Reclassifying the Unique Inhibitory Properties of Social Support Figures: A Roadmap for Exploring Prepared Fear Suppression

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ABSTRACT

Recent work has revealed that social support cues are powerful inhibitors of the fear response. They are endowed with a unique combination of inhibitory properties, enabling them to both inhibit fear in the short term and reduce fear in the long term. While these findings had previously been thought to suggest that social support cues belong to a category of prepared safety stimuli, mounting evidence clearly shows that the mechanisms underlying safety signaling cannot account for the unique effects of social support cues. Here, we propose a reclassification of social support cues as members of a prepared fear suppressor category. We present an argument for the prepared fear suppressor classification, discuss potential mechanisms underlying the unique effects of prepared fear suppressors, and outline next steps to build an understanding of this category and its clinical implications. This review is meant to serve as a roadmap for exploring this novel category of prepared fear suppressors, whose never-before-seen range of inhibitory effects makes them an important and impactful discovery with implications for both fear learning theory and clinical application.

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Although there is little doubt that loved ones provide us with a powerful sense of protection, only recently have investigations begun to explore the impact of close social ties on the ways in which fears are learned. Specifically, images of social support figures, one type of social support cue, have been shown to not only inhibit the fear response while present but also lead to lasting fear inhibition even after being removed, a combination of effects never before seen in a fear inhibitor (1–3). Initially, these properties were interpreted to indicate that these social support cues belonged in a category of prepared safety stimuli, cues that have historically signaled safety and are thus less easily associated with fear (1,4). However, given increasing evidence that the mechanisms underlying safety signaling cannot entirely explain the effects of social support cues (2,3), a revision of this classification is required.

We suggest placing social support cues in a new category of prepared fear suppressors—a novel classification that encompasses the unique inhibitory properties found for images of social support figures. Importantly, by unyoking social support cues from the safety label, we hope to reframe understanding of social support cues or other undiscovered prepared fear suppressors as a new class of cues that are distinct from other known inhibitors, such as safety signals (5–8), owing to their ability to uniquely mitigate both short-term and long-term fear. Prepared fear suppressors represent an important advance in the fear conditioning literature that may have substantial implications for clinical practice, such as reducing the harmful fears associated with disorders such as anxiety or posttraumatic stress disorder.

This review details the ways in which social support cues act as prepared fear suppressors and outlines a roadmap for exploring this new category. First, we review the unique properties of social support cues, highlighting where their effects diverge from those of known inhibitors. Then, we propose a potential model of the origins and pathways that lead to these effects. Finally, we identify next steps to test this model and more thoroughly probe the prepared fear suppression category.

REVIEW OF FEAR INHIBITION

When a cue becomes associated with a certain outcome, the presentation of the cue comes to elicit a response in preparation for that outcome, a process described as excitation (6). Inhibition is the contrasting process by which these excitatory responses are suppressed (6–8). In the case of fear, inhibition would be measured as a suppression of the fear response typically elicited by a certain cue, context, or event.

To highlight the unique inhibitory properties of social support cues during fear learning, it is important to place their effects in context. Therefore, we will first review processes that lead to short-term fear inhibition, the ability of certain cues to lead to acute suppression of fear responding while they are present during fear learning. Next, we will review processes that lead to long-term fear reduction, the ability of certain cues to lead to persistent suppression of fear responding after their removal. The ability of social support cues to successfully engage both of these processes is unique and may rely on discrete mechanisms. Therefore, for each section we offer a

separate interpretation of the divergent effects of social support cues and potential underlying mechanisms.

Short-term Fear Inhibition

Safety signaling is perhaps the most widely known type of short-term fear inhibition. As opposed to the colloquial meaning of safety, which implies comfort or security, here we are referring to the Pavlovian definition of safety, or the predicted absence of a specific aversive outcome (7,8). Thus, a safety signal is a cue that has been learned to indicate this absence and is therefore able to inhibit fear by reducing the predicted occurrence of that outcome. The most powerful type of safety signals are able to inhibit fear during the retardation-of-acquisition test, in which a cue resists becoming associated with fear during a fear acquisition procedure, and the summation test, in which a cue impedes the fear response elicited by another already feared cue (7). However, while safety signals are robust inhibitors, they are limited in that they must be learned, can only perform their inhibitory functions while present, and can only do so in the specific context and for the specific aversive events with which they have been trained (7,8).

Interestingly, safety signals are not the only cues that are able to pass the retardation-of-acquisition and summation tests. Appetitive cues, cues that signal the occurrence of a reward (e.g., a light paired with food), are also able to resist becoming associated with fear and inhibit the fear response (9,10). Appetitive and aversive systems are thought to work in opposition to one another (11–14), enabling cues that signal expected reward to compete with, and reduce, aversive expectations, reducing aversive processes while they are present. However, whereas appetitive cues are not limited to inhibiting fear for specific aversive events as safety signals are, similar to safety signals, they also require learning (to be associated with reward) and may only inhibit fear in the specific contexts in which they were trained (15).

Social support cues, or reminders of those we feel most supported by, also have inhibitory effects during fear learning (see Table 1 for comparison of short-term fear inhibition effects). Specifically, findings from our group have shown that similar to safety signals and appetitive cues, images of social support figures are less easily associated with fear, passing the retardation-of-acquisition test (1), and inhibit the fear response elicited by already feared cues, passing the summation test (1,2). Moreover, other types of reminders have similar effects during fear learning, suggesting that social support cues may take many forms. Thus, mental imagery of close others reduces fear acquisition in humans (16) and the presence of conspecifics reduces conditional fear responding and enhances fear extinction in animals (17–22). Yet, none of these social support cues share the limitations of the other known inhibitors discussed here. Specifically, they require no specific Pavlovian safety or appetitive training to enact these effects, and they are able to do so for novel aversive events in novel contexts (1,2,16–22) (while effects remained consistent across studies, the human examinations of these effects used small sample sizes, so more work is needed).

These divergent properties of social support cues may be based on their relevance for survival and the rich relationship history that is experienced with a supportive other. Indeed, social support figures provide protection, security, and resources—all critical for mammalian survival—and a strong body of research has demonstrated that social bonds afford benefits in the face of threat by reducing physiological and psychological stress in a process known as social buffering (see the Supplement for a discussion of this phenomenon). Importantly, although social buffering can be used to describe any threat-reducing effects of social ties (e.g., reduced pain/stress/fear/cortisol), here, we focus on the mechanisms underlying the ability of social support cues to specifically affect fear learning processes, as has been demonstrated in animals (17–22) and humans (1–3,16). In this fear learning context, instead of lessening threat expectation by signaling the absence of threat, as safety signals do, or competing with threat expectation by signaling expected reward, as appetitive cues do, social support cues may simply signal access to resources and care should a harmful event occur, increasing perceptions of one's ability to cope with the event and buffering against its expected impact without altering the expectation of its occurrence. Thus, it may be that social support cues inhibit fear by altering perceptions of the ability to cope with an aversive event, devaluing the anticipated impact or aversiveness of the event but leaving expectations of its occurrence intact (discussed below).

Long-term Fear Reduction

Multiple processes influence fear learning outcomes and lead to lasting reductions in fear responding, including those that prevent acquisition of new fear associations and lessen or weaken already formed fear associations.

There are several processes that can prevent fear from being associated with a cue. For example, blocking, when a cue previously associated with an aversive outcome is co-presented with a novel cue during fear acquisition, prevents fear from becoming associated with the novel cue. This occurs because there is no surprise when the aversive outcome occurs, as it is perfectly predicted by the previously learned fear cue, and it is this surprise that is needed to update predictions and drive the formation of new fear associations (8,23–25). This process is notable, for it engages underlying neurobiological systems (i.e., opioid system) (23) in the same patterns as social support processes (26), providing insight into the impact of social support cues on fear learning.

There are also numerous processes that can lessen or weaken already formed fear associations, such as fear extinction, which involves repeated presentations of already feared cues in the absence of the aversive outcomes with which they are associated, leading to new learning that these cues do not always predict threat (8,27). This process is notable because it forms the basis for exposure therapies, the most effective interventions to treat fear-related disorders to date (28). Thus, fear extinction has not only been the target of tests of social support cue effects but is highly relevant for translating these effects from learning theory to clinical practice (see the Supplement for discussion of other long-term fear reduction processes).

Although known inhibitors (safety signals, appetitive cues) elicit short-term fear inhibition while present, they have harmful

Table 1. Comparison of Short-term Fear Inhibition and Long-term Fear Reduction Effects, and Their Underlying Mechanisms, Across Known Inhibitors, Exciters, and Prepared Fear Suppressors

Type of Cue		Training Required	Short-term Fear Inhibition		Long-term Fear Reduction		Method of Action When Present During Fear Learning
			Retardation	Summation	Reduced Acquisition	Enhanced Extinction	
Known Inhibitors	Safety signal	Yes	Yes Conditioned inhibition (7)[a]	Yes Conditioned inhibition (7)[a]	No Superconditioning (30)	No Protection against extinction (7,29)	Indicates absence of aversive outcome, increasing aversive prediction error during acquisition and reducing aversive prediction error during extinction
	Appetitive conditioned stimulus	Yes	Yes Appetitive-aversive interactions (13,14)[a]	Yes Appetitive-aversive interactions (13,14)[a]	No Superconditioning (10,31)	No Protection against extinction (10)	Increases appetitive expectation, increasing aversive prediction error during acquisition and reducing aversive prediction error during extinction
Known Exciter	Concurrent exciter	Yes	Yes Fear association already fully formed (8)[a]	No Fear response is increased due to additional fear cue (8)	Yes Blocking (23)[a]	Yes Deepened extinction (40,41)[a]	Increases aversive expectation, decreasing aversive prediction error during acquisition and increasing aversive prediction error during extinction
Prepared Fear Suppressors[a]	Social support cues[a]	No[a]	Yes (1)[a]	Yes (1,2)[a]	Yes (3)[a]	Yes (1,2)[a]	Simultaneous survival-relevant pathways
	Physical warmth[a]	No[a]	Yes (53)[a]	Yes (53)[a]	Untested[a]	Yes (53)[a]	1. Short-term fear inhibition: devalues aversiveness of expected outcome but does not change aversive expectation. 2. Long-term fear reduction: underlying opioid mechanisms decrease aversive prediction error during acquisition and increase aversive prediction error during extinction[a]

Numbers in parentheses refer to supporting references for each type of demonstrated outcome or process.
[a]The effects of prepared fear suppressors and other cases in which these same outcomes occur.

effects on long-term fear reduction after their removal. Specifically, the very source of their inhibitory properties—the ability to lessen expectation that an aversive event will occur—results in changes to the calculations that drive fear associations and prevents the reduction of long-term fear in two ways (8,23). First, if these known inhibitors are present during fear extinction, when an already feared cue is presented in the absence of an aversive outcome, lowered aversive expectation prevents new learning, such that no new association between the feared cue and absence of shock is formed—a process known as protection from extinction (7,10,29). Second, if these known inhibitors are present during fear acquisition, when a separate conditional cue is being paired with an aversive outcome (i.e., shock), lowered aversive expectation results in more surprise when the shock does occur, leading it to become even more robustly associated with the conditional cue—a process known as superconditioning (9,10,30,31). Thus, known inhibitors not only reduce fear extinction but also enhance fear acquisition. In each case, when the inhibitor is removed, higher levels of fear responding occur than if either acquisition or extinction had been conducted in isolation, leading to increases, not reductions, in fear.

Interestingly, social support cues do not share these long-term effects (Table 1). When social support cues are paired with conditional fear cues during fear acquisition or already feared cues during fear extinction, an unexpected pattern of effects emerges—social support cues not only inhibit fear in the short term while they are present but also augment long-term fear reduction even after they are removed (1–3,16,21,22). Specifically, in the work from our group, when images of close others were co-presented with conditional fear cues during fear acquisition, fear associations did not form between conditional fear cues and aversive outcomes, such that conditional fear cues did not elicit a fear response even after the social support cue is removed (reduced acquisition) (3), and recent work from another team has shown similar effects with mental imagery (16). In additional work from our group, when images of social support figures (vs. neutral or stranger images) were paired with already feared cues during fear extinction, reductions in fear occurred to a greater degree, such that no fear response occurred following their removal or even 24 hours after removal during a procedure designed to reinstate fear (enhanced extinction) (1,2), an effect also found in animals when extinction is conducted in the presence of conspecifics (21,22). This ability to elicit more robust extinction of fear is of particular interest. While fear extinction is one of the most effective methods of reducing fear, its effects are often only temporary, with return of fear occurring over time (32). This limitation extends to exposure therapies that are based on extinction processes, contributing to the common occurrence of relapse in patients with fear-related disorders (28). Therefore, the potential of social support cues to enhance fear extinction and reduce return of fear in the clinical context is of major significance.

While there is not yet enough information available to precisely determine the mechanism underlying these effects, information gathered thus far suggests several possibilities. One possibility is that social support figures are processed as primary rewards, not signals of safety. However, while primary rewards can weaken already held fears in a process called counterconditioning (see the Supplement for discussion), as with fear extinction, return of fear remains a problem, and the presence of primary rewards does not prevent fear acquisition (9,31). Thus, this mechanism would not support the ability of social support cues to lead to long-term fear reduction (33). Hence, social support cues cannot be entirely placed in the safety category or the primary reward category, suggesting a more nuanced explanation.

As with their short-term fear-inhibiting properties, the divergent long-term fear-reducing properties of social support cues may be rooted in the survival-enhancing role played by close others throughout evolution, such that the need to maintain social bonds may have co-opted other neurobiological systems already in place. Notably, these social connection maintenance processes appear to rely heavily on the opioid system, which primarily evolved to manage pain in response to physical injury and thus plays a central role in the fear learning processes that evolved to predict and prepare for potential pain and harm (23,34). This system may have later been co-opted by the social attachment system, which ensures social connection by using the same opioid processes to signal the pain of social disconnection and the pleasure of social connection (26,35–37). Here, we will focus on this overlap and the ability of social support cues to trigger endogenous opioid release (other relevant overlaps are rooted in the dopaminergic, hypothalamic-pituitary-adrenal axis, and oxytocin systems, though evidence for these mechanisms is mixed: see the Supplement).

Opioid activity plays a critical role in the error correction calculations that support fear acquisition and extinction. Released when an aversive event is expected, opioids provide analgesia that reduces the aversiveness (pain) of the event when it occurs, generating the negative feedback (expected outcome minus experienced outcome) that drives expectation change (8,23,38). As such, increasing opioid activity leads to reduced acquisition (blocking) (39) and enhanced extinction (deepened extinction) (40,41), whereas blocking opioid activity leads to enhanced acquisition and reduced extinction (40,42–44). Hence, while social support–driven opioid release plays a reinforcing and buffering role with regard to social connection, the increase in opioids may also have the effect of mimicking fear expectation–driven analgesia (social support cues reduce pain) (18,19), ultimately influencing error correction calculations.

Substantiating this view, the effects of social support cues mirror those of other types of cues that increase opioid release. Specifically, the presence of concurrent exciters, already feared cues that increase expectation of an aversive outcome and the corresponding expectation-driven opioid release, prevent fear acquisition and enhance fear extinction (23,40,41), just like social support cues. However, while concurrent exciters trigger opioid release by increasing aversive expectation and fear, social support cues trigger opioid release by signaling connectedness—a far more pleasant experience (Table 1). It is notable that safety signals have the opposite effect, reducing opioid analgesia during fear learning (45), providing further evidence that social support cues are not engaging safety mechanisms. Indeed, social support cues may in fact mimic fear-driven opioid release during fear learning,
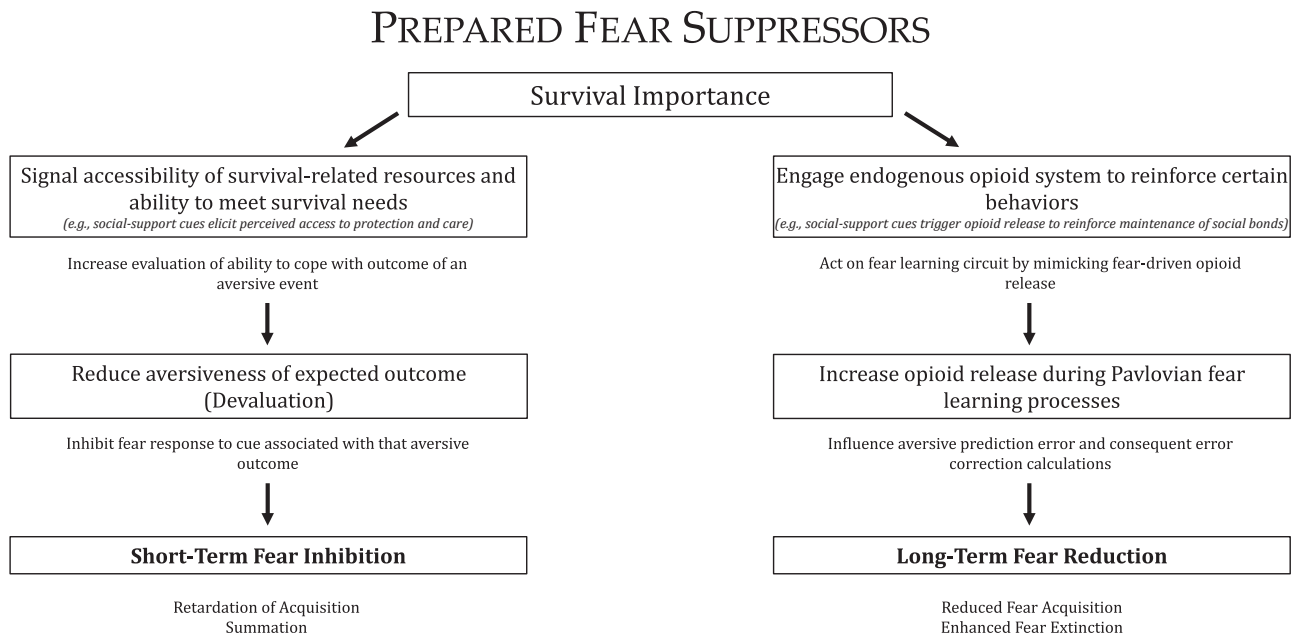
PREPARED FEAR SUPPRESSORS

Figure 1. A proposed model of the two-pathway model for prepared fear suppression. This hypothesized model depicts the two pathways by which prepared fear suppressors are able to simultaneously achieve inhibition of fear in the short term, described here as short-term fear inhibition, and reduction of fear in the long term, described here as long-term fear reduction. In the case of social support cues, in particular, the central role of close others in providing protection and care: 1) enables reminders of these individuals to reduce the aversive value of the outcome associated with a fear cue, resulting in retardation of acquisition and summation; and 2) leads social processes to co-opt the endogenous opioid system to monitor and maintain social bonds, disrupting the error correction calculations that drive fear learning and resulting in reduced fear acquisition and enhanced fear extinction.

resulting in reduced fear acquisition and enhanced fear extinction. Although only hypothetical at this point, this mechanism would fully explain the long-term fear-reducing effects of social support cues.

It is important to note, however, that potential mechanisms for the long-term fear-reducing effects of social support cues (e.g., opioids) cannot be used to explain their short-term fear-inhibiting abilities. Indeed, cues that increase release of opioids (concurrent exciters) are unable to inhibit short-term fear responding when they are present (and therefore fail the summation test), as social support cues do. Thus, an opioid argument cannot fully explain the range of social support cue effects.

PREPARED FEAR SUPPRESSION MODEL

We believe that a new classification, prepared fear suppressor, is required to synthesize the before-unseen combination of short-term fear inhibition and long-term fear reduction effects displayed by social support cues. This novel category will facilitate recognition of other stimuli that have this same pattern of effects, which may have been previously overlooked because they did not fall into the traditional categories of inhibitors. Here, we use evidence from explorations of social support cues to outline this concept of prepared fear suppression, but anticipate that other stimuli with similar features, specifically, those that are highly relevant for survival and resources, will also fall into this category. Thus, we put forward that the importance of social ties for survival has enabled social support cues to influence fear via two separate pathways,

one leading to short-term fear inhibition and one leading to long-term fear reduction (Figure 1).

We propose that short-term fear inhibition is achieved by the ability of social support cues to reduce the aversive value, not expected occurrence, of an outcome by signaling access to protection and resources, essentially reducing the perceived harmful impact of the event. This is best described as the process of devaluation—when the value of the outcome associated with a cue is altered, responses to that cue will reflect this new value (e.g., if a disliked flavor is associated with a light, animals will avoid the light, but if the flavor is trained to become preferred, the animal will approach the light) (46), without changing the degree to which the outcome is predicted to occur. In other words, the presence of social support cues reduces the aversive value of the outcome, reducing its perceived negative meaning and anticipated impact.

Because this route to short-term fear inhibition does not alter the expectation that an event will occur, it does not require specific training and is easily transferred from one type of event to another (and, importantly, leaves fear expectations intact for simultaneous long-term fear reduction). It is possible that this pathway is, in part, designed to meet adaptive needs. Specifically, by less easily becoming associated with fear (retardation of acquisition), social support figures maintain their affiliative and protective role even following threatening events. Moreover, by inhibiting the fear response while present (summation), the presence of social support figures facilitates other necessary processes, such as exploration, healing, and mating. Animal work has shown that in early developmental stages, maintaining access to maternal care and social

connection is critical (47), such that maternal presence reduces fear learning and aversive responding (48–51). This enables caregivers to engage in negative experiences required for survival (e.g., roughly moving a pup out of danger) without their young developing aversive associations to them. Similarly, the human attachment literature emphasizes the role of caregivers as a secure base that promotes learning and exploration in young children (52). Therefore, it is possible that the short-term fear inhibition pathway is a carryover of maternal/caregiver relationship maintenance processes into adulthood that has extended to include other types of close others.

We propose that long-term fear reduction is achieved by the ability of social support cues to influence the opioid processes that drive fear learning and ultimately reduce fear acquisition and extinction. In contrast to the short-term fear inhibition pathway, which appears to directly serve an adaptive purpose, it is less clear whether the long-term fear reduction pathway is adaptive or a secondary by-product of the opioid system— critical for pain and fear processing—being co-opted for the purposes of maintaining social attachment. Regardless, the opioid pathways engaged to reinforce close relationships overlap with those that play a central role in fear learning processes, and this point of intersection provides a window through which social support cues are able to influence fear learning outcomes.

Importantly, the ability of social support cues to engage short-term fear inhibition and long-term fear reduction appears to be prepared, in the sense that no specific Pavlovian training (i.e., no learning regarding the relationship between a cue and a certain outcome) (7,8) is required, and these functions can be applied to various and novel outcomes and contexts. This is not to say that no prior experience or learning is involved. Indeed, social support figures stem from a range of relationships (not just parental), and information about them certainly must have been acquired. Thus, we are not implying that individuals are born with specific social support figures that are prepared to inhibit fear. Instead, we suggest that individuals have a schema, which dictates that close others who meet certain criteria are able to protect against aversive experiences. We have previously described this as resulting in a social support figure placeholder, into which a select group of close others are able to fit (4). However, who fits into this placeholder and how and when it forms have yet to be tested.

Further support for the idea that prepared fear suppressors are critical for survival comes from evidence that similar to social support cues, physical warmth, which is critical for mammalian survival, also results in short-term fear inhibition and long-term fear reduction (53). As discussed above, this combination of effects is unique in fear learning, suggesting that the corresponding effects of physical warmth and social support cues are not random. Instead, based on their shared historical importance for survival, not to mention their shared engagement of the opioid system to reinforce their occurrence (34–37), these corresponding effects likely reflect prepared fear suppression. Although questions remain as to whether this role is innate or acquired through early learning (similar to questions regarding the innate vs. learned nature of prepared fear stimuli) (54), it appears to be rooted in survival relevance. Thus, prepared fear suppressors may be a proxy for protection and

relief and, in the course of engaging their own maintenance systems, may inadvertently interfere with fear learning processes, allowing them to both inhibit and reduce fear.

NEXT STEPS

Because of the novelty of the prepared fear suppressor category, there are more questions than answers as well as exciting new directions to be pursued. Here, we outline three that warrant immediate attention.

First, it is crucial to examine the route by which social support figures become prepared fear suppressors. Specifically, what determines whether a close other is able to fill the social support figure placeholder? Examining whether ambivalent close others, who cause both pleasure and pain, serve as prepared fear suppressors might illuminate the degree and quality of support history required. Next, is this placeholder innate or acquired? Examining whether individuals who experienced abuse from primary caregivers still show evidence of using social support cues as prepared fear suppressors might provide insight into the developed versus innate nature of the social support placeholder. If these abused individuals do not display prepared fear suppression effects, even with cues of other nonabusive supportive close others, it would suggest that the placeholder is shaped by early-life experiences. However, if these individuals continue to display prepared fear suppression effects, it would suggest that the placeholder was not affected by early caregiver trauma. Animal work suggests that abusive caregivers are still preferred (55), yet early-life abuse leads to differential neural and psychological development (56) and reduced social buffering in the face of threat (57), raising questions about how this early-life experience might affect the social support placeholder.

Next, it is important to examine the mechanisms supporting the short-term fear inhibition and long-term fear reduction pathways. For short-term fear inhibition, this includes exploring whether social support cues inhibit fear not by reducing expectation that an aversive event will occur but by reducing the anticipated harmful impact of the aversive event. In addition, evaluation is needed of whether the overlapping use of the opioid system by both social support and fear learning processes provides a point of intersection at which social support cues are able to influence long-term fear reduction outcomes.

Finally, given the relevance of this work for treating fear-related disorders, it is imperative to examine the boundaries of these effects in clinical populations. This is perhaps the most important next step because the demonstrated effects of social support cues hint that they may be especially useful for augmenting exposure therapy treatments. Even with their higher levels of success, exposure therapies are aversive to complete, leading to dropout and relapse (27). Thus, by both inhibiting fear in the moment and reducing fear in the long term, social support cues may be uniquely poised to improve treatment compliance and treatment outcomes. For example, viewing an image of a close other during therapy might not only reduce the aversiveness of completing exposure procedures, reducing dropout but also strengthen extinction processes, reducing relapse. Thus, the inclusion of social

support cues during exposure therapies may represent a low-cost, noninvasive, and easy-to-implement tool that can be added to treatments. Yet, thus far, the effects of social support cues have only been demonstrated in healthy individuals. Given the demonstrated differences in fear learning in individuals with anxiety disorders (58), a test of whether social support cues remain able to both inhibit and reduce fear in those diagnosed with anxiety is necessary before beginning to consider how social support cues might augment current treatments.

CONCLUSIONS

Mounting evidence shows that social support cues are not simply distinct safety or appetitive cues but rather an entirely new category of cues that are prepared to suppress the fear response. Whatever their underlying mechanisms, these prepared fear suppressors have a never-before-seen range of inhibitory effects, making them an important and impactful discovery with implications for fear learning theory and clinical application.

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REFERENCES

1. Hornstein EA, Fanselow MS, Eisenberger NI (2016): A safe haven: Investigating social-support figures as prepared safety stimuli. Psychol Sci 27:1051–1060.
2. Hornstein EA, Haltom KEB, Shirole K, Eisenberger NI (2018): A unique safety signal: Social-support figures enhance rather than protect from fear extinction. Clin Psychol Sci 6:407–415.
3. Hornstein EA, Eisenberger NI (2017): Unpacking the buffering effect of social support figures: Social support attenuates fear acquisition. PLoS One 12:e0175891.
4. Hornstein EA, Eisenberger NI (2018): A social safety net: Developing a model of social-support figures as prepared safety stimuli. Curr Dir Psychol Sci 27:25–31.
5. LoLordo VM (1979): Selective associations. In: Dickinson A, Boakes RA, editors. Mechanisms of Learning and Motivation: A Memorial Volume to Jerzy Konorski. New York: Psychology Press, 367–398.
6. Pavlov IP (1927): Conditioned Reflexes [Anrep GV, trans]. London: Oxford.
7. Rescorla RA (1969): Pavlovian conditioned inhibition. Psychol Bull 72:77–94.
8. Rescorla RA, Wagner AR (1972): A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. In: Black AH, Prokasy WF, editors. Classical Conditioning II: Current Research and Theory. New York: Appleton-Century-Crofts, 64–99.
9. Nasser HM, McNally GP (2012): Appetitive–aversive interactions in Pavlovian fear conditioning. Behav Neurosci 126:404–422.
10. Leung HT, Holmes NM, Westbrook RF (2016): An appetitive conditioned stimulus enhances fear acquisition and impairs fear extinction. Learn Mem 23:113–120.
11. Konorski J (1967): Integrative Activity of the Brain; an Interdisciplinary Approach. Chicago: The University of Chicago Press.
12. Dickinson A, Dearing MF (1979): Appetitive-aversive interactions and inhibitory processes. In: Dickinson A, Boakes RA, editors. Mechanisms of Learning and Motivation: A Memorial Volume to Jerzy Konorski. New York: Psychology Press, 203–231.
13. Dickinson A, Pearce JM (1977): Inhibitory interactions between appetitive and aversive stimuli. Psychol Bull 84:690–711.
14. Peck CA, Bouton ME (1990): Context and performance in aversive-to-appetitive and appetitive-to-aversive transfer. Learn Motiv 21:1–31.
15. Bouton ME, Sunsay C (2001): Contextual control of appetitive conditioning: Influence of a contextual stimulus generated by a partial reinforcement procedure. Q J Exp Psychol B 54:109–125.
16. Toumbelekis M, Liddell BJ, Bryant RA (2018): Thinking of attachment figures blocks differential fear conditioning. Soc Cogn Affect Neurosci 13:989–994.
17. Kiyokawa Y, Takeuchi Y, Nishihara M, Mori Y (2009): Main olfactory system mediates social buffering of conditioned fear responses in male rats. Eur J Neurosci 29:777–785.
18. Kiyokawa Y, Takeuchi Y, Mori Y (2007): Two types of social buffering differentially mitigate conditioned fear responses. Eur J Neurosci 26:3606–3613.
19. Kiyokawa Y, Takeuchi Y (2017): Social buffering ameliorates conditioned fear responses in the presence of an auditory conditioned stimulus. Physiol Behav 168:34–40.
20. Ishii A, Kiyokawa Y, Takeuchi Y, Mori Y (2016): Social buffering ameliorates conditioned fear responses in female rats. Horm Behav 81:53–58.
21. Mikami K, Kiyokawa Y, Ishii A, Takeuchi Y (2020): Social buffering enhances extinction of conditioned fear responses by reducing corticosterone levels in male rats. Horm Behav 118:104654.
22. Mikami K, Kiyokawa Y, Takeuchi Y, Mori Y (2016): Social buffering enhances extinction of conditioned fear responses in male rats. Physiol Behav 163:123–128.
23. Fanselow MS (1998): Pavlovian conditioning, negative feedback, and blocking: Mechanisms that regulate association formation. Neuron 20:625–627.
24. Kamin LJ (1968): "Attention-like" processes in classical conditioning. In: Jones M, editor. Miami Symposium on the Prediction of Behavior: Aversive Stimulation. Miami: University of Miami Press.
25. Kamin LJ (1969): Predictability, surprise, attention, and conditioning. In: Campbell B, Church R, editors. Punishment: A Symposium. New York: Appleton-Century-Crofts.
26. Nelson EE, Panksepp J (1998): Brain substrates of infant–mother attachment: Contributions of opioids, oxytocin, and norepinephrine. Neurosci Biobehav Rev 22:437–452.
27. Bouton ME (2004): Context and behavioral processes in extinction. Learn Mem 11:485–494.
28. Craske MG, Hermans D, Vervliet B (2018): State-of-the-art and future directions for extinction as a translational model for fear and anxiety. Philos Trans R Soc Lond B Biol Sci 373:20170025.
29. Lovibond PF, Davis NR, O'Flaherty AS (2000): Protection from extinction in human fear conditioning. Behav Res Ther 38:967–983.
30. Rescorla RA (1971): Variation in the effectiveness of reinforcement and nonreinforcement following prior inhibitory conditioning. Learn Motiv 2:113–123.
31. Dickinson A (1976): Appetitive-aversion interactions: Facilitation of aversive conditioning by prior appetitive training in the rat. Anim Learn Behav 4:416–420.
32. Vervliet B, Craske MG, Hermans D (2013): Fear extinction and relapse: State of the art. Annu Rev Clin Psychol 9:215–248.
33. van Dis EAM, Hagenaars MA, Bockting CLH, Engelhard IM (2019): Reducing negative stimulus valence does not attenuate the return of

fear: Two counterconditioning experiments. Behav Res Ther 120:103416.

34. Weber M, McNally GP, Richardson R (2006): Opioid receptors regulate retrieval of infant fear memories: Effects of naloxone on infantile amnesia. Behav Neurosci 120:702–709.

35. Atzil S, Touroutoglou A, Rudy T, Salcedo S, Feldman R, Hooker JM, et al. (2017): Dopamine in the medial amygdala network mediates human bonding. Proc Natl Acad Sci U S A 114:2361–2366.

36. Panksepp J, Nelson E, Bekkedal M (1997): Brain systems for the mediation of social separation-distress and social-reward. Evolutionary antecedents and neuropeptide intermediaries. Ann N Y Acad Sci 807:78–100.

37. Young LJ, Wang Z (2004): The neurobiology of pair bonding. Nat Neurosci 7:1048–1054.

38. Bolles RC, Fanselow MS (1980): A perceptual-defensive-recuperative model of fear and pain. Behav Brain Sci 3:291–301.

39. Fanselow MS, Bolles RC (1979): Triggering of the endorphin analgesic reaction by a cue previously associated with shock: Reversal by naloxone. Bull Psychon Soc 14:88–90.

40. McNally GP, Pigg M, Weidemann G (2004): Blocking, unblocking, and overexpectation of fear: A role for opioid receptors in the regulation of Pavlovian association formation. Behav Neurosci 118:111–120.

41. Rescorla RA (2000): Extinction can be enhanced by a concurrent excitor. J Exp Psychol Anim Behav Process 26:251–260.

42. Young SL, Fanselow MS (1992): Associative regulation of Pavlovian fear conditioning: unconditional stimulus intensity, incentive shifts, and latent inhibition. J Exp Psychol Anim Behav Processes 18:400–413.

43. Fanselow MS (1986): Conditioned fear-induced opiate analgesia: A competing motivational state theory of stress analgesia. Ann N Y Acad Sci 467:40–54.

44. McNally GP, Westbrook RF (2003): Opioid receptors regulate the extinction of Pavlovian fear conditioning. Behav Neurosci 117:1292–1301.

45. Wiertelak EP, Maier SF, Watkins LR (1992): Cholecystokinin anti-analgesia: Safety cues abolish morphine analgesia. Science 256:830–833.

46. Adams CD, Dickinson A (1981): Instrumental responding following reinforcer devaluation. Q J Exp Psychol 33:109–121.

47. Harlow HF, Dodsworth RO, Harlow MK (1965): Total social isolation in monkeys. Proc Natl Acad Sci U S A 54:90–97.

48. Landers MS, Sullivan RM (2012): The development and neurobiology of infant attachment and fear. Dev Neurosci 34:101–114.

49. Moriceau S, Roth TL, Sullivan RM (2010): Rodent model of infant attachment learning and stress. Dev Psychobiol 52:651–660.

50. Moriceau S, Sullivan RM (2006): Maternal presence serves as a switch between learning fear and attraction in infancy. Nat Neurosci 9:1004–1006.

51. Richardson R, Siegel MA, Campbell BA (1989): Effect of maternal presence on the cardiac and behavioral responses to shock in rats as a function of age. Dev Psychobiol 22:567–583.

52. Bowlby J (1969). Attachment and Loss, vol. 1. New York: Random House.

53. Hornstein EA, Fanselow MS, Eisenberger NI (2021): Warm hands, warm hearts: An investigation of physical warmth as a prepared safety stimulus [published online ahead of print Oct 28]. Emotion.

54. Davey GCL (1995): Preparedness and phobias: Specific evolved associations or a generalized expectancy bias? Behav Brain Sci 18:289–297.

55. Raineki C, Sarro E, Rincón-Cortés M, Perry R, Boggs J, Holman CJ, et al. (2015): Paradoxical neurobehavioral rescue by memories of early-life abuse: The safety signal value of odors learned during abusive attachment. Neuropsychopharmacology 40:906–914.

56. Roth TL, Barr GA, Lewis MJ, Sullivan RM (2016): Neurobiology and programming capacity of attachment learning to nurturing and abusive caregivers. In: Sale A, editor. Environmental Experience and Plasticity of the Developing Brain. Hoboken: Wiley-Blackwell, 117–137.

57. Robinson-Drummer PA, Opendak M, Blomkvist A, Chan S, Tan S, Delmer C, et al. (2019): Infant trauma alters social buffering of threat learning: Emerging role of prefrontal cortex in preadolescence. Front Behav Neurosci 13:132.

58. Duits P, Cath DC, Lissek S, Hox JJ, Hamm AO, Engelhard IM, et al. (2015): Updated meta-analysis of classical fear conditioning in the anxiety disorders. Depress Anxiety 32:239–253.