. Extinction was confirmed using a one-sample t test comparing each PSI to a hypothetical value of 100%.

(F) Between-subjects analysis of test freezing in re-exposed (RE) compared with none re-exposed (No RE) groups confirms that long-term extinction only occurs in ≥3-min PSIs.

Data are presented as mean ± SE. Significance **$p < 0.01$, ***$p < 0.001$.

analogous to the contextual confusion proposed to underlie PTSD symptomatology [1–4]. To test this hypothesis, we placed rodents into a novel context and controlled the extent of context learning by delivering foot shock at different times thereafter (placement-shock interval; PSI [21–23]). We then tested whether two features of maladaptive fear are caused by short PSIs: (1) inability to differentiate situations similar to the aversive one from the aversive situation itself (overgeneralization [27]), and (2) difficulty in extinguishing fear evoked by situations resembling the traumatic ones [1–3, 28]. As we describe, both characteristics emerged when PSIs were long enough for robust conditioning but putatively too short for complete context encoding.

Given our hypothesis that the deficits produced by short PSIs are due to poor context learning, as well as theories that memories can be altered following recall, it seemed plausible that the deficits caused by short PSIs might be ameliorated by post-conditioning context re-exposure [8, 29–40]. This would lead to further learning about the feared context even after conditioning had occurred. This too turned out to be the case and led to two further important observations. First, updating also occurred in other contexts to which fear was overgeneralized. This caused memory distortion by incorporating erroneous information into the retrieved memory. Second, these changes were mediated by direct alteration and reconsolidation of the existing memory rather than consolidation of a new one [8, 29–40].

Our findings finally led us to hypothesize that the effects of poor context learning and later updating could be explained by their influence on the degree of certainty about where events occurred. This was explored neurocomputationally using the Bayesian context fear algorithm (BACON), a hippocampal-neocortical model that computes the degree of certainty about the identity of the current context and uses it to decide how much fear to express and whether to update existing memories or create new ones [31]. Combined, these findings yield insights into the cognitive and neural operations that deal with poor context learning and its later correction or distortion after recall.

RESULTS

Poor Context Encoding Causes Overgeneralized and Inextinguishable Fear

Our first goal was to determine whether poor context encoding can cause overgeneralization and poor extinction. We altered the PSI in context A to modify the extent of context learning and assessed generalization between context A and a slightly (B) or very different context (C) 24 h later (Figure 1A) [41–44]. Consistent with previous findings [21–23, 31, 45–48], little conditioning occurred after 0.25-min PSIs, but fear became robust and reached near asymptote at 0.5-min PSIs (Figure 1B). In contrast, differentiation between A and B only emerged at 1-min PSIs and continued improving thereafter, with lower fear in B at 12-min PSIs compared with 3-min PSIs. This indicates that fear learning and differentiation are dissociable, and that differentiation continues to improve across PSIs. Moreover, fear in C was lower than B at ≥0.5-min PSIs, indicating that discrimination in a given context is determined by its degree of similarity to the conditioning context and the PSI (Figure 1B; n = 12/group; 2-way ANOVA of PSI x context: interaction, $F_{(8, 165)} = 17$, $p < 0.0001$; PSI, $F_{(4, 165)} = 24.6$, $p < 0.0001$; context, $F_{(2, 165)} = 168.3$, $p < 0.0001$).

To assess the effect of PSI on extinction, we altered the PSI, provided a 30-min extinction session the next day, and tested fear in the same context 24 h later (Figure 1C) [44, 49–52]. Fear decreased across the extinction session at all PSIs, consistent with intact within-session extinction (Figure 1D). However, long-term extinction assessed at test required an even longer PSI than that required for differentiation, emerging only after ≥3-min PSIs (Figures 1E and 1F). Together, these findings demonstrate that poor context encoding alone causes overgeneralization and impairs long-term extinction (n = 12/group; 1-way ANOVA of percentages: $F_{(4,\ 55)} = 13.32$, $p < 0.0001$. 2-way ANOVA of PSI x re-exposure: interaction, $F_{(4,\ 110)} = 9.73$, $p < 0.0001$; PSI, $F_{(4,\ 110)} = 21.4$, $p < 0.0001$; re-exposure, $F_{(1,\ 110)} = 39.9$, $p < 0.0001$).

Poor Context Fear Memory Improves with Further Context Exposure and Learning

We next investigated whether further context exposure could repair already-consolidated context-impoverished memories by adding contextual information into them without affecting their associative value. If so, re-exposure to context A 24 h after conditioning might improve short-PSI memories and alleviate the differentiation and extinction deficits they produce.

Consistent with this, when PSI was sub-optimal (0.5- or 3-min PSIs), 3-min A re-exposure resulted in improved memory specificity, with retained fear of A but lower fear of B compared with no re-exposure (Figures 2A–2C). Moreover, after 30-min re-exposure, this improvement was observable at 0.5-min but not 3- or 12-min PSIs, suggesting it was either absent, prevented, or obscured by extinction in the latter conditions (Figures 2B–2D). Additionally, the improvement was absent after 0.5-min re-exposure at all PSIs, indicating that like context learning, it depends on time (Figures 2B–2D). Finally, the improvement appeared selective for impoverished memories, as it was absent at 12-min PSIs (Figures 2B–2D; n = 15 or 16/group; 2-way ANOVA of updating session duration x test context for each PSI. 12-min PSI: interaction, $F_{(3,\ 119)} = 13.6$, $p < 0.0001$; 3-min PSI: interaction, $F_{(3,\ 120)} = 8.84$, $p < 0.0001$; 0.5-min PSI: interaction, $F_{(3,\ 119)} = 19.8$, $p < 0.0001$; see Table S1 for full ANOVAs; see Figure S1A for freezing during A re-exposure).

Critically, 3-min A re-exposure also facilitated subsequent long-term extinction after a 30-min extinction session at 0.5-min PSIs but had no effect at 12-min PSIs (Figures 2E and 2F). Together, these findings suggest that context-impoverished memories can be selectively improved after context re-exposure, increasing their specificity and amenability to extinction (n = 12/group; 1-way ANOVA of test freezing. 0.5-min PSI: $F_{(2,\ 33)} = 12.8$, $p < 0.0001$; 12-min PSI: $F_{(2,\ 33)} = 46.8$, $p < 0.0001$; see Figure S1B for all freezing data).

Further Context Learning in the Wrong Context Causes Memory Distortion

The overgeneralized and malleable nature of context-impoverished memories led us to hypothesize they might also become distorted by post-conditioning exposure to contexts similar to the conditioning context. This would occur if the same process that improved memory was active during exposure to the similar context and erroneously incorporated contextual information from that context into the memory of the conditioning context. If so, exposure to context B after short PSIs would erroneously shift fear toward that context (Figure 2G).

Consistent with distortion, 3-min B exposure produced low and generalized fear at 3-min PSIs and reversed which context produced fear after 0.5-min PSIs, with retained fear of B and less fear of A compared with no re-exposure (Figures 2H and 2I). Additionally, although the distortion was evident after 30-min B exposure in 0.5-min PSIs, it was absent after 30-min B exposure in 3-min PSIs and at all B exposures at 12-min PSIs (Figures 2H–2J). This suggests that better initial context encoding increases resistance to distortion (n = 12/group; 2-way ANOVA of updating session duration x test context for each PSI. 12-min PSI: interaction, $F_{(3,\ 88)} = 0.4$, $p = 0.75$; 3-min PSI: interaction, $F_{(3,\ 88)} = 5.32$, $p = 0.002$; 0.5-min PSI: interaction, $F_{(3,\ 88)} = 16$, $p < 0.0001$; see Table S2 for full ANOVAs; see Figure S1C for freezing during B exposure).

Finally, the memory improvements and distortions did not occur due to strengthening of fear to the re-exposed context, because a within-subjects analysis comparing fear in the updating versus test sessions revealed no fear increment (Figures S2A–S2D). Moreover, these effects did not occur because conditioning was weak, because neither was prevented by conditioning at a 0.5-min PSI with a stronger shock (Figures S2E–S2G). Thus, the same mechanisms that improve poor memories appear to render them susceptible to distortion through erroneous updating.

The Extent of Initial Context Learning Determines Memory Stability after Recall

Changes to the contextual content of memory, such as those proposed here, require new information to be linked to the existing memory. However, whether such linkage is exclusively mediated by formation and consolidation of a new memory [36, 53] or can also be mediated by reconsolidation and direct updating the existing memory remains unclear [29–37]. Memory-updating theories propose that reconsolidation and alteration of existing memories should occur when the training and updating situations are similar, whereas consolidation of new memories should occur when the situations are very different [31, 54]. This led us to hypothesize that the memory improvements and distortions we observed, which occurred after updating in the same or a slightly different context, would be mediated by reconsolidation and not consolidation.

To begin testing this hypothesis, we injected mice intraperitoneally with anisomycin, a protein synthesis inhibitor that impairs both consolidation and reconsolidation, immediately after no re-exposure or re-exposure to context A for 3 or 30 min following a 0.5-, 3-, or 12-min PSI [49]. We then tested fear in A 1 and 21 days later (Figure 3A). Fear was persistently impaired in every situation where we previously found generalization reduction, consistent with the co-occurrence of reconsolidation and generalization reduction (Figures 3E, 3F, and 3H; cf. Figures 2B and 2C). Wherever we previously observed long-term extinction, anisomycin restored rather than reduced fear, consistent with impaired consolidation of the new extinction memory (Figures 3I and 3J; cf. Figures 2C and 2D). Finally, where no re-exposure occurred or re-exposure previously had no effect, no effect of anisomycin was seen (Figures 3B–3D and 3G; cf. Figures 2B–2D). These findings demonstrate a strong correspondence between generalization reduction and reconsolidation (n = 10–12/group;

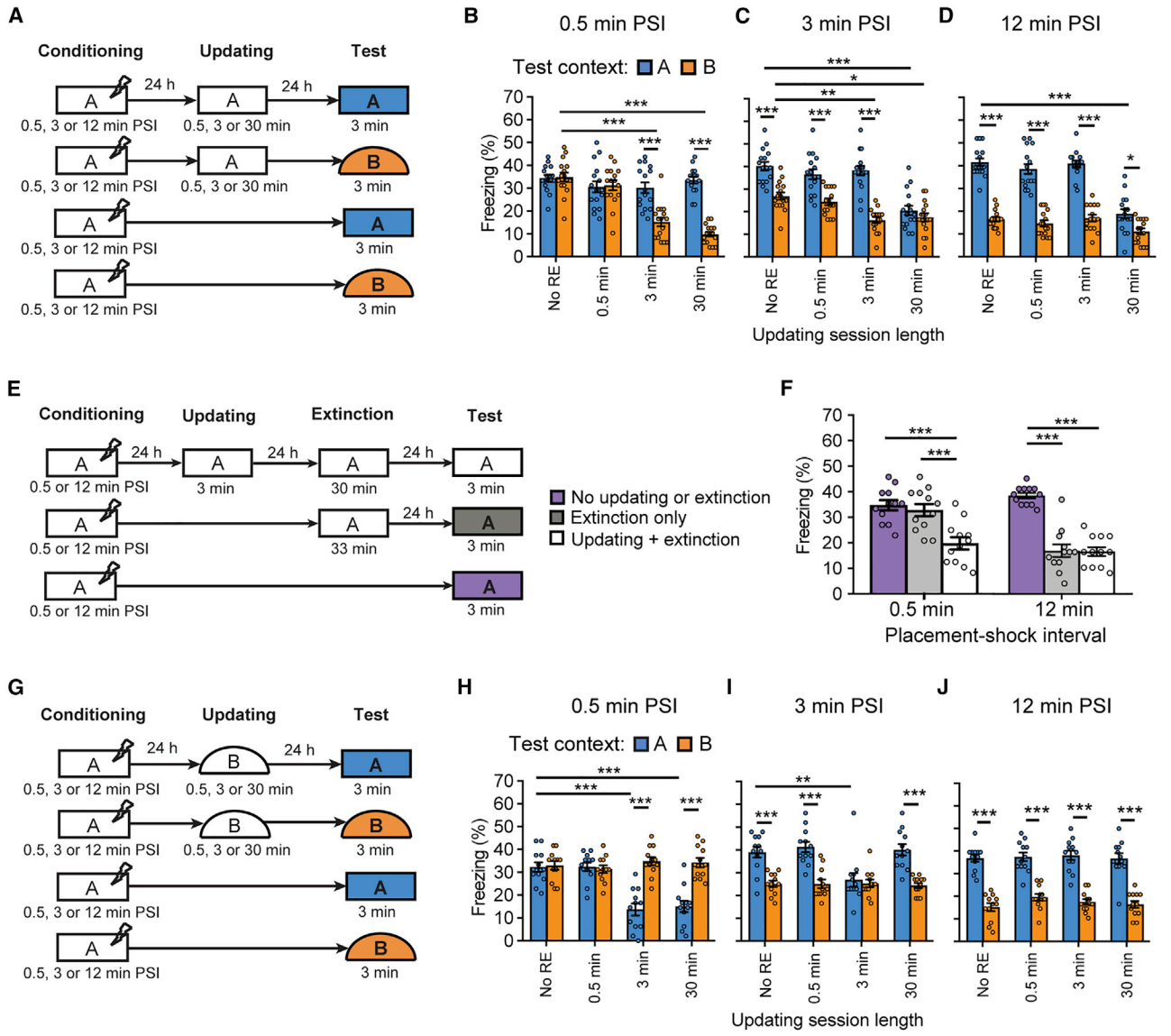

Figure 2. Context Re-exposure Enables Improvement or Distortion of Impoverished Memory

(A–D) Effect of re-exposure to the conditioning context (A) on subsequent generalization.

(A) Experimental design.

(B–D) Context A re-exposure (RE) for 3 min reduces generalization in 0.5-min (B) and 3-min (C) PSIs but not 12-min PSIs (D).

(E and F) Effect of re-exposure to the conditioning context on subsequent extinction.

(E) Experimental design.

(F) Re-exposure to A improves capacity for extinction in 0.5-min but not 12-min PSIs.

(G–J) Effect of exposure to a context B, which is slightly different from context A, on subsequent fear.

(G) Experimental design.

(H–J) B-Exposure skews fear towards context B in 0.5-min PSIs (H), equalizes fear between A and B in 3-min PSIs (I), and has no effect at 12-min PSIs (J).

See also Tables S1 and S2 and Figures S1 and S2. Data are presented as mean ± SE of test freezing. Significance *p < 0.05, **p < 0.01, ***p < 0.001. PSI, - placement-shock interval.

2-way repeated-measures [RM] ANOVA of time x treatment; see Table S3 for full ANOVAs).

Memory Improvement and Distortion Are Mediated by Hippocampal Reconsolidation

We next directly investigated whether the memory improvements and distortions were mediated by memory reconsolidation or consolidation. We targeted hippocampal brain-derived neurotrophic factor (BDNF), which is required for consolidation but not reconsolidation, and protein degradation pathways, which are required for the destabilization phase of reconsolidation, to doubly dissociate between the two processes [55–57].

We first confirmed that intrahippocampal infusion of BDNF-antisense oligonucleotides prior to conditioning at different

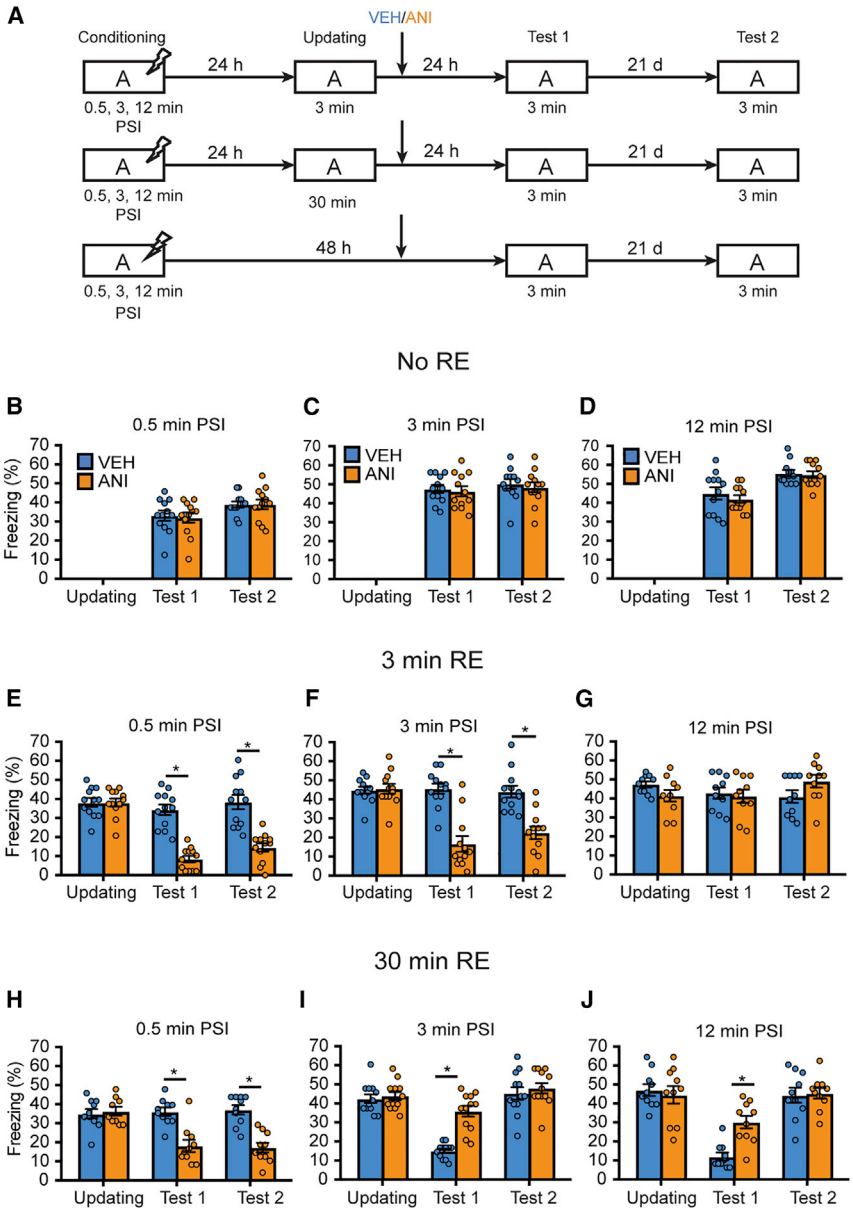

Figure 3. The Extent of Initial Context Learning Determines Memory Stability after Recall

(A) Experimental Design.

(B–D) Effect of anisomycin (ANI) or vehicle (VEH) injection without context re-exposure (RE) after conditioning using 0.5-min PSIs (B), 3-min PSIs (C), and 12-min PSIs (D).

(E–G) Effect of anisomycin injection after 3-min re-exposure following conditioning using 0.5-min PSIs (E), 3-min PSIs (F), and 12-min PSIs (G).

(H–J) Effect of anisomycin injection after 30-min re-exposure following conditioning using 0.5-min PSIs (H), 3-min PSIs (I), and 12-min PSIs (J). ANI persistently reduces fear compared with VEH wherever generalization was previously reduced, consistent with the presence and disruption of reconsolidation (E, F, and H; c.f. Figures 2B and 2C). ANI has no effect where no behavioral change was previously observed (B–D and G; c.f. Figures 2B–2D). Finally, ANI increases fear wherever extinction previously occurred, consistent with impaired consolidation of extinction (I and J; c.f. Figures 2C and 2D).

See also Table S3. Data are presented as mean ± SE. Significance *p < 0.05. PSI, placement-shock interval.

See also Table S3. Data are presented as mean ± SE. Significance *p < 0.05. PSI - placement-shock interval.

PSIs impairs long-term fear, consistent with disruption of consolidation (Figure 4B; n = 9–12/group; 2-way RM ANOVA of treatment x test day. Main effect of treatment: 0.5-min PSI, $F_{(1, 20)}$ = 78.5, p < 0.0001; 3-min PSI, $F_{(1, 18)}$ = 74, p < 0.0001; 12-min PSI, $F_{(1, 18)}$ = 67.8, p < 0.0001; see Table S4 for full ANOVAs).

Next, we showed that intrahippocampal infusion of the protein degradation inhibitor clasto-lactacystin β-lactone (β-lac), but not BDNF antisense, impaired recall-induced memory improvements and distortions after 0.5-min PSIs (Figures 4C–4F). This is consistent with memory updating occurring through reconsolidation and alteration of the existing memory rather than consolidation of a new memory (n = 9–12/group; 2-way ANOVA of treatment x test context. A re-exposure: BDNF: interaction, $F_{(1, 35)}$ = 0.1, p = 0.7; β-lac: interaction, $F_{(1, 36)}$ = 10, p = 0.003; B exposure: BDNF: interaction, $F_{(1, 32)}$ = 0.02, p = 0.9; β-lac: interaction, $F_{(1, 38)}$ = 34.8, p < 0.0001; see Table S5 for full ANOVAs).

Simulations by a Neurocomputational Model of Hippocampal-Neocortical Function

We finally asked what cognitive and neural operations could account for the effects of poor context encoding and later updating. Given that the content of context memories appears to form the basis upon which contexts are identified in the future [26], we hypothesized that poor context encoding produces maladaptive effects by generating ambiguity about where events occurred, and that updating alters this ambiguity. To explore the viability and possible neurobiological basis of this claim, we used BACON [31], a neurocomputational model of hippocampal-neocortical function that controls context representation creation, updating, and fear conditioning and expression by calculating the Bayesian weight of evidence for representation validity (called "B_{Rep}" in BACON) that the identification of the current context is correct.

During conditioning, BACON acquires contextual attributes as an increasing function of PSI, associates them with a new hippocampal representation (Rep-A), and pairs Rep-A to the hedonic representation of shock in the amygdala (Figure 5A). Thereafter, whenever BACON enters a context whose features best match those associated with Rep-A, it computes B_{Rep} from the degree of match between the attributes associated with Rep-A and those sampled from the current context thus far. The better the match, the more positive the B_{Rep}, and the worse the match the smaller or more negative the B_{Rep}. The greater the B_{Rep},

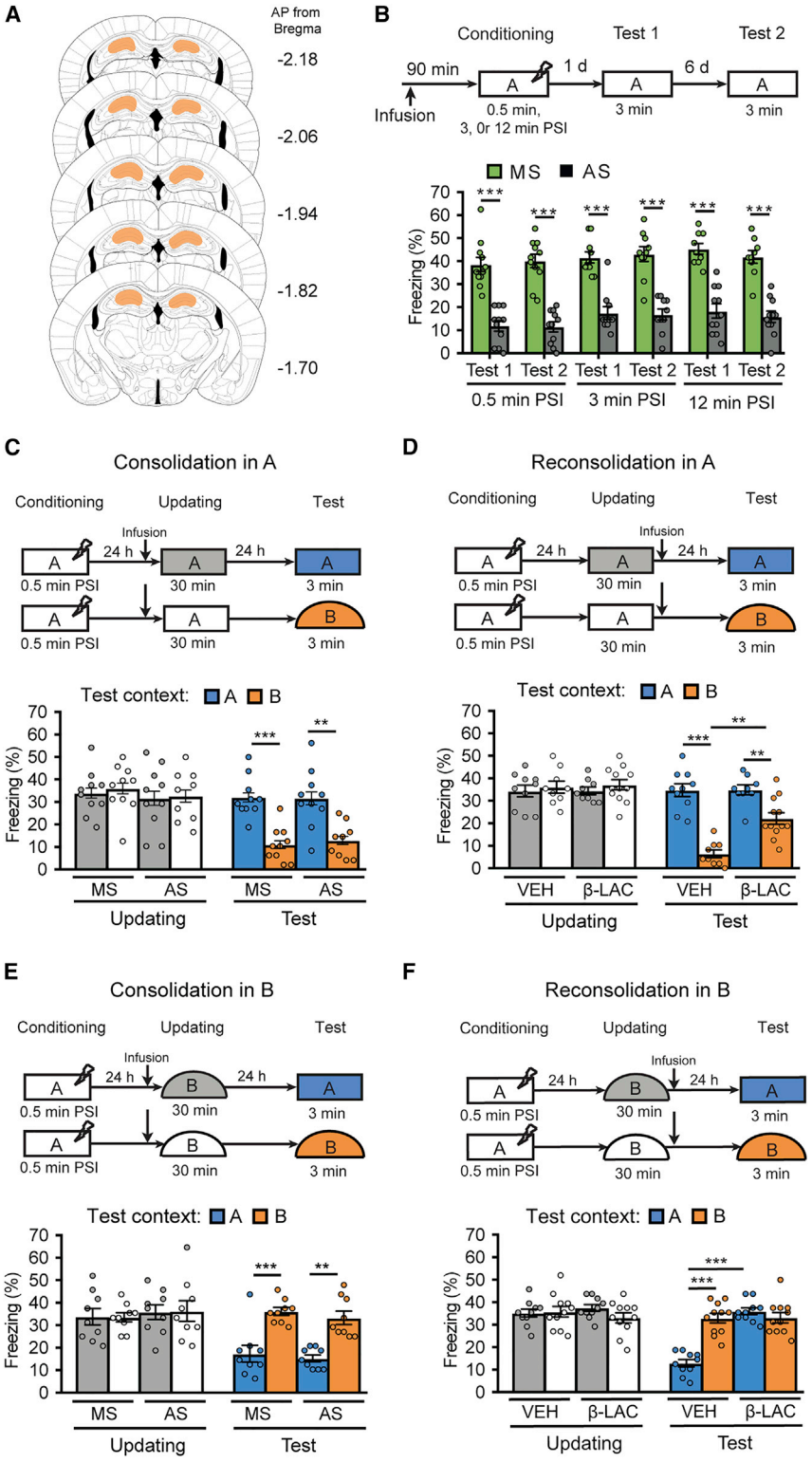

Figure 4. Memory Improvement and Distortion Require Hippocampal Memory Reconsolidation but Not Consolidation

(A) Inclusion zone (orange) for all cannula placements.

(B) Inhibiting hippocampal BDNF with antisense (AS) compared with missense (MS) oligonucleotides prior to conditioning impairs fear memory.

(C and E) BDNF AS prior to the updating session does not impair the reduction in generalization caused by context A re-exposure (C) or the fear reversal caused by context B-exposure (E).

(D and F) Inhibiting protein degradation after the updating session using β-lac impairs both the generalization reduction caused by context A re-exposure (D) and the fear reversal caused by context B-exposure (F).

See also Tables S4 and S5. Data are presented as mean ± SE. Significance **p < 0.01, ***p < 0.001. Context A, - conditioning cotnext. Context B, - slightly different context.

the greater the expression of conditional fear (Figure S3). If B_{Rep} falls below a negative threshold (B_{New}), Rep-A is found invalid and a new neutral representation of the context is created. Finally, if at the end of a session B_{Rep} exceeds a positive threshold (B_{Add}), Rep-A is updated by associating any new features sampled with it (see STAR Methods for more information) [31].

These properties led to accurate emulation of our experimental findings (Figures 5B–5G). Because context B shared many features with A, context B exposure after short PSIs initially caused activation of Rep-A and almost as great a B_{Rep} as in context A (Figure 5I). Consequently, fear was evoked. When a sufficient number of context B's attributes had been sampled, B_{Rep} fell, causing a new representation of context B to be created (Rep-B). At that point fear fell, but this happened only at the end of the session (Figure 5I). Consequently, average fear across the session was high, producing strong fear generalization overall (Figure 5E). In contrast, after longer PSIs, less time was required for BACON to become certain it was not in A ($B_{Rep} < B_{New}$) and form a new Rep-B (Figures 5J and 5K). Consequently, average fear in B across the session was reduced with longer PSIs, producing less generalization (Figure 5E).

When BACON was re-exposed to context A after short PSIs, B_{Rep} climbed slowly across the session. Therefore, exceeding B_{Add} took time and updating was absent after short re-exposure (Figures 5H and 5L). However, once updating emerged after longer re-exposure, BACON incorporated any new information it sampled into Rep-A (Figure 5H). Consequently, B_{Rep} fell rapidly in B at test, producing little generalization (Figures 5F, 5M, and 5N). Moreover, the more that was learned originally about the context, the less there

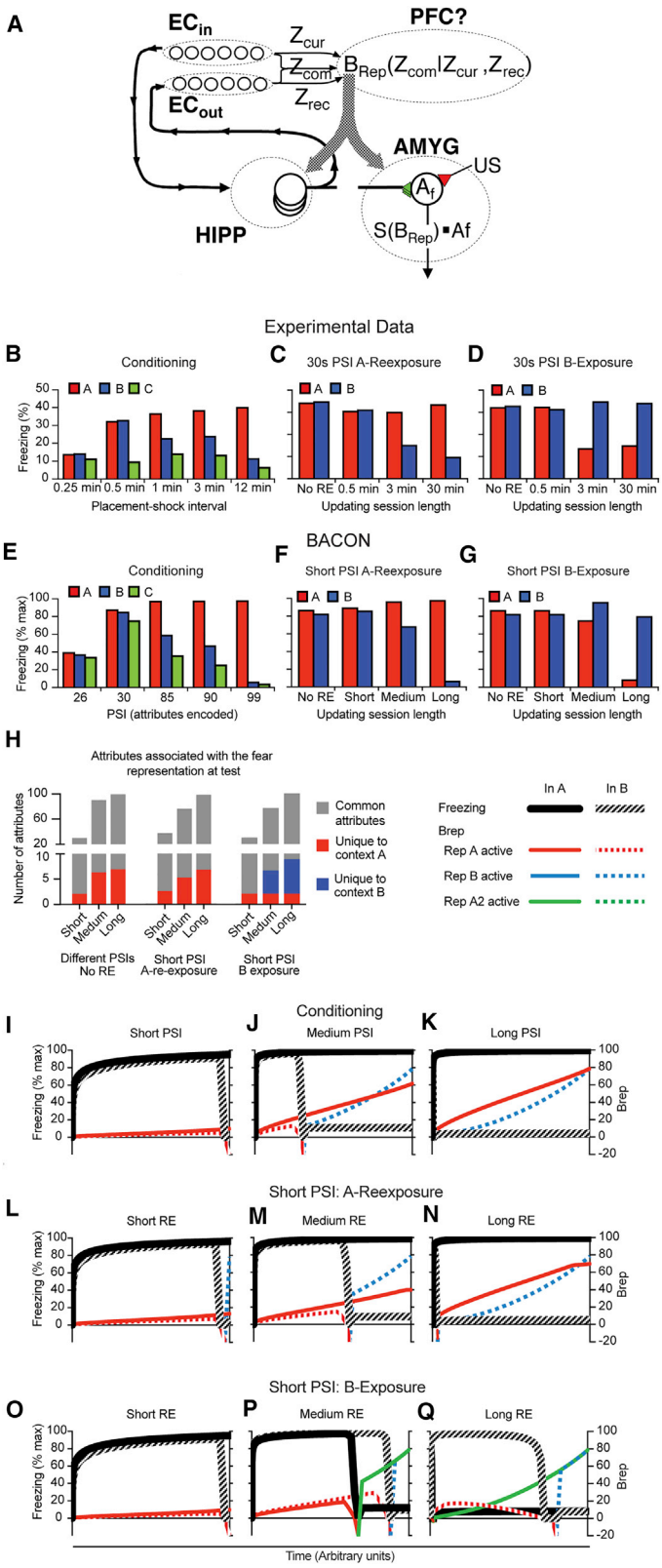

Figure 5. Neurocomputational Simulation and Explanation of the Empirical Findings by BACON

(A) Schematic of BACON circuitry. See STAR Methods for more information. PFC, prefrontal cortex. Hipp, hippocampus. EC, entorhinal cortex. Amg, amygdala.

(B–G) BACON accurately reproduces the effects of PSI (E), A re-exposure (RE; F) and B exposure (G) presented in Figures 1B, 2B, and 2H (the latter are duplicated for comparison in Figures 5B, 5C, and 5D, respectively).

(H) Attributes associated with the fear representation at test in the above conditions.

(I–Q) Time courses of test sessions after conditioning at different PSIs without re-exposure (I–K) or after short PSIs and different lengths of re-exposure to A (L–N) or B (O–Q). The specific conditions are listed in each panel. See the legend to the right of (H) for a description of the different lines.

See also Figures S3–S5. PSI, placement-shock interval. Context A, conditioning cotnext. Context B, slightly different context.

was to learn during re-exposure, so the effect of updating predominated at short PSIs, as seen experimentally (see Figure S4 for all A re-exposure simulations).

BACON does not yet deal with extinction. However, given that like updating, extinction in the wrong context could be maladaptive, some threshold of B_{Rep} must presumably be exceeded to allow extinction. This would explain the effect of PSI on extinction.

Finally, it might be expected that B_{Add} would be high to prevent incorrect updating [31]. However, the distortions produced by B exposure showed this to be wrong. We therefore set B_{Add} to a level interpreted as the low end of "reasonably confident" [58]. Consequently, B exposure after short PSIs caused attributes unique to B to become associated with Rep-A (Figure 5H). Because there was now more B- than A-specific information recalled at test, it took longer for discrepancies to be detected in B than A and for a new neutral Rep-A (Rep-A2) to be created (Figures 5P–5Q). Therefore, average fear was greater in B than A, producing fear reversal similar to that observed *in vivo* (Figure 5G; see Figure S5 for all B exposure simulations).

DISCUSSION

Prompted by findings on the duration of exposure needed for context encoding together with suggestions from the clinical literature, we studied how PSI and contextual re-exposure affect the degree of conditioning, generalization, and extinction. We found that fear memories acquired using short PSIs overgeneralized and resisted long-term extinction. However, re-exposure to the conditioned context rescued these deficits, whereas exposure to slightly different contexts caused memory distortion. Moreover, both these updating effects required reconsolidation as opposed to new learning. Finally, with BACON's aid, we explained these findings as occurring due to the variable nature of context learning and its influence on animals' ability to determine their whereabouts, as discussed below.

Effect of PSI on Generalization

Generalization of contextual fear is traditionally conceived to occur because an irrelevant context is mistaken for the conditioning context and, at the cellular level, because hippocampal representation cells to which fear is conditioned are shared by the representation of a similar context [26, 31, 42, 59, 60]. Our findings extend this to suggest that the degree of context learning interacts with the degree of contextual similarity to determine the level of generalization. In our account, instantiated by BACON, acquiring fewer unique features after short PSIs results in memories that contain mostly general features. This decreases the confidence with which any given similar context will be recognized as different, and thus increases the frequency of defensive overgeneralization. Future studies can explore the neural underpinnings of such general learning and determine whether it is also reflected in increased overlap with the feared representation.

Effect of PSI on Extinction

The failure of long-term extinction at short PSIs can be explained on similar principles. A key requirement for extinction is non-reinforced re-exposure to the CS [61, 62]. However, our findings suggest that, at least for complex CSs like contexts, animals must first be sure they were re-exposed to the CS in order to extinguish. In this account, when animals form poor memories and receive extensive non-reinforcement, they extinguish within the session because no immediate danger is present. However, they do not consolidate the experience into a long-term extinction memory because they cannot be sure whether they were in the conditioning context, in which case the lack of shock means that the feared context is no longer dangerous, or whether they were simply somewhere else, in which case the experience was irrelevant to their learned fear and they should not extinguish. Consequently, they err on the side of caution and do not consolidate their extinction learning.

The failure of long-term extinction at short PSIs can also be explained mechanistically according to trace dominance theory, which proposes that only one memory trace can be modified during a given session [49, 63, 64]. In this theory, consolidation of extinction is prevented at short PSIs because the fear memory is being updated with new contextual information, and vice versa at longer PSIs. This would be consistent with our anisomycin findings, which showed that after 30-min re-exposures, anisomycin caused a fear increase at 3- and 12-min PSIs, indicating impaired consolidation of extinction but reduced fear at 0.5-min PSIs, indicating reconsolidation disruption.

Updating

A key question is how re-exposure rescued the overgeneralization and resistance to extinction produced by short PSIs. To our knowledge, rescue of extinguishability 24 h after re-exposure has not been observed previously. However, re-exposure-induced generalization reductions have been reported elsewhere. Several studies found that re-exposure improved the specificity of old memories that had become generalized through systems consolidation [65–67]. Yet, the memories studied here were only 2 days old, so their mechanism of generalization and its amelioration was likely different. Another study showed improvement in the specificity of young discriminable memories, such as the 3-min PSI studied here [41]. However, the explanation given was based on extinction, which could not have been responsible for the improvements for two reasons. First, extinction did not occur in any re-exposure that produced generalization decrement. Second, long-term extinction requires consolidation, which was not required for the generalization decrement. Finally, others have shown that non-reinforced re-exposure to the conditioning context can strengthen fear of the conditioning context [67–69]. If such strengthening were specific to the conditioning context, it could have led to a relative reduction in generalization. Yet, this did not occur here, as we observed no fear increase in context A after re-exposure.

Instead, we found that the generalization reduction after 30-min re-exposure partly required protein degradation but not BDNF. This partial effect suggests that protein degradation, or memory destabilization itself, plays a limited role in the underlying processes, and that other processes might cooperate to produce the full improvement. However, it also indicates that the updated behaviors depend at least partly on updating and reconsolidation of the existing memory rather than formation of a new one. It is reasonable to assume based on our scheme and BACON's simulations that this same mechanism accounts for

the generalization reduction seen after 3-min re-exposure. However, this requires future experimental confirmation. Nonetheless, inasmuch as our findings can be generalized to all the updating conditions used, we propose that re-exposure corrected the maladaptive properties of poor memories by allowing integration of more contextual information into the fear memory. This would have improved the animal's confidence about their whereabouts in the future, reducing generalization and restoring extinguishability.

Distorted Updating

Perhaps our most surprising finding was that exposure to a context slightly different from the conditioning context could skew fear toward that context. It has long been known that post-recall processes can cause memory distortions [5–8]. Moreover, such distortions have been proposed, although not clearly demonstrated, to be mediated by direct memory updating [8, 29–40]. We propose, based on BACON's simulations and the dependence of this skewing on protein degradation but not BDNF, that the fear reversal we detected emerged from memory distortion caused by erroneous memory updating in the wrong context. In this account, updating is enabled even when animals are only marginally confident they are in the conditioning context. This adaptation means that animals that learned little about the conditioning context and therefore cannot extinguish or form an independent representation of a similar context can learn more about the context and perform these functions subsequently. However, it also means that animals can sometimes erroneously update their memories in contexts they cannot initially differentiate from the conditioning context. This causes animals to be inappropriately confident that the safe context is dangerous and vice versa, leading to fear reversal. If so, this may indicate that at least in the conditions assessed, distortion can emerge because the benefits of updating memories in uncertain situations outweigh the negative consequences of occasionally distorting them.

Our findings also provide useful insights into the conditions that produce memory distortion. First, although 0.5-min PSIs produced complete fear reversal, 3-min PSIs produced fear equalization between the contexts, and 12-min PSIs produced no changes. This suggests that the degree of initial learning determines both the advent and extent of distortion. Second, we found that at 0.5-min PSIs, both 3- and 30-min B exposure produced distortion, whereas in 3-min PSIs, only the 3-min B exposure produced distortion. Based on BACON's computations and the reconsolidation literature [31, 70], we propose these findings can be explained on the basis that animals must decide whether they were in the conditioning context or elsewhere at the end of the session in order to update and distort their memories. Thus, animals spend the B exposure sampling the environment and comparing its features to those of memorized representations. The longer they spend in the context, the more information they acquire and the more confident they are that they were elsewhere. Conversely, the less they originally learn about the conditioning context, the more difficult it is for them to determine where they were. Accordingly, 0.5-min PSI-conditioned animals that learned little about context A could not be confident they were in a different context even after a 30-min B exposure. This produced distortion regardless of session duration. In contrast, 3-min PSI-conditioned animals initially learned a significant amount about context A. It therefore took them less time (>3 min but <30 min) to be confident they were elsewhere, thus preventing updating and distortion.

Reconsolidation-Mediated Updating

Our findings that generalization reduction and distortion depend partly on reconsolidation could have useful implications. First, it provides evidence that reconsolidation can directly update the contextual content of memory and thus improve or distort it. This has been previously hypothesized but not comprehensively demonstrated [8, 29–40].

Second, it may help resolve inconsistencies between views that reconsolidation is triggered by novelty and prediction error [38–40, 71] and observations that reconsolidation occurs after brief non-reinforced context re-exposure. Such re-exposure would traditionally be expected to produce extinction, not reconsolidation, as the only apparent source of discrepancy is the absence of shock [49–51, 72]. However, our findings suggest that a second source of novelty and prediction error could be the contextual representation itself, and that this can drive reconsolidation during non-reinforced re-exposure.

Finally, provided our assumption is correct that reconsolidation is a causal process in all the behavioral updating cases we detected, our observations could help reconcile views that reconsolidation updates the content of memory with findings in second-order conditioning that such updating is only mediated by consolidation of new memories [36, 53]. They could strengthen the interpretation that the mechanism of updating depends on the degree of similarity between the training and updating contexts [31, 54]. When the two contexts are very different, as occurred in the second-order conditioning study, updating would occur through consolidation of a new memory. However, when the contexts are similar or identical, as occurred here, updating would occur through reconsolidation and modification of the existing memory.

Practical Implications

Incorrect memory updating could affect many aspects of our lives. Although speculative, our findings raise the possibility that vulnerability to such updating partly relates to how well the memories were initially acquired. Moreover, they suggest that such distortions could, in some instances, involve direct alteration of existing memories, which could render them more entrenched and difficult to correct. This could have implications for understanding post-event memory malleability in a variety of situations, including the effect of suggestion and interrogation on witness testimony [5–8].

Our findings may be more directly relevant to PTSD. Fear in PTSD is complex and multifactorial, and likely involves conditional and unconditional components as well as aberrant context processing [1–4]. Our findings suggest that one component of this could be the formation of impoverished contextual representations that cause overgeneralized and inextinguishable context fear. Moreover, PTSD is heterogeneous and emerges in only a subset of trauma sufferers; however, the cause for this remains unclear [73]. Our findings suggest that the variability of context learning and its influence by numerous factors, including the

learning situation and the sufferer's neurological integrity, could partly underlie this variability. If so, it may help explain why dysfunction of the hippocampus, which is the locus of context encoding, correlates with PTSD onset and severity [74–76].

Our findings might also provide insights into PTSD treatment. They suggest that one reason extinction-based exposure therapy fails in PTSD is that extinction of context fear tied to complex situations is only achievable if the memories are sufficiently detailed. They also suggest that the persistence of maladaptive responses in PTSD could be due to failed engagement, or fundamental dysfunction, of adaptive memory-updating processes that would otherwise have corrected them. If so, one approach may be to correctly re-engage updating to improve differentiation and extinction.

Although speculative, the potential of updating to modify the contextual content of memory suggests a novel approach to exposure therapy. According to our findings, exposure therapy will only produce lasting extinction if the attributes of the therapy context match those of the feared one sufficiently that the subject (or their hippocampus) firmly believes they are where the US occurred. But even if the therapy situation faithfully emulates the conditioning one, such certainty may be difficult to achieve if initial context encoding was poor. However, if, as suggested by our findings, the level of certainty required for updating is relatively low, updating during initial therapy sessions could cause features of the therapy context to become associated with the representation of the traumatic situation. This would increase the match between recalled attributes and those of the therapy context during subsequent sessions. It would thereby increase confidence that the therapy context is the feared one, and thus promote long-term extinction.

Our findings also indicate that updating in the therapy context might be facilitated by drugs that promote reconsolidation, because reconsolidation stabilizes updating. This contrasts with recent ideas of attenuating fear by pharmacologically blocking reconsolidation or extinguishing memories within the reconsolidation window [11, 77, 78]. Finally, our findings suggest that models like BACON could be utilized to simulate neural and cognitive operations during therapy sessions. Combined with information on the nature of the traumatic event, this could aid in structuring sessions to maximize the therapeutic effect of updating, reconsolidation, and extinction.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.cub.2020.04.040.

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AUTHOR CONTRIBUTIONS

R.Z., conceptualization, data curation, formal analysis, supervision, investigation, methodology, project administration, visualization, and writing – original draft and review & editing; J.L., investigation, formal analysis, visualization, validation, and writing – review & editing; F.K., conceptualization, data curation, investigation, formal analysis, methodology, software, visualization, and writing – review & editing; M.F., conceptualization and writing – review & editing; B.V., conceptualization, funding acquisition, methodology, project administration, supervision, and writing – review & editing.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, Peptides, and Recombinant Proteins		
Anisomycin: ANI	Sigma Aldrich	#A9789
Clasto-lactacystin β-lactone: β-lac	Sigma Aldrich	#L7035
Ketamine	MAVLAB from Provet (NSW) Pty Ltd	KETA M I
Xylazine	Provet (NSW) Pty Ltd	XYLA Z 2
ACSF	Tocris	3525
DMSO	Sigma Aldrich	CAS Number: 67685 Product Number: D2650
HEPES	GIBCO	15630080
Paraformaldehyde	Sigma	CAS Number: 30525-89-4 Product Number: 158127
Cresyl violet	ProSciTech	C0941
Isopropanol	Sigma Aldrich	CAS Number: 67630 Product Number: W292907
Xylene	Ajax Finechem	AJA577-20L
Bupivacaine	Provet (NSW) Pty Ltd	BUPI I 2
Ketoprofen	Provet (NSW) Pty Ltd	KETO I P1
Experimental Models: Organisms/Strains		
Mouse: C57BL/6J	Australian BioResources Facility MossVale	*RRID*: IMSR_JAX:000664
Oligonucleotides		
BDNF Missense/antisense	Sigma Aldrich	Custom oligos
Software and Algorithms		
GraphPad Prism	Graphpad	*RRID*: SCR_002798
FreezeFrame	Actimetrics	*RRID*: SCR_014429
Other		
Bilateral cannula	PlasticsOne	#C235G-3.0-SPC
Dummy cannula	PlasticsOne	#C236DC/SPC
Bilateral injectors	PlasticsOne	#C235I-SPC

RESOURCE AVAILABILITY

Lead Contact

Further information and requests for resources, reagents, and data should be directed to and will be fulfilled by the Lead Contact, Bryce Vissel (Bryce.Vissel@uts.edu.au).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Original data for Figures 1, 2, 3, and 4 reported in this paper have been deposited to Mendeley data: [https://doi.org/10.17632/mtfpb8vycb.2], https://doi.org/10.17632/mtfpb8vycb.1. Simulation data will be made available on request.

Experimental Model and Subject Details

Male C57BL/6J (RRID: IMSR_JAX:000664) adult 8-11-week-old wild-type healthy drug and test naive mice initially weighing 20-30 g were obtained from the Australian BioResources facility in Moss Vale, NSW. The mice were maintained under a 12-hour light-dark cycle with *ad libitum* access to food and water in standard Individually Ventilated Cages. They were housed in groups of 2-4 unless cannulated, in which case they were single housed due to reports and experience of infighting. Mice were given at least seven days to

acclimatize prior to commencement of experiments, which were all performed during the light cycle. In all experiments, animals were littermates and randomly assigned to specific groups prior to commencing experiments. All experimental procedures were approved by the ethics committee at the Garvan Institute of Medical Research and St Vincent's Hospital and in accordance with the National Health and Medical Research Council animal experimentation guidelines and the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (2013).

METHOD DETAILS

Contextual fear conditioning

Basic information

All experiments were performed at the Garvan Institute of Medical Research in Darlinghurst, Australia. We used context fear conditioning as it is rapid, reliable, easily manipulated, widely used and allows manipulation of context memory formation by PSI.

Apparatus.

Training and testing took place in four identical cube-shaped fear conditioning chambers (32x27x26 cm; Med Associates Inc) that had a clear Plexiglas door, ceiling and rear wall and gray aluminum sidewalls. These chambers were located within individual cubicles. Each chamber had a removable grid floor which consisted of 36 parallel rods spaced 8 mm apart. Positioned under the grid was a removable gray aluminum tray for collection of waste. When in place the rods connected to a shock generating and scrambling system which delivered a current through the rods and elicited a foot-shock. This system was connected to and controlled by computer software (FreezeFrame2, Actimetrics). A video camera which was positioned in front of the chambers recorded the behavior of the mice during training and testing.

Contexts.

In context A, animals were carried from the holding room in their home-cages to the fear conditioning room under full fluorescence. The fear conditioning chamber was cleaned with 70% ethanol and the waste tray was scented with aniseed essence. Context B was identical to context A except that a white plastic dome was inserted, and the grid floor was overlaid with a white plastic sheet. In addition, the B chamber was not scented with aniseed essence and was cleaned with 70% isopropanol. In context C, mice were removed from their home-cages in a room located between the holding room and fear conditioning room. From there, they were carried into the fear conditioning room in a new cage. Within the fear conditioning room, the fluorescent light and the chamber houselight were both turned off. Instead, two lights located at the top back of the sound attenuating cubicles were used. The chamber itself was exactly like context B.

Shock and post-shock duration.

In all experiments, shock was 1 mA and 2 s long, with a 30 s post-shock duration. The exception was the experiment in Figure S2, where shock was 1.5 mA and 2 s long, with a 30 s post-shock duration.

Scoring.

For behavioral tests, freezing was defined as the absence of all movement except for that required for breathing [43]. Freezing was measured manually using a sampling method whereby each mouse was scored as either freezing or not freezing once every 4 s.

Randomization, replication and blinding.

Animals were randomly allocated to groups at the start of the experiment. The experimenter was blind to treatment and condition during scoring. In all experiments, data are presented as a pool of at least 3 separate replicates with n = 4 mice per replicate. All findings showed similar trends across replicates.

Stereotaxic surgeries

Mice were anesthetized with ketamine (8.7 mg/ml; Mavlab, Slacks Creek, QLD) and xylazine (2 mg/ml; Troy Laboratories Pty Ltd, Smithfield, Australia). Bilateral guides spaced 3.0 mm apart (PlasticsOne; #C235G-3.0-SPC) were then implanted at −1.9 AP, ± 1.5 ML, −0.7 DV from bregma. These were capped with a dummy (PlasticsOne; #C236DC/SPC) at all times. The internals (PlasticsOne; #C235I-SPC) were 33 gauge and projected 1.0 mm below the end of the cannula, to a total depth of −1.7 DV from bregma. For analgesia, mice received topical bupivacaine at the incision site and subcutaneous ketoprofen injections (5 mg/kg in units/g volume) immediately after surgery and 24-h later. Mice were given 6-7 days to recover prior to testing.

Drug infusions

Antisense oligonucleotides and β-lac were infused intrahippocampally via cannula in a total volume of 0.3 μl at a rate of 0.3 μl/min using a PHD ultra-syringe pump (Harvard Apparatus). The internals were left in place for 1.5 min before removal to minimize backflow. BDNF oligonucleotides (Sigma Aldrich) were HPLC purified 18-mer sequences end-capped with phosphorothioate at the 3 terminal nucleotides on both the '5 and '3 ends. BDNF oligonucleotides (antisense: 5'-TCT TCC CCT TTT AAT GGT-3'; missense: 5'-ATA CTT TCT GTT CTT GCC-3'; 1 nmol/brain side) were infused 90 min prior to conditioning or re-exposure [56]. A BLAST search using Reference mRNA sequences (refseq_rna) with restriction to mouse revealed the antisense had 100% identity and coverage with mouse BDNF transcript variants 1-11, an E value of 0.022 and max and total scores of 36.2, indicating only a single alignment was present. There were no other significant matches. The control sequence also revealed no significant matches. Clasto-lactacystin β-lactone (β-lac. Sigma Aldrich; #L7035) was prepared fresh in every trial to a final concentration of 32 ng/μl in aCSF with 2% DMSO, pH 7.6 [55, 57]. Anisomycin (Sigma Aldrich; #A9789) was dissolved in equimolar HCl and then reconstituted in sterile saline to a final

concentration of 15 mg/ml, pH 7.0-7.6 [49]. Anisomycin was then injected intraperitoneally on a by-weight basis (150 mg/kg) immediately after re-exposure.

Histology and placement confirmation

After testing, all cannulated mice studied were sacrificed via CO_2 inhalation followed by cervical dislocation. Brains were removed and post-fixed in 4% paraformaldehyde at 4°C for 2 days and then cryoprotected in 30% sucrose. Brain coronal sections (40 μm) were cut on a cryostat and mounted onto gelatin-coated slides. The slides were stained with 0.1% (w/v) cresyl violet solution, dehydrated with ethanol and xylene and coverslipped. Cannula placements were analyzed using a light microscope (Leica DM4000). We established an inclusion zone aimed specifically at the dorsal hippocampus. This zone included the following borders: AP, from −1.6 to −2.2 mm from bregma. DV, from below (and excluding) the CA1 layer to above (and excluding) the suprapyramidal blade of the DG. ML, medial to (and excluding) the CA1/CA3 layers and no medial boundary. To determine whether a given placement was within the inclusion zone, we found the section in which the cannula indentation was deepest. Because the needle was very thin and rarely produced a needle track, we drew a line extending 1 mm below the most inferior extent of the indentation into the tissue, as this was the depth to which the needle extended beyond the cannula. Only data from animals with placements within the inclusion were analyzed.

BACON modeling

The Bayesian context fear algorithm (BACON) is a neurocomputational model of hippocampal-neocortical function that incorporates conventional views about how animals form and retrieve contextual fear memories but adds a novel updating mechanism that allows the contextual content of these memories to be improved with experience. For full details see reference [31].

BACON proposes that animals randomly sample contextual features. This generates cortical activity that becomes distilled to a pattern of entorhinal cortex input cell activity. Like most hippocampal models based on Marr [79], BACON then assumes this information is fed to the hippocampus where input to a sparse, relatively non-overlapping set of representation cells becomes strengthened. Similar strengthening also occurs between input from those cells back to entorhinal output cells matching the set of input cells that were active at encoding. Subsequently, activity of a sufficient fraction of the originally active entorhinal input set (corresponding here to contextual features) can reactivate the representation whose associated attributes best match those of the context currently being observed.

Uniquely, however, BACON adds that following such representation reactivation, some as yet unidentified (potentially cortical) region calculates the Bayesian Weight of Evidence that this ''best matching'' representation actually is that of the current context (B_{Rep}, for Bayesian Weight of Evidence for Representation validity) [31, 58]. This metric is computed from the number of attributes that were previously encoded into the representation and are now being recalled (Z_{Rec}, for ''recalled''; influenced by PSI), the number of attributes that have been sampled in the current environment (Z_{Cur}, for ''current''; influenced by the length of the session thus far), and the number that are common between the two sets (Z_{Com}, for ''common''). When a representation's validity is totally uncertain, $B_{Rep} = 0$. The greater the certainty that a representation is correct, the more positive B_{Rep} goes and the greater the certainty of non-validity, the more negative B_{Rep} becomes.

The value of B_{Rep} modulates fear conditionability and expression. It also controls new representation creation and updating. Conditioning occurs only when B_{Rep} exceeds a value called B_{Old} (= 0.5) and increases linearly up to a value called B_{mxcnd} (= 1). Expressed fear is the firing rate of the amygdala neuron (A_f) multiplied by a function $S(B_{Rep})$. $S(B_{Rep}) = B_{Rep} / (B_{Rep} + 0.5)$; it is graphed in Figure S3. The currently active representation is updated if at the end of a session $B_{Rep} > B_{Add}$ (= 2; so that some incorrect updating can occur, this value corresponds to the low end of ''substantial,'' as opposed to ''very certain''). New representations are created when $B_{Rep} < B_{New}$ (= −3) and Z_{Cur} is at least Z_o (= 23). The values used for the parameters B_{Add}, B_{Old}, B_{mxcnd}, and Z_o and the form of $S(B_{Rep})$ were altered from those of the original paper to better reflect aspects of the current data, mainly the discovery that incorrect updating could occur.

QUANTIFICATION AND STATISTICAL ANALYSIS

See the main text and Experimental Design and Statistical Analysis for Each Experiment below for details and rationale of statistical tests as well as exact animal numbers for each experiment. All data were obtained from 3-4 trials with equal numbers of animals per trial. All trials showed similar results, so the results were combined in the final analysis. All data were analyzed using GraphPad Prism version 8. All data were confirmed as normally distributed using the Shapiro-Wilks test. Where appropriate, 1-Way or 2-Way ANOVAs were used with Tukey's post hoc comparisons, as Tukey's has the greatest power when comparisons are made between all groups. In Figure 1E, a one-sample t test comparing each PSI to a hypothetical value of 100% was used to assess extinction. Wherever the extinction or updating session was longer than 3-min, the averages were from the first 3-min of that session. ''n'' denotes the number of animals used in each group and is noted in each section of the results and in the following section. In all figures, histograms represent means of each group, with error bars representing the standard error (SE). Statistical significance was defined by $\alpha = 0.05$. Randomization was performed prior to experiment commencement and was structured to counterbalance the context, treatment, and chamber used.

EXPERIMENTAL DESIGN AND STATISTICAL ANALYSIS FOR EACH EXPERIMENT

Figures 1A and1B: Effect of PSI on context fear and differentiation

Aim.

This experiment aimed to determine if the completeness of context encoding, operationalized by PSI, affects generalization of fear to different contexts.

Design.

On day 1, mice were conditioned using either 0.25, 0.5, 1, 3, or 12-min PSI to alter the level of initial context learning. On day 2, mice from each PSI were re-exposed to either context A (conditioning context), B (a slightly different context), or C (a very different context) for 3-min without shock to test fear. This experiment used 15 groups (5 PSIs x 3 contexts), with n = 12/group (180 mice total).

Statistical analysis.

Analysis was via a 2-way ANOVA of PSI x context, with post hoc comparisons using Tukey's correction.

Figures 1C–1F: Effect of PSI on extinction

Aim.

This experiment aimed to determine if the completeness of context encoding, operationalized by PSI, affects extinction, defined as the reduction of conditioned fear following extensive non-reinforcement.

Design.

On day 1, mice were conditioned in context A using either 0.25, 0.5, 1, 3, or 12-min PSI to alter the level of initial context learning. On day 2, mice from each PSI were re-exposed to context A for 30-min without shock or received no re-exposure and were instead handled in the holding room as a control. On day 3, all mice were tested for long-term extinction in context A for 3-min without shock. This experiment used 10 groups (5 PSIs x 2 re-exposure conditions), with n = 12/group (120 mice total).

Statistical analysis.

Within-session extinction was analyzed using linear trend analysis. Between session (long-term extinction), which is more functionally relevant, was analyzed in two ways. The first was within-subjects. We converted the freezing of each mouse at test to a percentage of its freezing at the first 3 min of the extinction session on day 2 and then averaged them. We then performed a 1-Way ANOVA to confirm a PSI effect. Additionally, we performed a 1-sample t test on each PSI to determine whether it differed significantly to a hypothetical value of 100%, thus demonstrating extinction. The second analysis method was to compare freezing at test between mice that received 30-min extinction at day 2 and those that did not. This analysis was via a 2-Way ANOVA of PSI x re-exposure status, with post hoc comparisons using Tukey's correction.

Figures 2A–2D: Effect of re-exposure to the conditioning context on generalization

Aim.

These experiments aimed to determine if re-exposures to context A of varying durations could support more learning and thus improve generalization at each PSI.

Design.

On day 1, mice were conditioned using either 0.5, 3 or 12-min PSIs to alter the initial level of context learning. On day 2, mice from each PSI were re-exposed to context A (the conditioning context) for 0.5, 3, or 30-min or were not re-exposed to any context and were instead handled in the holding room as a control. On day 3, each of these groups was tested in either context A or context B for 3-min. No shock was delivered during either day 2 or 3. This experiment used 24 groups (3 PSIs x 4 re-exposure conditions at day 2 × 2 contexts at test on day 3), with n = 15-16/group (382 mice total).

Statistical analysis.

Data were analyzed separately at each PSI. At each PSI, Day 2 (re-exposure) and day 3 (test) were analyzed separately as we were primarily interested in the test freezing and did not expect re-exposure freezing to differ between relevant groups. In both cases, analysis of raw freezing was via 2-Way ANOVA of day 2 re-exposure duration x day 3 test context, with post hoc comparisons using Tukey's correction. See full ANOVAs for test sessions in Table S1. Freezing data for the day 2 re-exposure can be found in Figure S1A. Since it shows no differences between relevant groups, ANOVAs for day 2 are not reported.

Figures 2E and 2F: Effect of re-exposure to the conditioning context on long-term extinction

Aim.

This experiment aimed to determine if a 3-min "updating" session prior to extinction could rescue extinction deficits produced at short but not long PSIs.

Design.

Mice were conditioned using 0.5 or 12-min PSIs on day 1 and tested on day 4. On intervening days, they either (i) received no re-exposure and were instead handled in the holding room as a control, (ii) received a long extinction session on day 3, or (iii) received an "updating" session on day 2 followed by an extinction session on day 3. The duration of the updating session was 3-min, which based on previous experiments (Figures 2A–2D) caused enough learning to alleviate generalization. Further, the duration of the extinction session was set at 33-min in group ii and 30-min in group iii so that the total amount of unreinforced time prior to the

day 4 test session would be the same between these groups. No shock was delivered during any re-exposure. This experiment had 6 groups (2 PSIs x 3 RE conditions), with n = 12/group (72 total mice). See all session freezing data in Figure S1B.

Statistical analysis.

Each PSI was analyzed separately. In each PSI, analysis was of the raw freezing at test on day 4. Analysis was via 1-Way ANOVA of re-exposure history for each PSI with post hoc comparisons using Tukey's correction.

Figures 2G–2J: Effect of exposure to a slightly different context on fear and generalization

Aim.

These experiments aimed to determine if re-exposure to context B of varying durations could support more learning and erroneous updating and thus cause memory distortion at each PSI.

Design.

On day 1, mice were conditioned using either 0.5, 3 or 12-min PSIs to alter the initial level of context learning. On day 2, mice from each PSI were exposed to context B (a context slightly different to A, the conditioning context) for 0.5, 3, or 30-min or were not re-exposed to any context and were instead handled in the holding room as a control. On day 3, each of these groups was tested in context A or B for 3-min. No shock was delivered during day 2 or 3. This experiment used 24 groups (3 PSIs x 4 re-exposure conditions at day 2 × 2 contexts at test on day 3), with n = 12/group (288 mice total).

Statistical analysis.

Data were analyzed separately at each PSI. At each PSI, Day 2 (re-exposure) and day 3 (test) were analyzed separately as we were primarily interested in the test freezing and did not expect re-exposure freezing to differ between relevant groups. In both cases, analysis was via 2-Way ANOVA of day 2 re-exposure duration x day 3 test context, with post hoc comparisons using Tukey's correction. See full ANOVAs in Table S2. Freezing data for the day 2 B-exposure can be found in Figure S1C. Since it shows no differences between relevant groups, ANOVAs for day 2 are not reported. Also see Figure S2.

Figure 3: The extent of initial context learning determines memory stability after recall

Aim.

These experiments aimed to determine whether the alleviation of generalization produced by re-exposure to the conditioning context after sub-optimal PSIs was correlated with the presence of reconsolidation.

Design.

On day 1, mice were conditioned using either 0.5, 3 or 12-min PSIs to alter the initial level of context learning. On day 2, mice from each PSI were either re-exposed to context A (the conditioning context) for 3 or 30-min or were not re-exposed to any context as a control. Mice then either received saline vehicle or anisomycin immediately after the re-exposure session. On day 3 and 24, each of these groups was tested in context A for 3-min. No shock was delivered during day 2, 3 or 24. This experiment used 18 groups (3 PSIs x 3 re-exposure conditions at day 2 × 2 treatments), with n = 12/group except 0.5-min PSI with 30-min RE and 12-min PSI with 3 or 30-min RE, which had n = 10/ group (210 mice total).

Statistical analysis.

Each subfigure was analyzed separately using a 2-Way RM ANOVA of treatment x test day with post hoc tests using Tukey's correction. See Table S3 for full ANOVA results.

Figure 4B: BDNF inhibition impairs long-term fear after different PSIs

Aim.

This experiment aimed to determine if BDNF antisense (AS) impairs memory consolidation when infused before conditioning at different PSIs.

Design.

On Day 1, cannulated mice were intrahippocampally infused with BDNF missense (MS) or AS 90-min before conditioning using 0.5, 3- or 12-min PSIs to alter the level of initial context learning. This timing was chosen based on previous studies showing an effect of AS on consolidation [55, 56]. On day 2 and 8, mice were re-exposed to context A for 3-min without shock. There were 6 groups (3 PSIs x 2 treatments) with n's as follows: 0.5-min PSI, MS: n = 11, AS: n = 11; 3-min PSI, MS: n = 10, AS: n = 10; 12-min PSI, MS: n = 9, AS: n = 11 (62 mice total).

Statistical analysis.

2-way RM ANOVA of test day x treatment per PSI with Post hoc tests using Tukey's correction. See Table S4 for full ANOVA results.

Figures 4C–4F: Effect of intrahippocampal inhibition of protein degradation or BDNF on differentiation improvement and distortion after re-exposure to the conditioning context or a similar context

Aim.

These experiments aimed to determine if the behavioral improvements and distortions that occurred after short PSIs and re-exposure to context A or B respectively were mediated by BDNF-dependent consolidation or protein-degradation-dependent reconsolidation.

Design.

On day 1, cannulated mice were conditioned using the 0.5-min PSI to produce poorly formed memory. On day 2, they were re-exposed to context A (Figures 4C and 4D) or B (Figures 4E and 4F) for 30-min. 90-min before or immediately thereafter, they received

intrahippocampal infusion of BDNF missense/antisense or β-lac/vehicle, respectively. These timings were chosen based on previous studies showing effects of these drugs on consolidation/reconsolidation [55–57]. On day 3, each of these groups was then either re-exposed to context A or to B for 3-min. No shock was delivered on day 2 or 3. For each subfigure there were 4 groups (2 treatments x 2 test contexts on day 3) with n = 9-12/group (Figure 4C: MS tested in A, n = 10, MS tested in B, n = 10, AS tested in A, n = 10, AS tested in B, n = 9; Figure 4D: VEH tested in A, n = 10, VEH tested in B, n = 9, β-lac tested in A, n = 9, β-lac tested in B, n = 12; Figure 4E: MS tested in A, n = 9, MS tested in B, n = 9, AS tested in A, n = 9, AS tested in B, n = 9; Figure 4F: VEH tested in A, n = 10, VEH tested in B, n = 11, β-lac tested in A, n = 10, β-lac tested in B, n = 11).

Statistical analysis.

Each subfigure was analyzed separately. Since we were primarily interested in fear at the final test and the effect of drug on fear in each context, we analyzed the freezing on day 2 and 3 separately. On each day, analysis was via a 2-Way ANOVA of treatment x test context with post hoc comparisons using Tukey's correction. See Table S5 for full ANOVAs of day 3 data. Since there was no difference between groups on day 2, and this was borne out in the statistics, the latter are not reported.