

# Role of the Hippocampus and Amygdala in the Extinction of Fear-Motivated Learning

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**Abstract:** Fear-motivated learning is at the root of phobias, panic, generalized anxiety and the posttraumatic stress disorder. This makes the inhibition of fear-motivated behavior a therapeutic desideratum in these diseases. The simplest way to accomplish this is by extinction, a procedure by which a given association between a conditioned stimulus or context (CS) and a fearsome event is replaced by a new association between the CS and the lack of the fearsome stimulus. This is a new learning for the subject and, in rats, it requires gene expression and protein synthesis both in the hippocampus and the basolateral amygdala, alongside with the activation of various metabolic signaling pathways. These requirements are similar to, but not identical with those for consolidation of the original memory. In addition, some systems uninvolved in original consolidation appear to be involved in extinction, namely, the endocannabinoid system. Extinction can be enhanced by prolonging the exposure to the lack of fearsome stimulation; e.g., in rats, by increasing the time of permanence in the compartment where the animals no longer receive a footshock. Further research into the possibilities of enhancing extinction at the expense of the original fearsome learning is desirable.

**Key Words:** Amygdala, extinction, fear-motivated behavior, hippocampus, learned fear, psychotherapy.

## INTRODUCTION

Fear-motivated behavior is a major adaptive faculty that confers animals the ability to recognize and behave appropriately when exposed to danger. Fear memories are solidly stored in the brain and the mechanisms of fear acquisition have been intensively investigated in the last decades (McGaugh, 2000).

Aside from the biological relevance of fear-motivated behaviors, the inhibition of learned fear is also crucial for adaptive behavior. The overstatement of fear or the difficulty to inhibit fear have substantial biological, psychiatric and societal consequences, being at the root of phobias, panic attacks, generalized anxiety disorders, post-traumatic stress disorders (PTSD) and at least some types of depression and/or bipolar disorders (Jeffrey and Jay, 1998; Quirk & Gehlert, 2003; Cammarota *et al.*, 2003; Myers and Davis, 2002; Lee *et al.*, 2002).

Behavioral procedures to inhibit learned fear responses have long been known and employed in the treatment of fear related disorders in humans even though until very recently the biological mechanisms of fear inhibition have not received much attention. When Pavlov and his disciples demonstrated the process of extinction of learned responses in 1903-1926 (see Pavlov, 1927), a gateway was opened for the treatment of anxiety disorders. In the 1920s Freud proposed the application of extinction (which he called "habituation" to the treatment of phobias, and it has been used successfully till today.

Later, extinction, under various names (habituation, flooding, exposure techniques) was applied to the treatment of other anxiety disorders, and more recently it has been applied, again with success, to the treatment of PTSD (Beckett, 2002; Rothbaum & Schwartz, 2002).

The recently renewed interest on the mechanisms of memory extinction, in part guided by the increasing prevalence of fear-related disorders and the seek for effective treatments for PTSD (Myers and Davis, 2002; Cammarota *et al.*, 2003) directed the search of neural, cellular and molecular substrates for the extinction of fear motivated behaviors. As a result, an increasing number of demonstrations of the involvement of different brain areas in the extinction of different aversive tasks have emerged (Myers and Davis, 2002).

The evidence accumulated so far in different behavioral paradigms demonstrated the involvement of specific molecular events in different brain regions both for consolidation and extinction of aversive tasks. Different neocortical areas have been implicated (Dudai *et al.*, 1995; Quirk & Gehlert, 2003) and importantly the amygdala and the hippocampus have been correlated with different processes involved in fear-motivated memories.

The hippocampus is suggested to be the central structure in contextual information processing and has been shown to be crucial to fear conditioning involving complex, contextual information acquisition and retrieval (Hirsh, 1974; Phillips & Ledoux, 1992; Eichenbaum *et al.*, 1996; Lorenzini *et al.*, 1996; Izquierdo & Medina, 1997). The basolateral amygdala nucleus complex is thought to be the central brain structure in fear processing and in the formation and extinction of conditioned emotional responses (Davis, 1992; Maren & Fanselow, 1996; Cahill *et al.*, 2000; McIntyre *et al.*, 2003).

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There is general agreement as to a crucial role of the hippocampus in memory storage (eg., Izquierdo & Medina, 1997; Izquierdo & McGaugh, 2000), but there is debate on whether the basolateral amygdala plays a role in storage (Schafé *et al.*, 1999) or modulation at the time of storage (Parent *et al.*, 1995; McIntyre *et al.*, 2003).

The hippocampus is connected via the subiculum and entorhinal cortex to the nearby amygdala and to most of the neocortex (Iijima *et al.*, 1996; Hyman *et al.*, 1990). The amygdala receive projections from frontal, associative and sensory cortical areas as well as related structures from medial temporal lobe and parts of the limbic system and send its afferents to brain stem nuclei, cortical and hypothalamic nuclei and to the hippocampus (Van Hoesen, 1985). Thus, the hippocampus and the amygdala are strategically positioned in order to handle information of various sources pertinent to learning and to the making and unmaking of new connections between different types of information.

### EXTINCTION AND FORGETTING, AND THE SITE(S) OF EXTINCTION

So far, studies on the molecular basis of extinction have centered on the structures most likely to be involved in the acquisition and consolidation of each task: the basolateral amygdala for fear-potentiated startle (Davis, 1992; Myers & Davis, 2002; Lu *et al.*, 2001; Walker *et al.*, 2002); the CA1 region of the dorsal hippocampus for one-trial inhibitory avoidance (Vianna *et al.*, 2001, 2003; Szapiro *et al.*, 2003), and the insular cortex for conditioned taste aversion (Miserendino *et al.*, 1990); the insular cortex for conditioned taste aversion (Berman & Dudai, 2001).

Perhaps the underlying notion in all these studies is an error that is subjacent in the minds of many and results from confusing extinction with forgetting (see below). The error consists of believing that if a given learned association is installed in a given set of synapses, it can only be uninstalled at the same set of synapses. Eccles (1955) showed that while the repeated use of a synapse leads to its strengthening, its disuse leads to its weakening. But extinction does not result from disuse and is not the equivalent of forgetting. As will be commented below, extinction consists of the acquisition of a new learning in which the original conditioned stimuli or context (CS) is no longer associated with a given unconditioned stimulus (US); in the case of fear motivated learning, a fearsome US. Extinction relies, thus, on a CS-no US association that superimposes upon and overwhelms the original CS-US (CS-fear) association (Rescorla, 1988, 2001; Vianna *et al.*, 2001, 2003; Myers and Davis, 2002).

Like the original learning process, memory extinction is also believed to be stored as functional and morphological modifications of synapses (Bouton, 2002). The fact that extinction is usually measured by the gradual inhibition of performance of a previously established CR may lead an unadvised observer to think that extinction consists merely of response inhibition and not of a special form of learning; and this may lead to a confusion, as is seen in some of the medical literature, between extinction and forgetting. Forgetting is perhaps the "most salient characteristic of memory" (Dawson & McGaugh, 1971). But, unlike extinction, forgetting is thought to be the result of either

synaptic disuse (Eccles, 1955) or of synaptic or neuronal loss (Vianna *et al.*, 2003).

However, a thorough extinction training can eventually lead to the effective uninstatement of a previously acquired CR. In a recent series of experiments, Cammarota *et al.* (2003) merely prolonged, in extinction trials, the time that rats spent in the compartment where they had once received a footshock. In other words, the "no US" component of the new CS-no US association was prolonged. This enhanced extinction to the point of a complete loss of the original CR; as complete as to require again protein synthesis and gene expression in the hippocampus for its re-installment (Cammarota *et al.*, 2003).

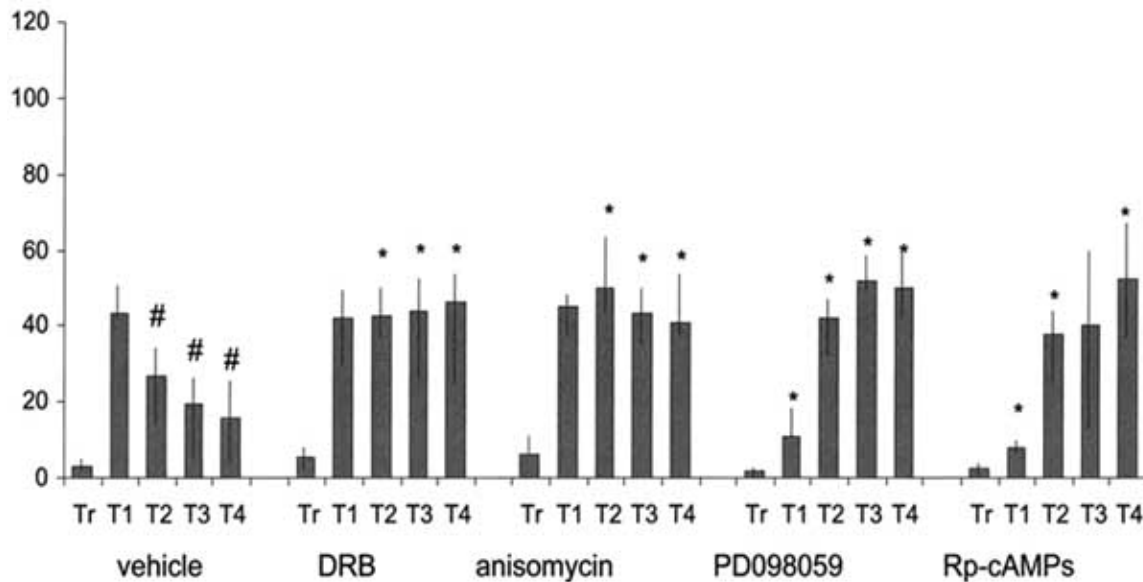
### THE MOLECULAR BASIS OF EXTINCTION

Extinction depends on brain protein synthesis. Systemic administration of the protein synthesis inhibitor, anisomycin blocks brain protein synthesis and extinction of an active avoidance response (Flood *et al.*, 1977). Subsequent work has shown that extinction requires protein synthesis in restricted and localized areas of the brain. The infusion of anisomycin into the insular cortex (Berman & Dudai, 2001) or the basolateral amygdala (Bahar *et al.*, 2003) at the time of the first test session blocks extinction of conditioned taste aversion. Anisomycin infused into the CA1 region either before or after the first of a series of test sessions blocks extinction of inhibitory avoidance (Vianna *et al.*, 2001, 2003). In the inhibitory avoidance task at least, extinction depends also on gene expression in the hippocampus: the infusion into CA1 of two different inhibitors of RNA polymerase II, 6-dichloro-1-beta-d-ribofuranosyl benzimidazole (DRB) and  $\alpha$ -amanitin prior to the first extinction test block extinction as much as anisomycin does (Vianna *et al.*, 2003) (Fig. 1).

In addition, extinction also depends on activation of NMDA receptors and various signaling pathways in brain sites specific for each task. Amygdalar NMDA receptors and the NMDA receptor-linked extracellularly regulated protein kinase (ERK) cascade have been shown to be involved in the extinction of fear-potentiated startle (Falls, *et al.*, 1992; Walker *et al.*, 2002; Lu *et al.*, 2001). The same applies to the hippocampus for one-trial inhibitory avoidance. When given bilaterally into CA1 either prior to, or right after, the first of a series of 4 retrieval tests, AP5, the protein kinase A (PKA) inhibitor, Rp-cAMPS, the inhibitor of calcium/calmodulin kinase II (CaMKII), KN62, and the extracellular regulated kinase (ERK) pathway inhibitor, PD098059 block extinction of this task (Szapiro *et al.*, 2003). Similarly, the extinction of fear-potentiated startle is hindered by PD098059 given into the basolateral amygdala prior to retention testing, suggesting that this molecular pathway is also essential in that area for extinction (Lu *et al.*, 2001).

In conditioned taste aversion, the pre-test administration into the insular cortex neither of PD098059 nor, for that matter, of scopolamine or AP5 has any effect on extinction; interestingly, the beta-blocker propranolol hinders extinction (Berman and Dudai, 2001). At the light of what will be discussed in the next section, however, it is possible that the paucity of biochemical findings in the insular cortex may be due to the fact that other brain structures may be additionally

## Hippocampus



**Fig. (1).** Mean (interquartile range) step-down latency, in seconds, in a training session (Tr) and in four daily test sessions (T1-T4). In the training session, a 0.5 mA, 2-sec scrambled shock was delivered to the rats as soon as they stepped down with their 4 paws from a 7 cm-wide, 2.5 cm-high platform onto a 25 x 43 cm grid composed of parallel stainless steel bars. The test sessions may be viewed as extinction sessions inasmuch as the footshock was omitted from them. The animals received 0.5  $\mu$ l infusions into the dorsal CA1 region of 2% DMSO in saline (vehicle), the gene expression blocker DRB (80  $\mu$ g/side), the protein synthesis inhibitor anisomycin (80  $\mu$ g/side), the inhibitor of the extracellular regulated kinase (ERK) pathway inhibitor, PD098059 (5.0  $\mu$ g/side) or the inhibitor of protein kinase A, Rp-cAMPs (0.5  $\mu$ g/side). Infusions were 15 min prior to T1. Note that there was extinction in the control group (#: different from T1 at  $p < 0.02$  in Mann-Wall U test, 2-tailed). The four treatments inhibited extinction (\*: different from T2, T3 and T4 values of control group at  $p < 0.02$  level in Mann-Wall U test, 2-tailed). In addition, note that retrieval in T1 was impaired relative to controls (here \* signals a difference at  $p < 0.02$  level with the T1 session of the vehicle group).

and perhaps importantly involved in consolidation and extinction of this task. Recently, Bahar *et al.* (2003) reported that there is a double dissociation between the role of the central and of the basolateral amygdala in consolidation and extinction of conditioned taste aversion in the rat. Anisomycin or propranolol infused into the former blocks consolidation but not extinction of this task, whereas when infused into the basolateral nucleus both drugs block extinction but not the original consolidation. This also indicates that the site(s) and mechanism(s) of consolidation and extinction should not be necessarily coincident, which is of course what would be expected in virtue of the nature of extinction as a new learning of opposite sign to the original learning (Rescorla, 2001; Vianna *et al.*, 2001, 2003).

Endogenous cannabinoids (endocannabinoids) and their receptor CB1 are found in many places in the brain (Marsicano *et al.*, 2002; Wilson & Nicoll, 2002), including the basolateral amygdala (Katona *et al.*, 1998) and the hippocampus (Porter *et al.*, 2002). Recently, Marsicano, Lutz and their coworkers (Marsicano *et al.*, 2002) have shown

that the extinction of auditory conditioned fear is inhibited in CB1 knockout mice and in animals treated with the CB1 antagonist SR141716A. This suggests that endocannabinoid systems, perhaps in the amygdala or hippocampus, control extinction of at least one fear-motivated task. It would be interesting to link these findings to the rest of the biochemical findings on the role of these two structures in extinction.

Some evidence suggests an involvement in extinction not only of protein kinases, but also of phosphatases. Preliminary findings suggest that phosphatase PP1 (Genoux *et al.*, 2002) and calcineurin (Lin *et al.*, 2003) are necessary for extinction. Further work is desirable on this.

### IS THERE A SITE FOR EXTINCTION OF EACH TASK?

As mentioned, so far the molecular pharmacology of extinction has been studied only in those brain areas that had been shown to be responsible for the consolidation of each

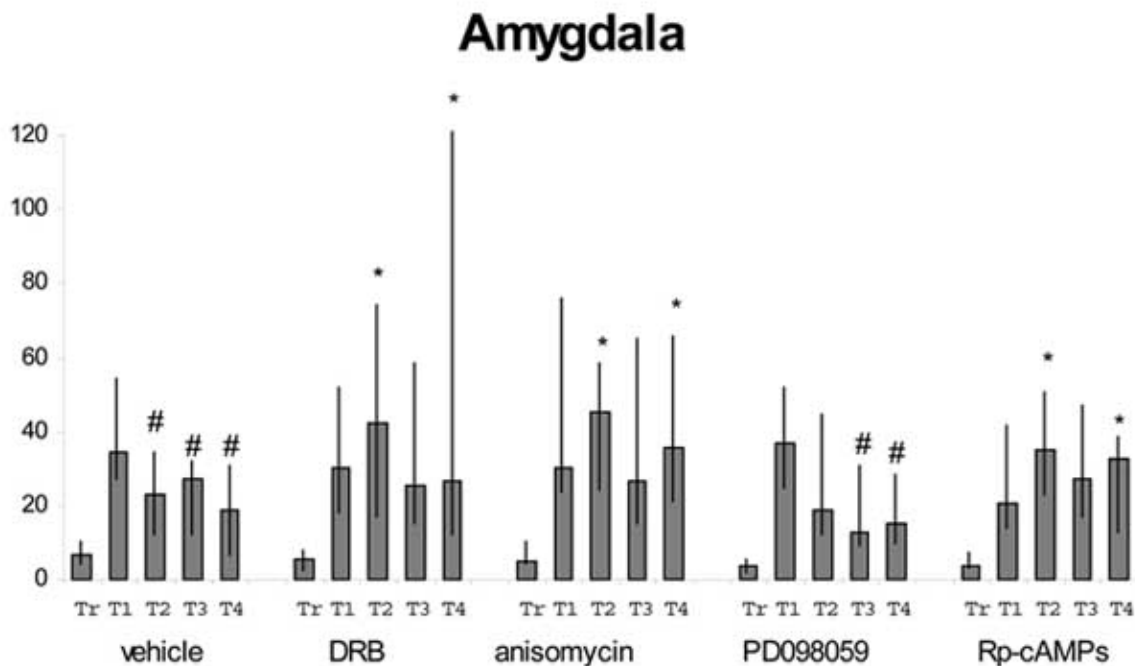
task. There is no study dedicated to characterize the involvement of more than one region in the extinction of the same paradigm. This would be crucial to establish if the structures important for memory extinction are related to specific memory types or represent an orchestrated involvement of different brain areas, such as is the case in memory consolidation (Izquierdo & Medina, 1997).

The possibility that more than one brain region is involved in the extinction of a given behavior is of clinical importance: in the case of lesions of vascular or other nature may impair the function of a given brain area, the stimulation of other regions may be used to bypass that damage and ameliorate the eventual extinction deficit caused by it. For example, intense traumatic experiences such as those that trigger PTSD may be accompanied by cell death in the hippocampus or other areas involved in extinction (Sapolsky, 2001). Stress- and/or depression-induced excessive glucocorticoid release has been shown to induce hippocampal cell death (Lee *et al.*, 2002) not mediated by apoptosis (Roy & Sapolsky, 2003). This may, of course, be at the root of the exacerbated responsiveness to fear seen in those circumstances, which may be associated with an inhibition of extinction. Extinction treatments may reverse the picture, and it is to be presumed that they may bypass the injured area by using other brain cells or structures.

Here we report that the extinction of one-trial step-down inhibitory avoidance can be blocked by DRB, anisomycin

and Rp-cAMPs given not only in the hippocampus, as reported (Vianna *et al.*, 2003) but also in the basolateral amygdala (Fig. 2). Thus, the pharmacology of extinction in the amygdala concerning these substances is similar in this task and in fear-potentiated startle (Myers & Davis, 2002). Further, with the exception of PD098059 which hinders extinction when given in the hippocampus (Fig. 1) but not the amygdala (Fig. 2), clearly the pharmacology of extinction of one trial avoidance is similar in hippocampus and amygdala, and indicates that: 1) gene expression; 2) protein synthesis; and 3) the ERK pathway is required both in the basolateral amygdala and the hippocampus in order to generate extinction.

The coincidences of the findings of (Fig. 1 and 2) suggest that it is likely that in other fear-motivated tasks extinction may be established by different brain structures acting in coordinated fashion, as indeed is the consolidation (Ardenghi *et al.*, 1997; Izquierdo *et al.*, 1997; Bonini *et al.*, 2003) and the retrieval (Barros *et al.*, 2000, 2003) of these same tasks. If this were so, then it might be expected that different regions might require different sets of signaling pathways in order to establish extinction. In this context, see also the paper by Bahar *et al.* (2003) on the double dissociation between different nuclei of the amygdala concerning acquisition and extinction of conditioned taste aversion mentioned above.



**Fig. (2).** Same as Fig. 1, but with vehicle and drug infusions given 15 min prior to T1 into the basolateral amygdala. Here, extinction was blocked by DRB, anisomycin and Rp-cAMPs, but not by PD098059. None of the treatments had any detectable effect on retrieval in T1 when given into the amygdala. In this and the preceding experiment, cannula position was determined in all cases by infusing 4% methylene blue through the cannulae that had been used in the behavioral experiments, sacrificing the animals and measuring the extent of the dye (Vianna *et al.*, 2001, 2003). Only animals with correct cannula positions were used for statistic analysis (96% of the total).

## SOME COMMENTS ON THE NATURE OF EXTINCTION

Operationally, extinction is seen as a decline of the performance of a conditioned response (CR) over a series of test trials in which the reinforcement is omitted. Extinction is more difficult in instrumental conditioning paradigms (Konorski, 1948) because in them the unconditioned stimulus (US) is omitted every time the animals perform the correct CR, and so the subjects have a difficulty in establishing that the omission of the US may be permanent, rather than contingent.

The notion that the inhibition of the original learning that follows extinction does not "destroy" the initial memory trace (eg., Rescorla, 1988) was originally suggested by Pavlov (1927) and his followers (Konorski, 1948), based primarily on demonstrations of differentially triggered recovery relapse of the original learning after behavioral extinction, namely the reinstatement, renewal and spontaneous recovery phenomena (Bouton, 2002). Pavlov (1927) viewed extinction as a form of "internal inhibition", as opposed to the "external inhibition" brought about by distracting stimuli.

Evidence accumulated pointing to the possibility that the original/excitatory and the extinction-related/inhibitory learned information are stored in parallel in the brain and are recalled according to the hierarchical relation last established between them (Bouton, 2002). This is supported by demonstrations that most forms of extinction depends on transcription and translation processes and signaling pathways as much as memory consolidation does (Myers and Davis, 2002; see above).

## CLINICAL RELEVANCE

Fear extinction, although its biological mechanisms have not yet been fully characterized, has been used for almost a century as the base to behavioral treatment of phobias (Walker *et al.*, 2002), and recently applied to the treatment of panic and PTSD using "exposure", "flooding" or "desensitization" psychotherapeutic techniques. Overexpression/Exacerbation of fear and fear-motivated behavior are accounted for, at least in part, by an excessive activity of fear circuits in the amygdala. It has been speculated that it might result from insufficient gabaergic inputs primarily from prefrontal cortex to the former structure that permits unwanted or exacerbated associations of fear memories to occur (Quirk & Gehlert, 2003). The role of catecholaminergic and endocannabinoid-mediated pathways in fear inhibition has also been postulated (see above and Marsicano *et al.*, 2002). Evidence suggest the loss of afferent inhibitory tone as a biological substrate to anxiety disorders and it has been suggested that exaggerated amygdaloid activity underlie the cognitive and peripheral symptoms of panic attacks (Quirk & Gehlert, 2003; Jeffrey and Jay, 1998).

Perhaps behavioral treatments that enhance the "no US" component of extinction can be applied to the treatment of PTSD and other forms of anxiety. Clearly, emphasis on the "no US" side of the extinction contingency will reduce the likelihood that an eventually strong recall of the original stressful situation may bring about an undesired exacerbation of the condition (Beckett, 2002).

The comprehension of human anxiety disorders depends on the understanding of normal fear and fear-motivated behaviors. Similarly, the treatment of exaggerated fear and anxiety related disorders depends on the characterization of the physiological fear inhibition mechanisms.

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