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Molecular Specificity of Multiple Hippocampal Processes Governing Fear Extinction

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SYNOPSIS

Over many years, fear extinction has been conceptualized as one dominant process, new inhibitory learning, which serves to dampen previously acquired fear. Here we present an alternative view, that brain region-specific processing of representations, expectations and emotional attributes of the fear-provoking event, recruits unique mechanisms that interdependently contribute to the conditioning and extinction of fear. The co-occurrence of these mechanisms within the fear circuit can thus be tracked and differentiated at a molecular and cellular level. Among others, the transcriptional regulators cFos, cAMP-dependent response element binding protein (CREB), Zif268, and extracellular signal-regulated kinases (Erk) stand out as hippocampal nuclear markers signaling novelty, arousal, retrieval, and prediction error, respectively. Consistent with evidence from human studies, these findings indicate that, beyond inhibitory learning, fear extinction requires modification of the emotional attributes and expectations that define the threatening context. Given the likely dysregulation of one or more of these processes in anxiety disorders, a key research challenge for the future is the identification and enhancement of individual extinction mechanisms to target the specific components of fear.

Environmental stimuli lacking affective properties (conditioned stimuli, CS) rapidly become threatening if presented with stressful events (unconditioned stimuli, US). Consequently, based on a CS-US association, the presentation of the CS triggers species-specific fear responses until the US consistently stops occurring. At that point, new learning takes place and the fear response declines, a phenomenon termed extinction. The view that extinction occurs because a new, inhibitory CS-noUS association gains control over behavior [106], has remained dominant in the field (reviewed by [20,33,35,100]). The implications of impaired fear regulation in the development of anxiety disorders have stimulate-d intense research in this area. Rodent studies identified the circuits involved in the conditioning and extinction of fear of salient cues [99,98,85,93,150], generating data that were confirmed in humans with brain imaging approaches [114,130]. Nevertheless, research with experimental animals has not fully taken advantage of human data in order to better interpret extinction mechanisms in the framework of learning, expectation and emotion governing fear-motivated behavior.

The present article aims to summarize recent molecular evidence on fear extinction, focusing on hippocampal mechanisms and experimental models of contextual fear, and compare the results with other relevant fear paradigms and human imaging studies. Instead of conceptualizing extinction learning as one process, such as CS-noUS association or inhibitory learning [19,26,96], we propose that fear extinction reflects the behavioral output of several region-specific learning processes that modify different components of the conditioning memory. The significance of these findings is discussed in the framework of fear regulation and anxiety disorders.

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Keywords

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1. CONDITIONING AND EXTINCTION OF CONTEXTUAL FEAR

Contextual stimuli play an important modulatory ("occasion setting") role in fear to explicit cues [18] but also directly associate with stressful events [84]. As one of the most robust and rapid forms of associative learning, contextual fear conditioning has been extensively used in molecular studies of memory [1,134,142]. Extinction of contextual fear however, has only been recently studied. Advances in this area are important because contextual fear might best reflect the aversive expectation about potential dangers that characterizes anxiety. This view is based on observations that anxious patients are overly sensitive to threatening contexts, and that anxiety is neither triggered nor suppressed by explicit cues [7,49]. Accordingly, among multiple responses elicited by fear, context-specific freezing has been proposed as one of the main risks factors for the development of anxiety [23]. Whereas the relationship of contextual fear conditioning to individual disorders is yet to be systematically defined, its contribution to spatial phobias and posttraumatic stress disorder is considerable.

2. ANIMAL MODELS

In animal models, contextual fear memories are acquired after pairing a specific environment with an electric shock serving as an aversive reinforcer (US). These memories are behaviorally expressed as freezing [16] if the exposure to the context is inescapable as in contextual fear conditioning, or as avoidance if animals have the option to remain in a safe compartment as in passive avoidance paradigms [17]. The duration of freezing and latency to step-through or step-down from a safe to a shock-associated compartment are used as measures of learned fear. Passive avoidance and contextual fear conditioning have much in common, because both paradigms involve conditioning to the environmental context, exposure to a brief, mild shock, and induction of fear-motivated behavior (Fig. 1).

However, the training and extinction protocols have important differences. In contextual fear conditioning, animals are exposed for a period of time to a distinctive context, sufficient to form a representation of that context, and then presented with a brief, mild footshock. Extinction trials consist of re-exposure to the shock-paired context, leading to memory retrieval, induction of a central fear state, and freezing behavior. In contrast, passive avoidance is conducted in a two-compartment box, and initial exposure is to the non-preferred compartment or elevated platform. Rodents typically run to the preferred compartment or step-down where they immediately receive a footshock and are removed from the apparatus, Extinction consists of re-exposure to the safe area of the compartment, and the latency to move into the shock-paired area is measured. Here, the very short contextual exposure during training and ability to avoid the shock-paired context are critical differences from contextual fear conditioning.

2.1. Reinforcement during conditioning

The rate of fear extinction depends on the protocol used to condition fear [60] Indeed, several different reinforcement schedules can be used to induce fear learning. A single trial of a context-shock pairing is most common, in which the length of time in the context is sufficient to form and store a contextual representation. Other raining schedules include continuous reinforcement, consisting of multiple pairings of a given context with shock, or

partial reinforcement, consisting of randomly paired and unpaired shock presentations (Fig. 2). In addition, fear can be acquired through second-order conditioning by pairing novel stimuli with the previously conditioned instead of an unconditioned stimulus.

Typically, one presentation of shock after adequate contextual exposure is sufficient for the generation of robust and lasting freezing and avoidance behavior. Multiple or spaced trials are rarely employed for these paradigms, but the few studies performed so far indicate that their molecular requirements for fear conditioning are different [70,124] This omission leaves a significant gap for future research, because variations in US number, intensity, and contingency with CS, despite producing similar levels of avoidance or freezing, cause marked differences in the extinction rate of these behaviors [6,60]. More importantly, depending on the conditioning procedure, fear can be acquired by different processes that cause susceptibility or resistance to extinction. For example, whereas first-order conditioning requires a CS-US association, second-order conditioning does not depend on the US representation [119], but probably on a CS-response or CS-affective state associations [117,53]. Furthermore, continuous reinforcement fosters the formation of specific expectations of an imminent US, whereas a partial reinforcement schedule fails to do so and instead enhances the aversive emotional attributes (negative valence, arousal) of the context [60] Finally, single reinforcement probably engages both the expectancy and affective components, although they appear to be weaker than those found after continuous or partial reinforcement, respectively (Fig. 3). Although all the described fear conditioning situations trigger similar levels of freezing, extinction is rapid when fear is based on shock expectancy while markedly impaired if controlled by an aversive contextual valence [60] These findings are consistent with human observations indicating susceptibility and resistance to extinction after expectancy and evaluative learning, respectively [54,147]

2.2 Extinction protocols

The reduction of fear also depends on the timing of the extinction trials that can be presented as massed versus spaced [24] or short versus long (reviewed by [100]). In that respect, exposures performed after fear conditioning and passive avoidance training are very different. In passive avoidance, it is unclear when contextual representations are formed because the training exposure seems much too short for their formation [152] Context exposures during extinction are always much longer than the conditioning episode as they are controlled by the animal's avoidance behavior, and likely trigger additional processing of contextual representations. Further, it is notable that extinction largely involves exposure to the safe compartment of the apparatus, as animals are immediately removed from the shock-paired compartment after entry. Finally, it is not clear whether the option to avoid the threatening compartment attenuates the development of a central fear state.

In fear conditioning, exposure to the context is tightly controlled by the experimenter and optimized for the formation of contextual representation [152]. During extinction, the context is inescapable and the animals thus experience intense fear. The trials involve exposures of similar or longer duration when compared to training. It is believed, based on the generally anticipated amnestic effects of anisomycin, that short trials trigger memory reconsolidation whereas long trials trigger extinction [107]. In our view, this differentiation is not substantiated, unless additional evidence is provided for reconsolidation versus extinction, because although short nonreinforced trials are not sufficient to trigger within-session extinction they do result in a stable reduction of fear after several repetitions. Therefore, most known molecular mechanisms of contextual fear extinction are based on short repetitive exposures, as discussed below. Long trials, on the other hand, cause rapid but transient within-session effects [82]. These behavioral findings alternatively suggest that the extinction seen after short and long trials recruits different learning processes and molecular mechanisms.

Based on these paradigmatic differences and related molecular findings (discussed below), we will argue that hippocampal mechanisms of extinction of passive avoidance leads to the formation of new contextual representations embedded in a competing, but not necessarily inhibitory, memory. Extinction mechanisms of conditioned fear, on the other hand, predominantly involve modifications of shock expectancy and a decrease of the affective contextual attributes.

3. HIPPOCAMPAL PROCESSES IN FEAR EXTINCTION

Whereas the amygdala is a major mediator of conditioned fear responses in general, the hippocampus is selectively involved in contextual and trace fear conditioning. Contextual fear conditioning involves hippocampal encoding of contextual representations that are subsequently associated with the US [89,156]. Here, contextual stimuli can be the main CS, or a background modulator of a discrete cue. Trace conditioning, which occurs when the CS and US are separated in time, requires hippocampal activity to bridge the temporal gap between these stimuli [90]. Delay paradigms, in which a salient cue co-terminates with or is immediately followed by a US, are hippocampus-independent [131,65,108]

Hippocampal lesions produce severe deficits in habituation and extinction processes in a number of paradigms[37,75,36,66,128,71,11]. Yet, because the hippocampus is neither involved in conditioned inhibition [136] nor direct control of fear-motivated behavior, this area was overlooked in fear extinction research until recently. Currently, both animal [148,126,41] and human studies [94,5,74] show hippocampal involvement in fear extinction when the main CS is a threatening environmental context. Most theories of hippocampal function, with the exception of the cognitive mapping theory [102], take into account its significance in processing affective states. Hirsh's contextual retrieval theory [56] posits that information transfer from storage to performance is prompted by motivational cues resulting in anticipation of stimuli. According to Cormier's match-mismatch theory [30] and consistent with later comparator views of hippocampal function [135,127,50,48], this brain area performs continual analysis of the relationship of cues to reinforcement and thus, when reinforcement is omitted, contributes to habituation and extinction. This is supported by evidence for significant functional interactions between the hippocampus and amygdala [59,132]. In addition, the hippocampus processes almost all modalities of sensory input [149], and surprising events such as novelty and prediction errors [58, 109,113,73]. Finally, emotional and motivational states strongly alter hippocampal activity associated with specific contexts and goals [97,63]. Together, these theoretical and experimental analyses indicate that the hippocampus contributes to fear extinction by processing the sensory/discriminative, motivational/affective, and unexpected properties of contextual stimuli.

4. MOLECULAR MECHANISMS

4.1 Extinction of passive avoidance

Much initial data on hippocampal mechanisms of extinction came from studies utilizing the passive avoidance paradigm. In this protocol, many of the mechanisms required for consolidation are replicated during extinction. Like conditioning, extinction of passive avoidance is disrupted by anisomycin [148,110] and dependent on protein kinase A, ERK, NMDA receptors, CaMKII [143] and p38 MAPK [120] These data supported the concept of extinction as new learning, resulting in a memory that competes for retrieval with the original fear-provoking memory [21]. However, these studies have not revealed mechanisms for an extinction-specific, inhibitory association, consistent with the lack of earlier behavioral evidence for associative inhibition [72,116,80]

4.2 Extinction of contextual freezing

In contrast to passive avoidance, hippocampal mechanisms of contextual fear extinction exhibit many differences when compared to fear conditioning, independently of whether exposures involve short or long trials. These differences are notable at multiple levels and encompass general biochemical and metabolic processes as well as signaling within individual neurotransmitter and transduction pathways.

4.2.1. General biochemical processes—The use of anisomycin, cycloheximide, or other drugs that block protein synthesis [but also exhibit many other cellular effects on signal transduction and neurotransmitter release [46,112] is known to produce strong and lasting amnesia in many learning paradigms. Consistent with the view that protein synthesis is a biochemical process required for learning, these compounds impair fear conditioning, when injected systemically or locally, before or immediately after training [140, 125] Unexpectedly, extinction of contextual fear progresses when protein synthesis is blocked throughout the brain [76] or within the hippocampus [41,77,86]. These initial data suggested that molecular mechanisms of extinction would fundamentally differ from those governing contextual fear conditioning.

It should be noted that some general processes, such as dependence on cytoskeletal rearrangement [41], glutamate receptors [153], and histone acetylation [78,22] appear to be common. Given the primary role of histone acetylation in gene expression and protein synthesis, the evidence for a role of histone acetylation but not protein synthesis is puzzling. Among other possibilities, the expression of regulatory, non-protein coding RNAs [92], rather than production of new proteins, may be the predominant consequence of gene expression in fear extinction. The activation of the hypothalamo-pituitary-adrenal axis has been strongly associated with general metabolic changes and other effects of stress hormones (corticotropin-releasing factor, corticosterone) contributing to fear-motivated behavior [28]. Somewhat surprisingly, elevated levels of stress hormones enhance fear conditioning [122,118], and also enhance fear extinction [155,2,47] (but see opposite effects for passive avoidance [144]), Notably, low doses of stress hormones also seem to have beneficial effects in patients with PTSD, arachnophobia, and social phobia [3,137]. The extinction-enhancing effect of corticosterone has been attributed to impaired memory retrieval [2], however this contradicts the view that retrieval is required for extinction (see below) and needs to be further clarified.

4.2.2. Hippocampal mechanisms exhibiting opposite activity patterns and roles after fear conditioning and extinction—A number of molecules exhibiting a key role in fear conditioning emerge as irrelevant or inhibitory to fear extinction. cFos, an immediate early gene product and potent transcriptional regulator, is strongly activated by environmental stimuli and exhibits a highly conserved time course independently of stimulus duration. Hippocampal cFos is triggered by novel contexts [111,59,88] but rapidly habituates thereafter [105,95,151]. On this basis, the role of cFos in fear conditioning is most likely to promote the formation of contextual representations that are the integral part of a fear conditioning memory. Absence of cFos after short extinction trials therefore suggests that formation of a new contextual representation does not take place during extinction. Interestingly, extending the exposure to 1 hr increases cFos levels (Fig. 4), implying that despite the same spatial configuration, duration can also provide a novelty signal. Unlike cFos, the activation time-course of the transcription factor CREB both *in vitro* [15] and *in ivo* is highly variable. In the hippocampus, and in other brain areas [68,25] CREB regulation may be more related to arousal and anxiety, processes that markedly support consolidation of emotionally-relevant memory, as discussed earlier [139]. Accordingly, conditioning performed with spaced trials overcomes the requirement for CREB for contextual fear conditioning. Hippocampal pCREB levels decline after repeated short and individual long extinction trials

along with the decrease of freezing [145,86] and may thus reflect a change of the emotional attributes, such as valence and arousal, linked to the conditioning context. Although mice with a disrupted *CREB* gene exhibit impairments of contextual fear extinction, these effects seem to be hippocampus-independent and are instead mediated by the amygdala and prefrontal cortex [86]. A number of signaling pathways affecting gene expression and synaptic function exert opposite effects on conditioning and extinction. Brain-derived neurotrophic factor (BDNF) is an important mediator of contextual fear conditioning [83]. The same factor, however, impairs fear extinction, as revealed by enhancing effects of post-session injections of BDNF antisense or prevention of pro-BDNF processing in the hippocampus [10].

Protein kinase A (PKA) and protein kinase C (PKC) [4] as well as cyclin dependent kinase 5 (CDK5) [40], have been strongly implicated in the consolidation of contextual fear. These kinases, however, exhibit an inhibitory effect on fear extinction [61,123,101]. Notably, most of the protein kinases that are strongly activated by fear conditioning are not triggered by extinction trials. It is rather their baseline activity or subcellular redistribution that opposes fear extinction [123,145]. Contrary to these kinases, the phosphatase calcineurin that inactivates serine-threonine kinases, is required for extinction, but exerts an opposite, limiting effect on conditioning [52]. The protein kinases exhibiting an inhibitory role in extinction are therefore likely substrates for calcineurin.

4.2.3. Hippocampal mechanisms specific for fear extinction—Contextual fear extinction requires several mechanisms that are not induced during conditioning. Cannabinoids acting *via* CB1 receptors are one of the major mediators of fear extinction. Pharmacological inhibition of hippocampal CB1 impairs [14,104], whereas CB1 stimulation exhibits an opposite, enhancing effect on fear extinction [34]. Consolidation of contextual fear conditioning, on the other hand, is not affected by CB1-acting drugs[9] The cytoplasmic polyadenylation element binding protein (CPEB) also emerges as an important and selective mediator of contextual fear extinction, as revealed by persistent freezing behavior to shock-paired context in the CPEB knockout mouse [13] Although this mouse shows baseline changes in the expression of several hippocampal genes, the direct hippocampal role in this phenotype remains to be demonstrated.

Another interesting question is whether the extinction effects of CPEB are due to its RNA-regulatory or prion-like actions [133]. More subtle signaling differences, such as activation of ERK at different subcellular locations, occur between conditioning and extinction. After conditioning, pERK is predominantly localized to fibers, whereas during non-reinforced trials nuclear activation of ERK is required for extinction to progress [39, 146]. A differential role and pattern of ERK signaling in extinction compared to conditioning has also been suggested from transgenic mice with overexpression of Rap2. In these mice, both fear and pERK levels after conditioning are normal. In contrast, extinction and pERK induced by non-reinforced sessions are impaired [121]. Importantly, sustained nuclear activation of ERK linked to extinction was specifically observed after detection of prediction error, when expectations of shock were violated by lack of shock delivery, but not by novelty, retrieval, habituation or reinforcement [60] These findings demonstrate that habituation (as revealed by a downregulation of cFos and pCREB) of CA1 neurons mediating fear conditioning may contribute to, but is not sufficient for extinction of fear. Activation of a separate, pErk-positive cell subset by prediction errors plays a critical, extinction-specific key role in the reduction of fear.

4.2.4. Hippocampal mechanisms specific for memory retrieval—The most clearly defined process differentially required for extinction and consolidation is retrieval. Several extinction mechanisms initiated during nonreinforced contextual exposures have been attributed to retrieval processes. Ouyang and Thomas [103] demonstrated that adrenergic

signaling mediates contextual memory retrieval, and that this is critical for extinction. Similarly, hippocampal PI3K is required for both retrieval and extinction [27]. This molecular evidence has been supported by electrical stimulation studies showing that the hippocampus also modulates the recall of fear extinction[38]

The transcription factor Zif268 is activated in hippocampal CA1 neurons during contextual memory retrieval [51]. Although the cellular relationship of conditioning and retrieval has not been studied in the hippocampus, evidence from the amygdala indicates that neurons mediating fear conditioning (cFos-positive) are also involved, at least in part, in the retrieval of the same memory (Zif268-positive) [115]. Extinction, on the other hand, seems to be mediated by different cell populations both in the hippocampus [146] and amygdala [55]. Possibly, retrieval transiently destabilizes the conditioning memory [79], allowing extinction processes to take place. Alternatively, given the susceptibility of active memories to modulation, retrieval may initiate processes that modify the expectancy and affective attributes of the context, thus enabling extinction. Clearly our understanding of the relationship between memory retrieval and fear extinction needs to be further advanced.

4.2.5. Summary—The extinction of contextual fear requires an entirely different pattern of molecular and cellular responses when compared to conditioning (Fig. 5). These identified molecular mechanisms likely represent multiple processes engaged by extinction including retrieval, detection of prediction error, and mechanisms to alter contextual valence and arousing attributes.

5. A MULTITUDE OF LEARNING PROCESSES CONTRIBUTING TO FEAR EXTINCTION

The presented findings indicate that the model of CS-US and CS-noUS associations referring to the learning processes underlying conditioning and extinction of fear, respectively, may neither be sufficiently specific nor accurate. In addition to the animal studies presented above, evidence from human studies also supports this view. Emotion theorists have long acknowledged that fear conditioning does not entail “a” CS-US association but instead a multitude of different associations formed between the CS and the sensory/discriminative properties of the US, the CS and the affective/motivational properties of the US, the CS and different conditioned responses [42], the US and affective/hedonic states [44], and more (reviewed in detail by [32]). Depending on the conditioning protocol, the CS may be endowed with the emotional attributes of the US, such as negative valence or arousing properties, or linked to specific expectations that a CS will be followed by a US.[54] Based on a large body of human imaging studies, it appears that the specific components of these learning processes are mostly regionalized whereas the associative aspects are likely to reflect a network property. Specifically, the amygdala and orbitofrontal cortex encode the arousing attributes and valence of a reinforcing stimulus [8,64,81]; the prefrontal-hippocampal network is involved in formation and modification of expectancy [141,73] and responses to surprising events such as novelty [109, 154] and prediction errors; and the entire orbitofrontalamygdalar-hippocampal circuit is active during contextual conditioning and extinction [69, 94] Because of the general concordance between animal and human neurocorrelates of fear extinction [62,5], electrophysiological and molecular analyses with experimental animals have the potential to significantly expand our detailed knowledge at a mechanistic and microcircuit level. For example, the better resolution of electrophysiological approaches allows detection of different amygdalar populations representing positive and negative valence [12], whereas imaging studies only show responses to but not valence [64]. Similarly, molecular analyses identify segregated hippocampal

populations responding to novelty and prediction errors [146], two processes that in imaging studies activate the hippocampus indistinguishably [109]

6. SIGNIFICANCE

Studies of contextual fear conditioning and extinction have begun to unravel novel hippocampal mechanisms with significant pathophysiological implications for anxiety disorders. Although many of the learning processes discussed may take place after a single training trial, it has been known for a long time that, both from animal studies and patients suffering from anxiety disorders, conditioned responses, expectancies of aversive outcomes, and fear itself, extinguish independently from one another and at different rates. For example, somatic fear responses can show reduction even when expectations of aversive outcomes persist [67] Accordingly, anxious patients also differentially extinguish fear-motivated conditioned behaviors, somatic responses (heart rate, skin conductance), threat expectancies (human) and fear affect [31]. Possibly, hippocampal abnormalities observed in patients with PTSD [45] contribute to the persistence of selected aspects of fear. Identifying and activating those extinction mechanisms that specifically oppose the process governing fear in individual patients will enhance the success of developing therapeutic approaches for anxiety disorders.

7. FUTURE DIRECTIONS

Neuroanatomical and electrophysiological approaches in animals have advanced the understanding on how representations of stimuli, value, response, outcome and prediction error contribute to appetitive learning (reviewed by [129, 57]). Although the main brain circuit involved in fear conditioning is known [87,138], how other memory components are regionally processed remains unclear. The detection of prediction errors occurring when expected aversive events are omitted has been found in the periaquaeductal graymatter [91] and hippocampus [60] This type of expectation violation emerges as an important and specific determinant of fear extinction when compared to conditioning. Alterations of valence and arousal are also critical factors mediated by the amygdala [12], and orbitofrontal cortex [81]. These findings open broad opportunities for future research aiming to dissect the molecular substrates of individual process underlying conditioning and extinction of fear. While facing the difficulty of directly quantifying expectancies in animals, the use of continuous reinforcement schedules is very likely to foster this type of learning and associated molecular changes. The use of partial reinforcement, on the other hand, may be useful to preferentially study the role of affective states in fear regulation. The identification of molecular correlates of emotional valence and arousal will clarify whether contextual representations gain stable aversive attributes endowed in a single fear memory, or if emotional attributes are reevaluated on a trial-by trial basis. In addition to contextual fear extinction, the hippocampus serves as an important mediator of context-specific regulation of aversively [29] and appetitively motivated behaviors [43] in response to corresponding cues. It remains to be determined whether the molecular pathways described above also contribute to extinction in these situations.

Identifying a common mechanism would significantly advance treatment options for simultaneous extinction of contextual and other unwanted, context-specific, behaviors motivated by fear or reward. The relationship between memoiy retrieval and fear extinction remains to be further clarified as does the contribution of emotional factors caused by general arousal, anticipatory anxiety. Whether different memories compete for retrieval or if one contextual representation is retrieved and the decision made based on appraisal and US expectancy is still unclear. These important questions will be answered once the brain region-specific molecular correlates of the aforementioned processes have been elucidated.

Ultimately, the determination of the molecular identity of hippocampal and other regional processes governing fear extinction would stimulate the development of specialized molecular approaches toward fear relief based on distinctive abnormalities in individual patients with anxiety disorders.

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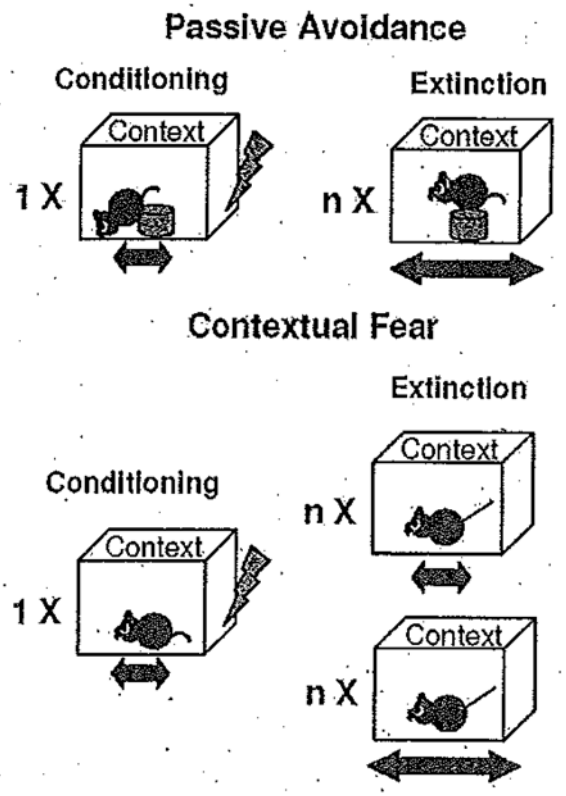

Fig. 1.
Schematic representation of the conditioning and extinction procedures employed in passive avoidance (upper panel) and fear conditioning (lower panel) paradigms.

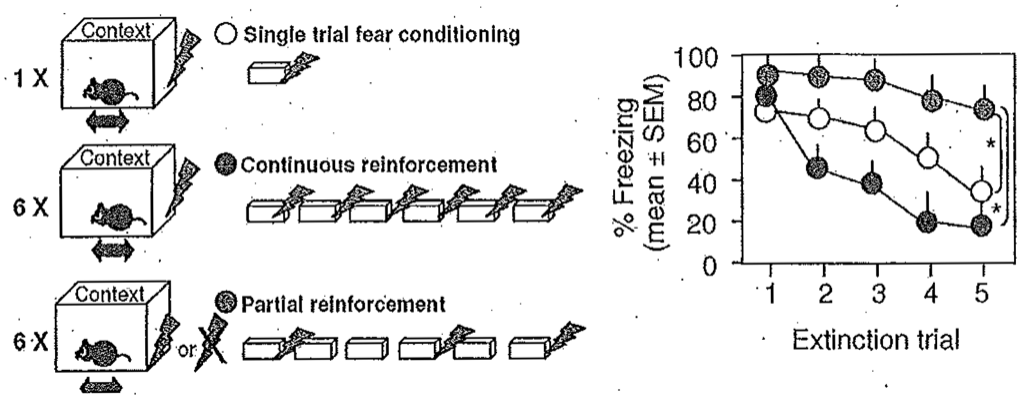

Fig. 2.

Effect of reinforcement during conditioning on the rate of fear extinction. Schematic representation of different reinforcement schedules (left) and freezing behavior over multiple extinction trials (right). Note rapid extinction after continuous and lack of extinction after partial reinforcement. Adapted from Huh et al., 2009.

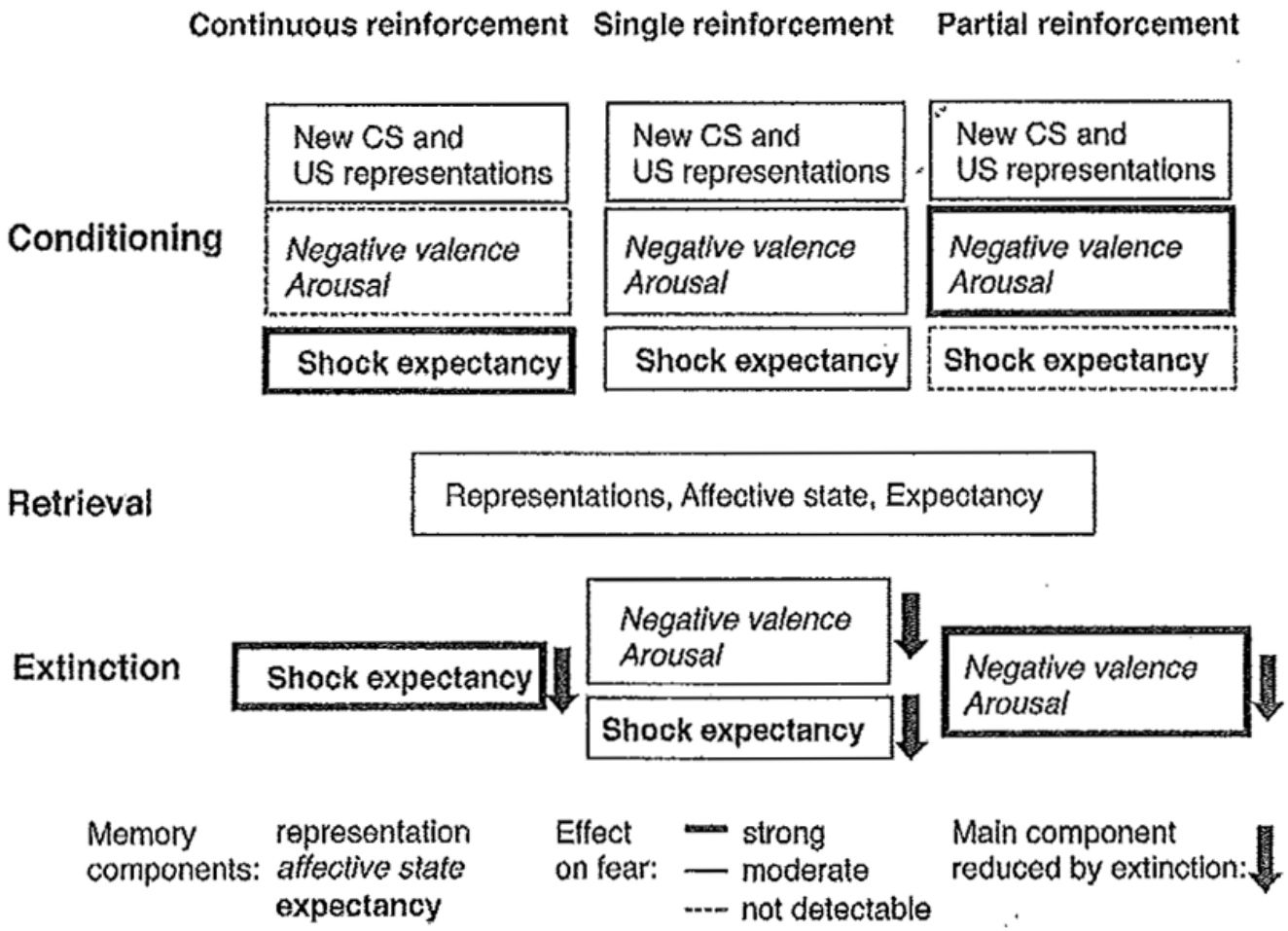

Fig. 3.

Proposed processes of conditioning and extinction of fear. Continuous, single, and partial reinforcement are established similar contextual representations but different levels of associated expectancy and affective attributes. Successful extinction therefore needs to target the main fear-provoking component.

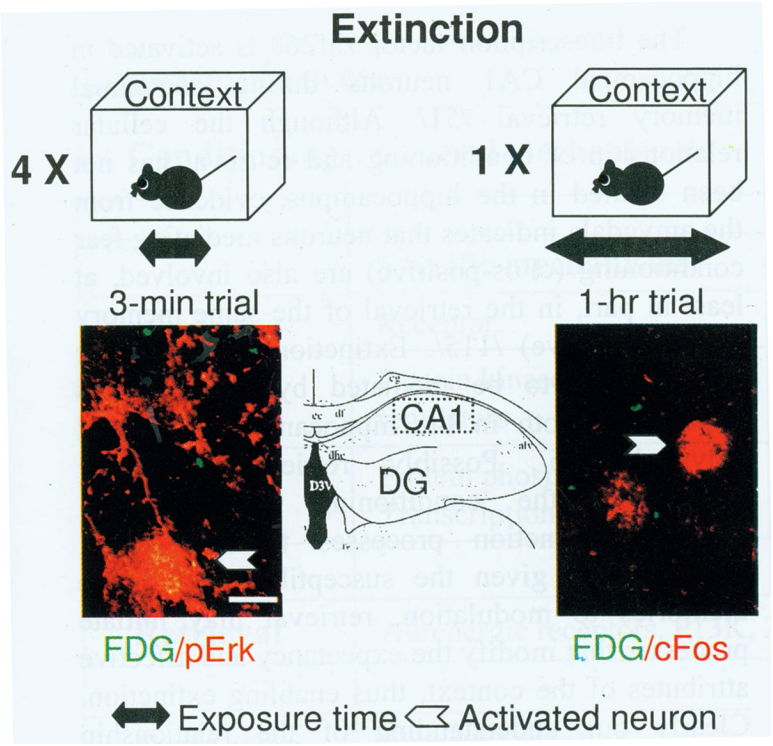

Fig. 4.

Molecular changes triggered in the CA1 hippocampal area after short and long extinction trials. Neurons activated by fear conditioning are fluorescently labeled (green) as described in Tronson et al., 2009. Short and long extinction trials activate either ERK (left) or cFos (right), respectively. Scale bar = 5 μm. FDG, fluorescein-di-beta-D-galactopyranoside New contextual representations that are not associated with shock may thus preferentially contribute to extinction after long exposures

Learning Process		Molecular Mechanism	
Conditioning	**General mechanisms:**	Chromatin remodeling, actin dynamics, sensitivity to protein synthesis inhibitors	
	Specific mechanisms:	**Mediator**	**Inhibitor**
	Receptor	TrkB (BDNF), mGluR5	
	Protein kinases and their regulators	PKA, PKC, Mek, Erk, Cdk5, CaMKII	
	Protein phosphatase Transcription factors	cFos, CREB	calcineurin
Retrieval	Adrenergic receptors, P13K, Zif268		
Extinction	**General mechanisms:**	Chromatin remodeling, actin dynamics	
	Specific mechanisms :	**Mediator**	**Inhibitor**
	Receptor	CB1, TrkB (BDNF), mGluR5, mGluR7, D1, cholinergic	
	Protein kinases and their regulators	Mek, Erk, CaMKII, Rap2, Pak1	PKA, PKC, Cdk5
	Protein phosphatase Transcription factors	Calci-neurin CPEB	

Fig. 5.
Overview of hippocampal molecular mechanisms mediating or inhibiting contextual fear extinction.