



Published in final edited form as:

Curr Opin Neurobiol. 2011 June ; 21(3): 460–466. doi:10.1016/j.conb.2011.04.003.

Hippocampal Regulation of Aversive Memories

Ki Ann Goosens¹

¹ McGovern Institute for Brain Research and the Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, 43 Vassar St, Cambridge, MA 02139, USA

Abstract

For many years, the hippocampal formation has been implicated in the regulation of negative emotion, yet the nature of this link has remained elusive. Recent studies have made important links between the hippocampus and regulation of stress hormones that affect aversive memory. Additional studies have shown that the hippocampus regulates the gating of fear by contextual information. An emerging literature also links the hippocampus to prediction errors during fear learning and extinction. The mechanisms by which the hippocampus regulates negative emotion are clearly complicated, but suggest that interventions aimed at restoring normal hippocampal function may help with disorders of negative affect, such as depression or post-traumatic stress disorder and depression.

Introduction

The canonical brain regions associated with negative emotions in mammalian systems include the amygdala, and bed nucleus of stria terminalis[1]. Damage to these regions leads to clearly defined impairments on cognitive tasks using fearful or anxiety-provoking stimuli. However, there is an increasing appreciation that other structures exert powerful modulatory influences over activity in these brain regions. One such structure is the hippocampal formation.

The hippocampus was first linked to emotional regulation by Papez [2], who hypothesized that increased anxiety and aggression following rabies infection could be attributed to damaged hippocampal circuits. The Papez circuit was ultimately linked to memory formation, rather than the control of emotionality, but this work established a connection between negative emotion and the hippocampus. Recent studies have shown that the role of the hippocampus in negative affect is complex. Some of this complexity arises because the hippocampus is a large structure with significant regional differences in gene expression and connectivity [3–5]. In particular, the dorsal hippocampus (posterior hippocampus in humans) has strong connections with the neocortex, while the ventral hippocampus (anterior hippocampus in humans) has strong, direct projections to subcortical structures, including the amygdala. This pattern of connectivity has led to the hypothesis that the dorsal and ventral hippocampus are differentially involved in mnemonic versus motivational aspects of learning [6].

In accordance with this, numerous studies have shown dissociations between these two hippocampal regions [7–9]. Ventral hippocampal damage reduces avoidance behavior in

© 2011 Elsevier Ltd. All rights reserved.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ethologically-based tests of innate anxiety. For example, hippocampal lesions reduce anxiety on tasks involving a choice between “safe” dark high-walled arms, or “risky” well-lit open arms [7,8,10,11]. Ventral hippocampal lesions also decrease anxiety during social interaction [10] and reduce food neophobia [7]. Damage to the ventral hippocampus also impairs fear, leading to reduced expression of defensive behaviors during exposure to predator odor [12] and decreased freezing following Pavlovian fear conditioning, in which innocuous discrete or contextual cues are paired with footshock [8,12]. In contrast, damage to the dorsal hippocampus does not typically affect innate anxiety, nor does it abolish conditional freezing to discrete cues.

Studies in humans have also linked hippocampal activity to aversive processing. In a recent study [13], functional magnetic resonance imaging was used to identify brain activation during Pavlovian fear conditioning in which a visual stimulus was paired with mild electric shock. The left hippocampus displayed a heightened BOLD response during Pavlovian fear conditioning in subjects receiving stimulus-shock pairings, relative to subjects receiving the stimulus and shock in an unpaired fashion. This hippocampal activity has been shown to be related to the subjects’ awareness of the predictive relationship between a stimulus and the aversive event that follows [14]. Activity in the hippocampus, specifically the entorhinal cortex, has also been linked to the anxiety associated with painful stimulation [15]: one visual stimulus was consistently paired with moderately painful stimulation, and a second visual stimulus was paired with the moderate pain stimulus on most trials, but paired with an intensely painful stimulus on a small number of trials. This second stimulus provoked a higher level of anxiety, as reported by the subjects, but also evoked higher levels of hippocampal activity.

Collectively, these studies reveal clear links between hippocampal activity and the regulation of negative affect. But what are the specific mechanisms by which aversive learning can be modulated? Is the role of the hippocampus in the regulation of aversive learning limited to the ventral hippocampus? We discuss three mechanisms by which the hippocampus exerts a modulatory influence over aversive learning (Figure 1), and consider how these mechanisms might be affected by pathological conditions.

Hippocampal inhibition of stress hormone secretion

One component of aversive memory formation is the secretion of stress hormones, which act throughout the brain and body to generate a set of coordinated responses to promote survival in the face of adverse circumstances. Upon encountering a stressor, neurons in the paraventricular nucleus of the hypothalamus (PVN) secrete corticotrophin releasing factor (CRF), which, through an additional intermediate step, leads to the secretion of glucocorticoids (corticosterone in rodents, cortisol in humans) into the bloodstream by the adrenal glands. Glucocorticoids induce many bodily changes following stress, including changes in metabolism, cardiovascular tone, and the immune system; they also promote the formation of fear memory.

The secretion of glucocorticoids is highly regulated. Numerous brain structures project to the PVN, and activity at these connections influences both the basal secretion of glucocorticoids, which peak at the time of awakening and decline throughout the day, and the acute secretion of glucocorticoids that accompany stress. The hippocampus projects to several sets of PVN-projecting neurons [16], suggesting that it may regulate the secretion of CRF by the PVN. In line with this, hippocampal damage leads to elevated basal secretion of CRF [17] and glucocorticoids [11,18], while also eliminating the glucocorticoid response to a social stressor [18]. Damage to the dorsal hippocampus is sufficient to induce these changes [17], though this does not preclude a role for the ventral hippocampus in the

inhibition of stress hormone secretion. These findings suggest that the hippocampus is not only important for controlling the secretion of glucocorticoids, but also plays a role in generating a “normal” stress response. Relationships between hippocampal volume and the cortisol response to a stressor have also been observed, with larger hippocampi associated with lower cortisol secretion in response to a stressor in humans [19]. In addition, studies have shown that humans who show cortisol secretion following an acute stressor also exhibited deactivation of the hippocampus, and the degree of deactivation was correlated to the release of cortisol in response to the stressor [20].

Collectively, these results show that larger hippocampal volumes are associated with stronger control over stress hormone secretion. This suggests that larger hippocampal volumes may enable faster recovery from stress. In accordance with this, small hippocampal volumes have been identified as a risk factor for the development of stress-related psychiatric disorders such as post-traumatic stress disorder [21] and depression [22]. It may be that elevated stress hormone secretion in humans with small hippocampi contributes to the development of these conditions. In animals, prolonged secretion of CRF or glucocorticoids promotes fear and anxiety. High levels of glucocorticoid activity act in the amygdala to enhance the consolidation of aversive experiences [23–25], and impair the extinction of learned fear [17,26]. High levels of CRF also promote anxious behavior through actions in the amygdala [27]. In this regard, interventions that prevent hippocampal atrophy may help with anxiety by promoting “normal” function within this stress hormone axis.

Hippocampus and contextual control of aversive memory

A substantial literature has linked the hippocampus to spatial and contextual learning, and contextual information regulates aversive memory in a number of ways. First, the physical environment in which an aversive stimulus is encountered may be associated with the aversive event, a phenomenon referred to as context conditioning. Second, the expression of the extinction of fear is context-specific. During extinction, the predictive stimulus is repeatedly presented in the absence of the aversive event that it once predicted, and the expression of fear is gradually suppressed. This extinction learning is context-specific. When the predictive stimulus is presented in a new environment, fear returns to high levels, a phenomenon termed fear renewal. The hippocampus has been linked to both of these forms of contextual control of aversive memory.

The role of the hippocampus in context conditioning is not without controversy. Postconditioning damage to the dorsal hippocampus produces a pronounced, but temporally graded, amnesia for contextual fear memory; lesions made shortly following conditioning produce significant reductions in contextual fear memory, while lesions made several weeks following conditioning produce little to no impairment [28,29]. Post-training manipulations in the ventral hippocampus also impair contextual fear memory [30]. These results are consistent with the idea that the hippocampus performs a time-limited role in the retrieval and systems-level consolidation of contextual representations. In contrast, pre-conditioning manipulations of the hippocampus often do not affect the ability to acquire contextual fear memory [29,31]. Although it has been argued that such findings suggest that animals acquire contextual fear by using elemental cues that comprise the context [32], other findings suggest that there are extra-hippocampal systems that can acquire contextual representations, but which are not as efficient [28]. Although the dorsal hippocampus plays an important role in acquiring contextual fear memories, the exact nature of its role is still unclear.

The role of the hippocampus in the contextual control of extinction is also complicated. To investigate the role of the hippocampus in the context-specific expression of extinction, rats

were administered auditory fear conditioning in which a tone was paired with footshock, followed by extinction training. Following extinction, fear memory to the tone was assessed either in the extinction context or a novel context. Dorsal hippocampal inactivation had no effect on auditory fear memory during extinction tests conducted in the context of extinction, but impaired fear renewal when the extinction test was conducted in a novel context [33,34]. This inactivation also prevented the contextual modulation of tone-evoked single unit firing in the lateral amygdala during extinction testing [35,36]. Ventral hippocampal inactivation prevented contextual renewal in a manner similar to that observed following dorsal hippocampal inactivation [37]. In accordance with this observation, a significant proportion of so-called “fear neurons” in the basolateral amygdala, identified because their spike firing directly correlates with the expression of fear, receive projections from the ventral hippocampus [38]; these inputs may enable the expression of fear following a shift in environmental context. Collectively, these studies show that both dorsal and ventral aspects of the hippocampus are critically involved in the contextual renewal of fear memories.

Contextual renewal is a phenomenon that is highly relevant in a clinical setting. Humans who have experienced fear conditioning in a laboratory setting experience contextual renewal of fear [39,40], but contextual shifts following extinction therapy in humans with anxiety disorders also promote relapse [41]. Thus, interventions that reduce hippocampal signals during contextual shifts may facilitate the context-independent extinction of fear, and reduce the incidence of relapse in clinical populations.

Hippocampus and unexpected aversive events

One early theory linking the hippocampus to anxiety was made by Gray [42,43], who noted that learning about stimuli that predicted either punishment or the absence of reward required increased attention to the environment. To explain this, Gray promoted the “comparator theory” of hippocampal function, suggesting that the hippocampus functions to compare predicted events with the actual occurrence of events. When a mismatch occurs, either because an event was incorrectly predicted, or because an event occurred unexpectedly, he theorized that the hippocampus sends signals to bias the organism towards behaviors that are adaptive in the face of aversive outcomes, such as the enhanced vigilance and attention that accompanies anxiety [44]. According to this theory, prediction errors, or differences between actual and expected events, are critical for the induction of an anxious or fearful state. Indeed, the necessity of prediction errors, or “surprise”, in associative learning has been well-documented [45]. Within aversive learning, prediction errors may occur during learning, when the ability to anticipate an aversive outcome is often quite poor, or during extinction, when aversive outcomes are unexpectedly omitted (Figure 2). The hippocampus has been linked to the unexpected presence and absence of aversive outcomes.

A variety of circumstances may contribute to the surprising occurrence of an aversive event. The expectancy of aversive events is low during the first trials of a multiple trial training session, as animals learn the predictive relationships between different stimuli. Accordingly, elevated hippocampal activity (relative to pre-training baseline) during standard fear conditioning is reported to be greatest in the early trials of training [46–48]. This enhanced hippocampal activity is correlated with the ability to accurately estimate the precise timing of an aversive event in humans [46], consistent with the idea that hippocampal prediction errors enhance aspects of aversive learning. Aversive events may also occur reliably, but at unexpected times. This unreliable timing both enhances fear and requires activity in the dorsal hippocampus during fear conditioning [49]. Finally, aversive events may occur in a completely unsignalled fashion, resulting in context conditioning, and the dorsal and ventral hippocampus both play critical roles in acquiring contextual fear memories [29,30].

Aversive events may also be predicted, yet unexpectedly absent. This occurs during fear extinction, in which predictive cues are explicitly presented in the absence of the aversive cue that once followed. Phosphorylation of extracellular signal-related kinase (ERK) in the dorsal hippocampus is strongly associated with prediction errors during the extinction of contextual fear memory, and pERK is expressed at peak levels early during extinction learning, when there is the greatest violation of expectation [50]. In humans, hippocampal activation during fear extinction has been observed only in the early trials of extinction learning [13], and the unexpected omission of a painful expected stimulus also triggers hippocampal activity [48]. Additionally, brain-derived neurotrophic factor (BDNF) levels in the dorsal hippocampus are correlated with the extinction of fear; high levels of hippocampal BDNF are associated with high levels of extinction [51]. Thus, the hippocampus does play a role in extinction. Aversive events may also be predicted but absent during schedules of partial reinforcement, in which the occurrence of an aversive event is only partly predicted by a cue. Pharmacogenetic silencing of cells in the dentate gyrus of hippocampus selectively reduced the expression of fear to a cue with a partially reinforced history, without affecting freezing to a cue with a history of complete reinforcement with footshock [52]. Additionally, mice with impaired inhibitory neurotransmission in hippocampus, due to a reduction in synaptic GABA_A receptor content, also show a selective enhancement in fear to partially reinforced cues, without any change in fear to a fully reinforced cue, relative to wild-type mice [53]. Thus, there is evidence that the hippocampus plays a role in generating prediction errors during fear conditioning with partial reinforcement.

Prediction errors may be maximal under conditions of weak learning, as the ability to form an accurate prediction may depend on the ability to form strong associations. Weak learning may occur either because an aversive event is only mildly aversive, or because pairing of a predictive stimulus with an aversive event was minimal. In support of the idea that the hippocampus generates prediction errors to enhance fear learning under conditions of weak learning, deficits in fear conditioning to discrete cues following hippocampal damage are more pronounced when either low intensity footshocks or limited training is used [54].

Finally, prediction errors may occur when environmental contexts are shifted and an animal encounters a fear-eliciting cue unexpectedly. As discussed in the preceding section, numerous studies have revealed a role for the dorsal hippocampus in the contextual renewal of fear.

Broadly conceived, hippocampal prediction errors serve to reinforce new learning. This may occur because these error signals trigger dopamine release from dopaminergic midbrain neurons to reinforce new learning [55], or these prediction errors may be conveyed directly to circuits of fear and anxiety. Because hippocampal prediction errors may either enhance (during unexpected aversive events, for example) or reduce (during extinction) fear, it is difficult to speculate how such errors might be manipulated to reduce aversive memory formation. Although patients with anxiety disorders display enhanced responsiveness to ambiguous cues (that is, cues that do not generate reliable predictions, and thus are associated with high prediction error rates), there is currently little direct evidence to show that prediction error rates are higher in patients with fear or anxiety disorders.

Conclusions

Current findings reveal multiple roles for the hippocampus in the modulation of aversive memory. Although the ventral hippocampus has been more strongly associated with anxiety, new findings show clear roles for the dorsal hippocampus. The use of sophisticated electrophysiological recording *in vivo* and molecular biological techniques will soon enable

a better understanding of the nature of the hippocampal signals that are conveyed to neural circuits for fear and anxiety. This will subsequently facilitate exploration of the ways in which chronic stress and affective mental illness perturbs these signals.

References and recommended reading

* Of special interest

**Of outstanding interest

1. Davis M, Walker DL, Miles L, Grillon C. Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology*. 2010; 35:105–135. [PubMed: 19693004]
2. Papez JW. A proposed mechanism of emotion. *Arch Neurol Psychiatry*. 1937; 38:725–743.
3. Dong HW, Swanson LW, Chen L, Fanselow MS, Toga AW. Genomic-anatomic evidence for distinct functional domains in hippocampal field CA1. *Proc Natl Acad Sci U S A*. 2009; 106:11794–11799. [PubMed: 19561297]
4. Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, Boe AF, Boguski MS, Brockway KS, Byrnes EJ, et al. Genome-wide atlas of gene expression in the adult mouse brain. *Nature*. 2007; 445:168–176. [PubMed: 17151600]
5. van Strien NM, Cappaert NL, Witter MP. The anatomy of memory: an interactive overview of the parahippocampal-hippocampal network. *Nat Rev Neurosci*. 2009; 10:272–282. [PubMed: 19300446]
6. Segal M, Richter-Levin G, Maggio N. Stress-induced dynamic routing of hippocampal connectivity: a hypothesis. *Hippocampus*. 20:1332–1338. [PubMed: 20082290]
7. Bannerman DM, Deacon RM, Offen S, Friswell J, Grubb M, Rawlins JN. Double dissociation of function within the hippocampus: spatial memory and hyponeophagia. *Behav Neurosci*. 2002; 116:884–901. [PubMed: 12369808]
8. Bannerman DM, Rawlins JN, McHugh SB, Deacon RM, Yee BK, Bast T, Zhang WN, Pothuizen HH, Feldon J. Regional dissociations within the hippocampus—memory and anxiety. *Neurosci Biobehav Rev*. 2004; 28:273–283. [PubMed: 15225971]
9. Kjelstrup KB, Solstad T, Brun VH, Hafting T, Leutgeb S, Witter MP, Moser EI, Moser MB. Finite scale of spatial representation in the hippocampus. *Science*. 2008; 321:140–143. [PubMed: 18599792]
10. McHugh SB, Deacon RM, Rawlins JN, Bannerman DM. Amygdala and ventral hippocampus contribute differentially to mechanisms of fear and anxiety. *Behav Neurosci*. 2004; 118:63–78. [PubMed: 14979783]
11. Kjelstrup KG, Tuvnes FA, Steffenach HA, Murison R, Moser EI, Moser MB. Reduced fear expression after lesions of the ventral hippocampus. *Proc Natl Acad Sci U S A*. 2002; 99:10825–10830. [PubMed: 12149439]
12. Pentkowski NS, Blanchard DC, Lever C, Litvin Y, Blanchard RJ. Effects of lesions to the dorsal and ventral hippocampus on defensive behaviors in rats. *Eur J Neurosci*. 2006; 23:2185–2196. [PubMed: 16630065]
13. Knight DC, Smith CN, Cheng DT, Stein EA, Helmstetter FJ. Amygdala and hippocampal activity during acquisition and extinction of human fear conditioning. *Cogn Affect Behav Neurosci*. 2004; 4:317–325. [PubMed: 15535167]
14. Knight DC, Waters NS, Bandettini PA. Neural substrates of explicit and implicit fear memory. *Neuroimage*. 2009; 45:208–214. [PubMed: 19100329]
15. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JN, Tracey I. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci*. 2001; 21:9896–9903. [PubMed: 11739597]
16. Canteras NS, Swanson LW. Projections of the ventral subiculum to the amygdala, septum, and hypothalamus: a PHAL anterograde tract-tracing study in the rat. *J Comp Neurol*. 1992; 324:180–194. [PubMed: 1430328]

17. Herman JP, Schafer MK, Young EA, Thompson R, Douglass J, Akil H, Watson SJ. Evidence for hippocampal regulation of neuroendocrine neurons of the hypothalamo-pituitary-adrenocortical axis. *J Neurosci.* 1989; 9:3072–3082. [PubMed: 2795152]
18. Buchanan TW, Tranel D, Kirschbaum C. Hippocampal damage abolishes the cortisol response to psychosocial stress in humans. *Horm Behav.* 2009; 56:44–50. [PubMed: 19281812]
19. Pruessner JC, Baldwin MW, Dedovic K, Renwick R, Mahani NK, Lord C, Meaney M, Lupien S. Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood. *Neuroimage.* 2005; 28:815–826. [PubMed: 16023372]
20. Pruessner JC, Dedovic K, Khalili-Mahani N, Engert V, Pruessner M, Buss C, Renwick R, Dagher A, Meaney MJ, Lupien S. Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biol Psychiatry.* 2008; 63:234–240. [PubMed: 17686466]
- 21*. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci.* 2002; 5:1242–1247. This paper overturned conventional wisdom regarding the relationship between hippocampal atrophy and stress. This study showed that a small hippocampal volume is a risk factor for developing stress-related mental illness, rather than hippocampal atrophy being a consequence of stress exposure. [PubMed: 12379862]
22. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am J Psychiatry.* 2004; 161:598–607. [PubMed: 15056502]
23. Zorawski M, Killcross S. Posttraining glucocorticoid receptor agonist enhances memory in appetitive and aversive Pavlovian discrete-cue conditioning paradigms. *Neurobiol Learn Mem.* 2002; 78:458–464. [PubMed: 12431429]
24. Donley MP, Schulkin J, Rosen JB. Glucocorticoid receptor antagonism in the basolateral amygdala and ventral hippocampus interferes with long-term memory of contextual fear. *Behav Brain Res.* 2005; 164:197–205. [PubMed: 16107281]
25. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. *Nat Rev Neurosci.* 2009; 10:423–433. [PubMed: 19469026]
26. Gourley SL, Kedves AT, Olausson P, Taylor JR. A history of corticosterone exposure regulates fear extinction and cortical NR2B, GluR2/3, and BDNF. *Neuropsychopharmacology.* 2009; 34:707–716. [PubMed: 18719621]
27. Matys T, Pawlak R, Matys E, Pavlides C, McEwen BS, Strickland S. Tissue plasminogen activator promotes the effects of corticotropin-releasing factor on the amygdala and anxiety-like behavior. *Proc Natl Acad Sci U S A.* 2004; 101:16345–16350. [PubMed: 15522965]
28. Wiltgen BJ, Sanders MJ, Anagnostaras SG, Sage JR, Fanselow MS. Context fear learning in the absence of the hippocampus. *J Neurosci.* 2006; 26:5484–5491. [PubMed: 16707800]
29. Maren S, Aharonov G, Fanselow MS. Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. *Behav Brain Res.* 1997; 88:261–274. [PubMed: 9404635]
30. Rudy JW, Matus-Amat P. The ventral hippocampus supports a memory representation of context and contextual fear conditioning: implications for a unitary function of the hippocampus. *Behav Neurosci.* 2005; 119:154–163. [PubMed: 15727521]
31. Matus-Amat P, Higgins EA, Barrientos RM, Rudy JW. The role of the dorsal hippocampus in the acquisition and retrieval of context memory representations. *J Neurosci.* 2004; 24:2431–2439. [PubMed: 15014118]
32. Rudy JW, Huff NC, Matus-Amat P. Understanding contextual fear conditioning: insights from a two-process model. *Neurosci Biobehav Rev.* 2004; 28:675–685. [PubMed: 15555677]
33. Corcoran KA, Maren S. Hippocampal inactivation disrupts contextual retrieval of fear memory after extinction. *J Neurosci.* 2001; 21:1720–1726. [PubMed: 11222661]
34. Corcoran KA, Maren S. Factors regulating the effects of hippocampal inactivation on renewal of conditional fear after extinction. *Learn Mem.* 2004; 11:598–603. [PubMed: 15466314]
35. Hobin JA, Goosens KA, Maren S. Context-dependent neuronal activity in the lateral amygdala represents fear memories after extinction. *J Neurosci.* 2003; 23:8410–8416. [PubMed: 12968003]

36. Maren S, Hobin JA. Hippocampal regulation of context-dependent neuronal activity in the lateral amygdala. *Learn Mem.* 2007; 14:318–324. [PubMed: 17522021]
37. Hobin JA, Ji J, Maren S. Ventral hippocampal muscimol disrupts context-specific fear memory retrieval after extinction in rats. *Hippocampus.* 2006; 16:174–182. [PubMed: 16358312]
- 38**. Herry C, Ciocchi S, Senn V, Demmou L, Muller C, Luthi A. Switching on and off fear by distinct neuronal circuits. *Nature.* 2008; 454:600–606. This paper provides evidence for two distinct neuronal populations in the basal amygdala. “Fear” neurons show increases in tone-evoked spike firing over fear conditioning, and decrease spike firing over extinction; these cells receive inputs from ventral hippocampus. “Extinction” neurons show increases in tone-evoked spike firing over extinction learning, and receive inputs from medial prefrontal cortex. [PubMed: 18615015]
39. Effting M, Kindt M. Contextual control of human fear associations in a renewal paradigm. *Behav Res Ther.* 2007; 45:2002–2018. [PubMed: 17451643]
40. Neumann DL, Kitlertsirivatana E. Exposure to a novel context after extinction causes a renewal of extinguished conditioned responses: implications for the treatment of fear. *Behav Res Ther.* 2010; 48:565–570. [PubMed: 20356572]
41. Kaplan GB, Heinrichs SC, Carey RJ. Treatment of addiction and anxiety using extinction approaches: neural mechanisms and their treatment implications. *Pharmacol Biochem Behav.* 2011; 97:619–625. [PubMed: 20723558]
42. Gray, JA. *The Neuropsychology of Anxiety.* Oxford: Oxford University Press; 1982.
43. Gray JA. A theory of anxiety: the role of the limbic system. *Encephale.* 1983; 9:161B–166B.
44. Davis M, Whalen PJ. The amygdala: vigilance and emotion. *Mol Psychiatry.* 2001; 6:13–34. [PubMed: 11244481]
45. Kamin, LJ. Predictability, Surprise, Attention, and Conditioning. In: Campbell, BA.; Church, RM., editors. *Punishment and Aversive Behavior.* Appleton-Century-Crofts; 1969. p. 279-298.
46. Knight DC, Cheng DT, Smith CN, Stein EA, Helmstetter FJ. Neural substrates mediating human delay and trace fear conditioning. *J Neurosci.* 2004; 24:218–228. [PubMed: 14715954]
47. Green JT, Arenos JD. Hippocampal and cerebellar single-unit activity during delay and trace eyeblink conditioning in the rat. *Neurobiol Learn Mem.* 2007; 87:269–284. [PubMed: 17046292]
48. Ploghaus A, Tracey I, Clare S, Gati JS, Rawlins JN, Matthews PM. Learning about pain: the neural substrate of the prediction error for aversive events. *Proc Natl Acad Sci U S A.* 2000; 97:9281–9286. [PubMed: 10908676]
49. Amadi, U.; Goosens, KA. Program No. 680.3/GG20. Chicago, IL: Society for Neuroscience; 2009. Hippocampus-based aversive prediction errors enhance conditional fear.
- 50**. Huh KH, Guzman YF, Tronson NC, Guedea AL, Gao C, Radulovic J. Hippocampal Erk mechanisms linking prediction error to fear extinction: roles of shock expectancy and contextual aversive valence. *Learn Mem.* 2009; 16:273–278. This is one of the first investigations into the molecular mechanisms that underlie prediction error formation in the hippocampus. [PubMed: 19318469]
- 51*. Peters J, Dieppa-Perea LM, Melendez LM, Quirk GJ. Induction of fear extinction with hippocampal-infralimbic BDNF. *Science.* 2010; 328:1288–1290. This paper demonstrates that the application of BDNF to the medial prefrontal cortex induces plastic changes that mimic extinction, even in the absence of behavioral training. Experiments were conducted to show that the hippocampus is the endogenous source of extinction-related BDNF signalling. [PubMed: 20522777]
- 52*. Tsetsenis T, Ma XH, Lo Iacono L, Beck SG, Gross C. Suppression of conditioning to ambiguous cues by pharmacogenetic inhibition of the dentate gyrus. *Nat Neurosci.* 2007; 10:896–902. The investigators used sophisticated molecular genetic techniques to selectively silence neurons in the dentate gyrus. This silencing reduces fear to partially reinforced cues, without affecting fear to fully reinforced cues. [PubMed: 17558402]
53. Crestani F, Lorez M, Baer K, Essrich C, Benke D, Laurent JP, Belzung C, Fritschy JM, Luscher B, Mohler H. Decreased GABAA-receptor clustering results in enhanced anxiety and a bias for threat cues. *Nat Neurosci.* 1999; 2:833–839. [PubMed: 10461223]

54. Quinn JJ, Wied HM, Ma QD, Tinsley MR, Fanselow MS. Dorsal hippocampus involvement in delay fear conditioning depends upon the strength of the tone-footshock association. *Hippocampus*. 2008; 18:640–654. [PubMed: 18306286]
55. Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron*. 2005; 46:703–713. [PubMed: 15924857]

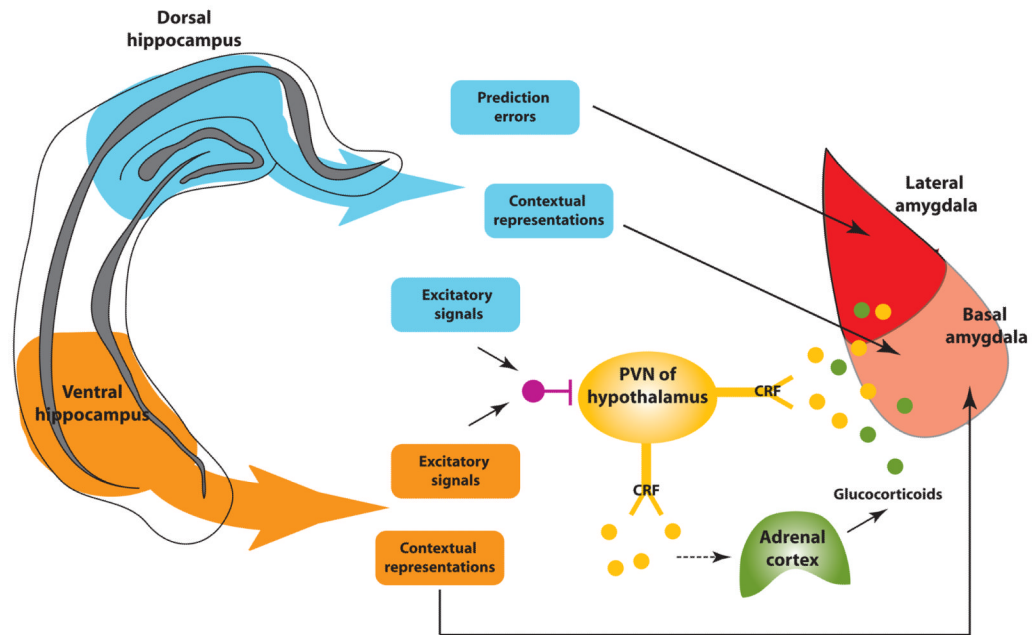


Figure 1. Diverse mechanisms for hippocampal enhancement of aversive memory

The hippocampus controls fear and anxiety through multiple mechanisms, including the regulated secretion of stress hormones, the facilitation of associations between environmental context and aversive outcomes, the enabling of context-dependent expression of fear extinction, and the enhancement of fear learning via prediction errors. The hippocampus may perform these roles by direct or indirect connections with circuits mediating aversive memory.

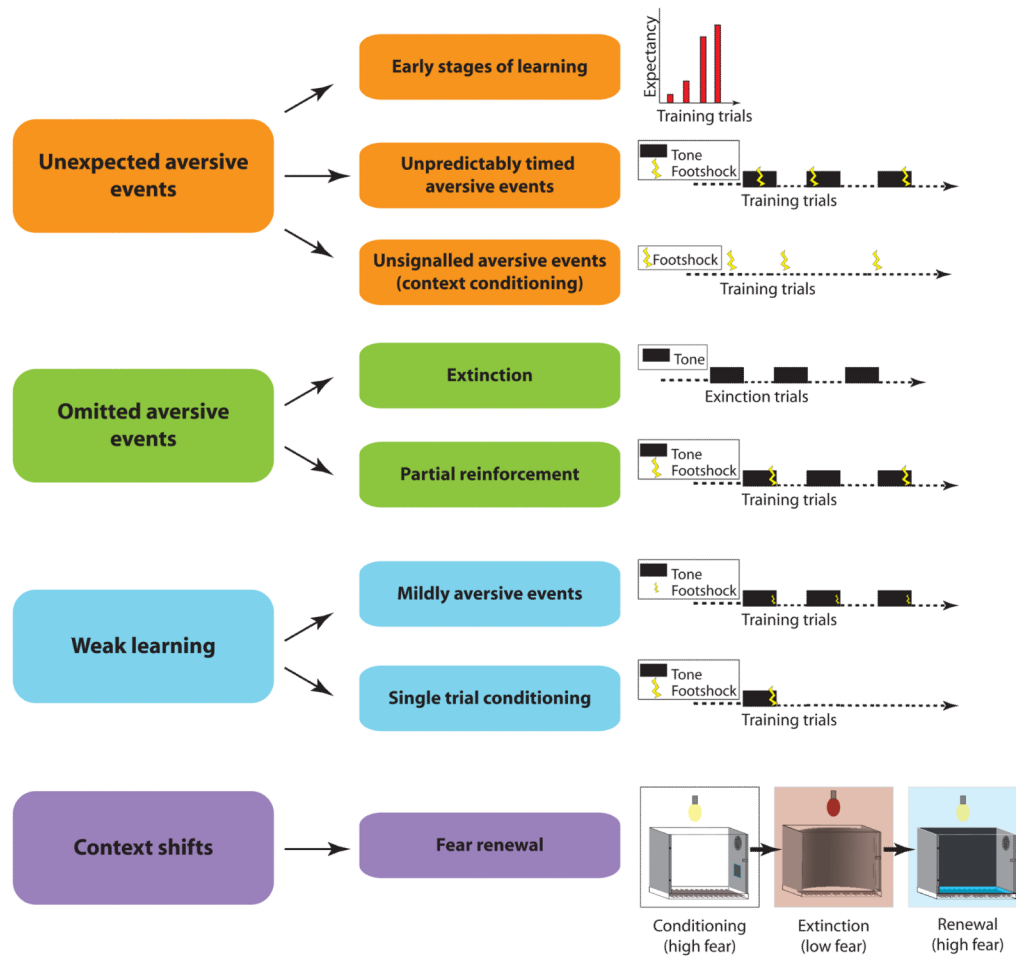


Figure 2. Sources of hippocampal prediction errors

The hippocampus participates in many forms of prediction errors, where outcomes are unexpected. These may be conceptualized as four broad classes of error, including unexpected aversive events, aversive events that were expected but absent, weak learning, and context shifts.