New Vistas on Amygdala Networks in Conditioned Fear

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Paré, Denis, Gregory J. Quirk, and Joseph E. LeDoux. New vistas on amygdala networks in conditioned fear. J Neurophysiol 92: 1–9, 2004; 10.1152/jn.00153.2004. It is currently believed that the acquisition of classically conditioned fear involves potentiation of conditioned thalamic inputs in the lateral amygdala (LA). In turn, LA cells would excite more neurons in the central nucleus (CE) that, via their projections to the brain stem and hypothalamus, evoke fear responses. However, LA neurons do not directly contact brain stem-projecting CE neurons. This is problematic because CE projections to the periaqueductal gray and pontine reticular formation are believed to generate conditioned freezing and fear-potentiated startle, respectively. Moreover, like LA, CE may receive direct thalamic inputs communicating information about the conditioned and unconditioned stimuli. Finally, recent evidence suggests that the CE itself may be a critical site of plasticity. This review attempts to reconcile the current model with these observations. We suggest that potentiated LA outputs disinhibit CE projection neurons via GABAergic intercalated neurons, thereby permitting associative plasticity in CE. Thus plasticity in both LA and CE would be necessary for acquisition of conditioned fear. This revised model also accounts for inhibition of conditioned fear after extinction.

INTRODUCTION

Classical fear conditioning is an experimental model used to study how organisms learn to predict danger from previous experiences. In this model, a neutral sensory stimulus (conditioned stimulus, CS) acquires the ability to elicit fear responses after pairing with a noxious unconditioned stimulus (US). Early on, it was recognized that the amygdala is critical for this form of learning (Blanchard and Blanchard 1972; Kellicut and Schwartzbaum 1963; Spevack et al. 1975). However, identification of pathways that mediate the expression of conditioned responses by way of amygdala outputs (Kapp et al. 1979) and pathways that transmit CS information from sensory systems to the amygdala (LeDoux et al. 1984, 1990b) greatly increased interest in the intra-amygdaloid substrates of Pavlovian fear learning. The number of papers on this issue rose from an average of ~25/y in the 1980s to ~200/y in the last few years.

Several factors account for this surge of interest. First, the simplicity of this experimental paradigm facilitates the study of underlying mechanisms in animal models; the entire neuroscientific armamentarium can be easily applied to the study of fear conditioning. Field potential responses to high-frequency stimulation (Bauer et al. 2002; Tsvetkov et al. 2002), patch-clamp recordings (Mahanty and Sah 1998; Royer et al. 2000a; Weisskopf et al. 1999), single-unit recordings (Collins and Paré 2000; Maren 2000; Quirk et al. 1995; Repa et al. 2001), pharmacological manipulations (Davis 2000; Schafe et al. 2001; Wilensky et al. 1999), and transgenic approaches (Impey et al. 1998; Shumyatsky et al. 2002) all implicate the amygdala in the acquisition of learned fear. Second, findings from animal studies have been confirmed in humans with functional magnetic resonance imaging (fMRI) techniques (Buchel et al. 1998; LaBar et al. 1998; Whalen et al. 1998), increasing the relevance of the animal model. Third, it is becoming increasingly apparent that the mechanisms underlying Pavlovian fear conditioning have much in common with human anxiety disorders (Bouton et al. 2001; Pitman et al. 1999; Sullivan et al. 2003). Thus understanding the acquisition and extinction of conditioned fear might help us find ways to treat these disorders.

Although controversy persists (Cahill et al. 1999), it is widely believed that the lateral nucleus of the amygdala (LA) is a key site of plastic synaptic events that contributes to fear learning (Blair et al. 2001; LeDoux 2000; Malkani and Rosen 2000; Maren 2001). According to the current model (Fig. 1A), convergence of CS and US inputs increases the efficacy of synapses conveying information about the CS to the LA (LeDoux 2000; Walker and Davis 2000). As a result, subsequent presentations of the CS alone evoke larger responses in the LA (Collins and Paré 2000; Quirk et al. 1995; Repa et al. 2001). The LA, in turn, evokes conditioned fear responses via its projections to the central amygdaloid nucleus (Fig. 1A; Kapp et al. 1979; Krettek and Price 1978; LeDoux et al. 1988; reviewed in Davis 2000), which is the main source of amygdala outputs to brain stem and hypothalamic sites that produce fear responses (Bellgowan and Helmstetter 1996; Davis 2000; De Oca et al. 1998; LeDoux et al. 1988). Thus, in the current model (Fig. 1A), the LA is seen as the major site of plasticity, whereas the central nucleus (CE) is viewed as a passive relay to downstream structures (LeDoux 2000).

This model has great explanatory powers and has done much to galvanize interest in fear conditioning. However, some new data, as well as older findings that went unnoticed, are difficult to reconcile with the current model. In particular, LA does not project directly to CE output neurons (Fig. 1B), and the CE may receive direct inputs from sensory-processing areas (Fig. 1B). Further, new evidence suggests that the CE might itself be a critical site of plasticity independent of LA. Thus we will attempt to reconcile the current model with these discrepant findings. We will also consider the ability of a revised model to account for how conditioned fear is extinguished. In advance,

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we wish to apologize for omissions in our coverage of the existing literature (~2,000 papers).

Evidence supporting the current model

The evidence supporting the critical role of the LA in the formation of tone-shock associations rests principally on four sets of observations (Blair et al. 2001; Davis 2000; Fanselow and LeDoux 1999; Maren 2001).

First, the LA receives auditory input from the medial section of the medial geniculate nucleus (MGm) and the posterior intralaminar nucleus (PIN) that are the target of inferior colliculus projections (LeDoux et al. 1990b; Turner and Herkenham 1991). Parallel inputs from the auditory cortex also reach the LA (Romanski and LeDoux 1993). Auditory inputs to the LA converge with somatosensory inputs from the same posterior thalamic regions (LeDoux et al. 1990b), which in turn receive input from the spinothalamic tract (LeDoux et al. 1987).

Second, lesions or temporary inactivation of LA during conditioning interferes with the acquisition of conditioned fear responses (Amorapanth et al. 2000; LeDoux et al. 1990a; Maren et al. 2001; Muller et al. 1997; Sacchetti et al. 1999; Wilensky et al. 1999).

Third, LA neurons show associative plasticity during fear conditioning at latencies consistent with potentiation of thalamic inputs (Collins and Paré 2000; Maren 2000; Ono et al. 1995; Quirk et al. 1995; Repa et al. 2001; Rogan et al. 1997).

Fourth, interfering with molecular-signaling mechanisms in LA including N-methyl-D-aspartate (NMDA) receptors (Fanselow et al. 1994; Walker and Davis 2002), protein kinases (Schafe et al. 2001), or protein synthesis (Bailey et al. 1999; Lamprecht et al. 2002; Nader 2003; Schafe et al. 1999) prevents long-term memory for fear conditioning.

Thus multiple lines of evidence appear to converge on the LA as a critical site of plasticity in fear conditioning.

Observations that cannot be easily reconciled with the current model

Although the current model correctly ascribes a critical role to LA as a site of plasticity in fear conditioning, some key features of amygdala anatomy are problematic for this view. In addition, some recent studies indicate that the CE might not be a passive relay after all. These points are considered in turn below.

LA IS NOT DIRECTLY LINKED TO BRAIN STEM-PROJECTING CE NEURONS. At the core of the current model are direct projections from LA to CE to brain stem. However, the CE is composed of several subnuclei, only one of which contributes significant projections to the brain stem: the medial sector of CE (CEm)

![Diagram of the amygdala and thalamus showing direct and indirect connections between LA and CE](http://example.com/diagram.png)
(Hopkins and Holstege 1978; Liubashina et al. 2000; Schwaber et al. 1982; Veening et al. 1984). The brain stem projections of the lateral part of CE are limited to the parabrachial nucleus in the pons (Petrovich and Swanson 1997). In contrast, CEm projects massively to various brain stem nuclei including the periaqueductal gray, which mediates freezing (reviewed in Davis 2000), and the pontine reticular formation involved in fear potentiated startle (Rosen et al. 1991) as well as the pedunculopontine, dorsal motor vagal, and solitary tract nuclei. This result was obtained in a number of species including the rat, cat, and rabbit (Hopkins and Holstege 1978; Schwaber et al. 1982; Veening et al. 1984) and was recently replicated in the rat with anterograde tracing methods (Liubashina et al. 2000).

The difficulty comes from the fact that LA has little if any projections to CEm, but rather projects to the lateral or amygdalo-striatal sectors (Fig. 1B). This was first reported in 1978, when Krettek and Price published their seminal study on the internuclear projections of the rat and cat amygdala (Krettek and Price 1978). Since then, this observation was replicated in the rat (Pitkanen et al. 1995), cat (Smith and Paré 1994), and monkey (Pitkanen and Amaral 1998). Thus there is an apparent disconnect in the amygdala between the site of plasticity and site of expression (see Fig. 1B).

Two solutions to this problem are commonly invoked. The first is that the lateral or amygdalo-striatal sector of CE (CEl) projects to the CEm (Jolkkonen and Pitkanen 1998; Petrovich and Swanson 1997). However, this projection, which is relatively minor (Paré and Smith 1993), is GABAergic (McDonald and Augustine 1993; Nitecka and Ben Ari 1987; Paré and Smith 1993). Given that chemical or electrical excitation of CEm elicits the behavioral correlates of fear (reviewed in Davis 2000), GABAergic input from CEl would decrease rather than augment fear expression. Thus CEl is an unlikely candidate for relaying CS inputs from LA to CEm.

A second possible solution to this problem is the existence of indirect projections from LA to CEm via the basal nuclei of the amygdala. There are indeed massive projections from the LA to basal nuclei (Krettek and Price 1978; Pitkanen et al. 1995; Smith and Paré 1994), which in turn project to all sectors of CE (Paré et al. 1995; Petrovich and Swanson 1997; Pitkanen et al. 1995). However, pretraining excitotoxic and electrolytic lesions of the basal nuclei do not interfere with the acquisition of conditioned fear (Amorapanth et al. 2000; Holihan and White 2002; Nader et al. 2001). Therefore this indirect pathway is not essential for fear conditioning, although one study reported that neurotoxic damage to the most anterior basal nuclei impaired fear conditioning (Goosens and Maren 2001). Additional studies, including posttraining lesions, will be needed to fully resolve this question.

Thus it is likely that the current model requires revision. Brain stem-projecting CEs cells do not directly receive information about the CS from LA axons (Fig. 1B), and the indirect pathway through the basal nuclei may not be essential for fear conditioning.

CE MAY RECEIVE DIRECT THALAMIC INPUTS ABOUT THE CS. The current model stipulates that posterior thalamic areas MgM/ PIN send information about the tone CS to the LA. This is a well-established and undisputed fact, confirmed in numerous studies (Doron et al. 2002; LeDoux et al. 1985; Linke et al. 2000; Shinonaga et al. 1994; Turner and Herkenham 1991; Woodson et al. 2000). However, the posterior thalamic nucleus (PO), located just medial to the PIN, also projects to the CEm and accessory basal (AB) nuclei (LeDoux et al. 1987; Linke et al. 2000; Turner and Herkenham 1991), raising the possibility that CEm receives auditory input from the thalamus (Fig. 1B). This possibility was initially considered (LeDoux et al. 1987) but later rejected on the basis of tracing data suggesting that the PO does not receive auditory input from the inferior colliculus (IC) (LeDoux et al. 1990b). However, a more recent tracing study indicates that PO receives input from the external and pericentral nuclei of the IC (Linke et al. 2000), areas known to contain auditory responsive neurons (Aitkin et al. 1986). This projection may have been missed in the earlier study (LeDoux et al. 1990b) because the tracer injections into IC largely spared the IC external nucleus. In addition to receiving inputs from IC (Kudo and Niimi 1980), the PO also receives auditory projections from the dorsal nucleus of the lateral lemniscus (Kudo et al. 1983) and the nucleus of the brachium of the IC (Kudo et al. 1984) as well as visual and somatosensory inputs from the superior colliculus and spinal cord (reviewed in Jones 1985). Finally, extracellular recordings in cats showed that neurons in PO respond to auditory, visual, and somatosensory stimuli (Poggio and Mountcastle 1960).

Although these older studies could not distinguish recordings in PO and PIN, the possibility that PO contains auditory neurons that project to CEm cannot be ruled out. This could be tested, as was done in LA (Bordi and LeDoux 1994), by stimulating CEm to antidromically activate PO neurons that project there and then determining whether these PO cells respond to auditory stimuli. Still the existence of an auditory input to CEm, in itself, would not be sufficient to refute the current model. It would, however, raise the possibility that CEm is not a passive relay in fear conditioning. Perhaps the CEm, like the LA, has access to information about both the CS and US and is a site of plasticity. This possibility is considered below.

CE RECEIVES NOCICEPTIVE INPUTS FROM THE BRAIN STEM AND THALAMUS. As previously acknowledged (LeDoux 2000), there is abundant evidence that the CE, including its medial sector, receives subcortical nociceptive (US) inputs. For instance, a number of physiological and anatomical studies have shown that CE receives nociceptive information from the spinal cord and trigeminal nucleus via the parabrachial nuclear complex of the pons (Alden et al. 1994; Bernard et al. 1990, 1992, 1993; reviewed in Bernard and Besson 1990; Bernard et al. 1996; Neugebauer and Li 2003). CE cells respond to both mechanical and thermal noxious stimuli. They generally have large receptive fields and rarely respond to innocuous stimuli. At present, it is unclear whether all nociceptive inputs are relayed to CE by the parabrachial complex. The posterior thalamic complex could also relay nociceptive signals from the spinal cord (Fig. 1B).

CE ITSELF MAY BE A CRITICAL SITE OF PLASTICITY. Deficits caused by CE lesions in aversive conditioning (Amorapanth et al. 2000; Iwata et al. 1986; Kapp et al. 1979; Killcross et al. 1997) are consistent with a critical role of CE in fear expression. More recent studies, however, show that local infusions of drugs that affect CE only during the acquisition phase are sufficient to prevent the formation of long-term fear memory.
For example, infusing the protein synthesis blocker anisomycin into the CE prevents the acquisition of conditioned taste aversion (Bahar et al. 2003). Similarly, infusing the NMDA receptor antagonist APV into the CE prevents long-term memory for classical fear conditioning (Goozens and Maren 2003). Consistent with this, NMDA synaptic currents in CE exhibit a high sensitivity to NR2B-selective antagonists and a slow decay time (Lopez and Sah 2003), which is optimal for associative plasticity. Moreover, thalamic inputs to CEm can undergo NMDA-dependent long-term potentiation (R. Samson and D. Paré, unpublished observations). Finally, preliminary reports indicate that temporary inactivation of CE with muscimol (Wilensky et al. 2000) or inhibition of protein synthesis in CE (Wilensky et al. 2001) prevents the formation of long-term fear memory. Therefore as originally suggested by Kapp and coworkers (Pascoe and Kapp 1985), CE may indeed be a site of plasticity in fear conditioning.

Resolution

If the LA does not project to CEm, how might it facilitate the activity of brain stem projecting CE neurons? We propose that the solution resides in the intercalated (ITC) cell masses. ITC cell masses are dense clusters of GABAergic neurons located between the basolateral amygdaloid complex and the CE (McDonald and Augustine 1993; Nitecka and Ben Ari 1987; Paré and Smith 1993). ITC cells receive glutamatergic inputs from the BLA and generate feed-forward inhibition in the CE (Paré and Smith 1993; Royer et al. 1999). There is a lateromedial correspondence between the position of ITC neurons, where they project in the central nucleus, and where they derive their inputs basolateral (Royer et al. 1999). Critical from the standpoint of the current discussion is the presence of unidirectional connections between ITC cell clusters, directed lateromedially (Fig. 1C) (Royer et al. 2000b). As a result, activation of LA excites ITC cells located at the same lateromedial level, which inhibit more medially located ITC neurons (Fig. 1C), disinhibiting medially located CE neurons (Royer et al. 1999). The end result is a facilitation of CEm output by LA activation (see Fig. 1C).

Thus we submit that the reason why increased CS responsiveness in the LA is critical to the acquisition of conditioned fear responses is that it causes, via ITC neurons, a disinhibition of brain stem projecting CEm cells (Fig. 1C). As discussed below, this disinhibition could allow auditory thalamic inputs to trigger activity-dependent plasticity in CEm (Fig. 1C) when they coincide with US information from the thalamus or parabrachial nucleus. In support of this idea, conditioned increases in tone responses of CE neurons (Pascoe and Kapp 1985; Toyomitsu et al. 2002) occur at approximately the same latency as recently described in LA (30–50 ms) (Repa et al. 2001; Toyomitsu et al. 2002). However, the existence of shorter latency responses in LA (e.g., 10–30 ms) suggests that early initial plasticity in this region plays a key role. Indeed, two sets of plastic cells have been found in LA—one involved in rapidly learning the association in the initial trials and the other acquiring the association more slowly but retaining it longer (Repa et al. 2001). A detailed comparison of the latency and rate of acquisition of conditioned responses in CEm and LA unit will be needed to determine whether thalamic inputs are potentiated in both structures at the same or different times. Given the foregoing, it is likely that the acquisition of conditioned fear responses depends on distributed storage in the amygdala (Fig. 1C) and possibly other regions, such as sensory input regions in the thalamus and cortex (Weinberger 1995), and even in the brain stem (Sanders and Fanselow 2003). Potentiation of CS-responses in the LA would enable plasticity in the CEm. This view does not exclude the possibility that LA inputs to ITC cells can undergo plasticity. In fact, inputs from the basolateral and LA nuclei to ITC cells express NMDA-dependent LTD and LTP (Royer and Paré 2002, 2003).

Relevance of the revised model for extinction of conditioned fear

MEDIAl PREFRONTAL CORTEX AND EXTINCTION MEMORY. Substantial behavioral evidence indicates that extinction inhibits the expression of conditioned fear rather than erase the fear memory (Bouton 1993; Pavlov 1927; Quirk 2002; Rescorla 2001). Because of its divergent projections, inhibition of CEm via ITC cells would be an efficient way of dampening multiple fear responses after extinction. This would require that some set of inputs to ITC cells increase their responsiveness to the CS after extinction.

One candidate mechanism for achieving this could involve the infralimbic region (IL) of medial prefrontal cortex (mPFC), which projects strongly to ITC cells (Freedman et al. 2000; McDonald et al. 1996; Sesack et al. 1989). In support of this, lesions of IL impair extinction (Morgan et al. 1993, 2003; Quirk et al. 2000), and electrical stimulation of IL reduces the expression of conditioned fear (Milad and Quirk 2002). Interestingly, IL stimulation reduces conditioned freezing only if delivered at tone onset (Milad et al. 2004), suggesting gating of the response of downstream structures to tone stimuli. IL neurons do not respond to tones during the first extinction session but respond robustly 24 h later, when rats are recalling extinction (Milad and Quirk 2002) (see Fig. 2). Furthermore, the degree of mPFC potentiation was correlated with recall of extinction, suggesting a causal relationship between prefrontal activity and extinction memory (Herry and Garcia 2002, 2003; Milad and Quirk 2002). Together, these findings implicate the mPFC, not in the initial learning of extinction (within-session), but in the consolidation and subsequent recall of extinction memory.

Although mPFC may inhibit CEm via a projection to ITC cells, other routes are also possible. For example, the mPFC projects to CE’s targets in the hypothalamus and brain stem (Fisk and Wyss 2000; Floyd et al. 2000) and could act independently of the amygdala. In support of an amygdala route of activation, however, we recently observed that mPFC stimulation reduced the excitability of brain stem-projecting CEm neurons (Quirk et al. 2003). Basolateral activation of CEm neurons could be prevented by mPFC prestimulation, suggesting feed-forward inhibition of CE by ITC cells (see Fig. 3). There is also evidence that mPFC inhibits CS processing within the basolateral nucleus itself (Rosenkranz and Grace 2002; Rosenkranz et al. 2003).

INPUTS TO INTERCALATED CELLS ARE MODIFIABLE. It was recently reported that basolateral inputs to ITC cells exhibit NMDA-dependent LTP and LTD (Royer and Paré 2002). This
result suggests that, in addition to inhibiting the expression of conditioned fear, ITC cells may participate in storage of extinction memory. It is now well established that NMDA antagonists given systemically (Baker and Azorlosa 1996; Santini et al. 2001) or directly into the amygdala (Falls et al. 1992; Lin et al. 2003) prevent long-term memory for extinction. Therefore extinction memory might be stored in both ITC cells and mPFC. While it is not known if mPFC inputs to ITC cells are also modifiable, mPFC stimulation paired with extinction tones strengthened extinction memory at a 24-h test (Milad and Quirk 2002). The mechanism of this potentiation could involve plasticity in mPFC inputs (or BL inputs) to ITC cells. Thus the robust tone responses observed in IL during recall of extinction may serve to strengthen extinction memory as it is recalled.

IMPLICATIONS FOR ANXIETY DISORDERS. As originally suggested (LeDoux 1996; Morgan et al. 1993), insufficient inhibition of the amygdala by mPFC could predispose an individual to develop anxiety disorders. In fact, recent neuroimaging studies of patients with posttraumatic stress disorder (PTSD) show decreased activity in medial prefrontal/anterior cingulate areas, correlated with increased activity in the amygdala (Bremner et al. 1999; Shin et al. 2001, 2004). Given that extinction is the basis of exposure therapy for PTSD (Bouton 1988), an obvious therapeutic strategy would be to strengthen extinction consolidation. Recent experiments in rats suggest that extinction can be facilitated with intra-amygdala infusion of D-cycloserine, a glycine site agonist of NMDA receptors (Ledgerwood et al. 2003; Walker et al. 2002). ITC cells in the amygdala are a likely site of action of D-cycloserine, which may facilitate potentiation of prefrontal or basolateral inputs. In addition to NMDA receptors, ITC cells express dopamine type 1 receptors whereas IL axon terminals onto ITC cells express type 2 receptors (Fuxe et al. 2003; Maltais et al. 2000;}

**FIG. 2.** Extinction-induced increases in infralimbic (IL) activity could inhibit fear expression via intercalated (ITC) cells. Top left: scheme of a coronal section of the rat brain showing IL projection to ITC cells (dark ovals in lower scheme). The orientation of the coronal sections is indicated by the cross. Excitation of ITC cells by IL axons produces a feed-forward inhibition of CEm neurons projecting to the brainstem. Top right: histogram of tone-evoked activity before (left) and 24 h after (right) extinction. Dashed lines indicate tone onset. Bin width, 50 ms. Modified after Milad and Quirk (2002).

**FIG. 3.** IL stimulation produces feed-forward inhibition of CEm neurons via the ITC cell masses. The orientation of the coronal section is indicated by the cross. A: experimental set-up. Neurons were recorded extracellularly in CEm (REC). Stimulating electrodes were positioned in the BLA and IL. IL prestimulation blocked the BLA-evoked orthodromic activation of CEm cells. Modified after Quirk et al. (2003).
Pinto and Sesack 2003). Importantly, the dopaminergic input to ITC cell masses is much stronger than to LA (Fallon and Ciofi 1992; Fuxe et al. 2003). Thus modulation of ITC cells via these mechanisms may offer additional ways to augment inhibition in the amygdala for potential clinical benefit.

Predictions of the revised model

A number of testable predictions arise from our revised model. Many of these follow the strategy used to implicate the LA in acquisition of conditioned fear. For example, reversible inactivation of CEm during conditioning should prevent the acquisition of conditioned fear responses. Thalamic inputs to CEm neurons should display activity-dependent LTP, which would be sensitive to NMDA antagonists. Furthermore, if LA inputs have the disinhibiting effect proposed here, LA lesions or inactivation should reduce but not abolish LTP of thalamic inputs to the CEm.

Several predictions concern ITC cells. For example, ITC cells located at different lateromedial levels should exhibit contrasting responses to the CS: laterally versus medially located ITC cells should, respectively, exhibit increased or decreased CS responsiveness after conditioning. IL projections to ITC cells are equally robust at all lateromedial levels of the amygdala (A. O. Pinto and D. Paré, unpublished observations). Thus IL stimuli should excite ITC cells globally, in contrast to LA inputs, which affect a restricted portion of lateral ITC cells. If IL inhibits fear via ITC cells, then paring stimulation of IL with CS onset should reduce the acquisition of conditioned fear responses. In fact, long-term potentiation of IL inputs prior to conditioning might even prevent animals from conditioning.

Conclusion

We have proposed a revision to the current model of fear conditioning in which LA disinhibits CEm output neurons, thereby enabling synaptic plasticity in CEm. We suggest that distributed plasticity in multiple amygdala targets of the thalamus and CEm is required for normal fear learning. Given the pharmacological and molecular differences between LA and CEm, this suggests additional mechanisms for modulation of fear learning and fear expression after extinction. We hope that this revised model might stimulate further investigation of the mechanisms underlying the acquisition and extinction of conditioned fear.

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