




REVIEW

Fear conditioning and the basolateral amygdala [version 1; peer review: 3 approved]

Yajie Sun¹, Helen Gooch¹, Pankaj Sah ^{1,2}

¹Queensland Brain Institute, University of Queensland, Queensland, Australia

²Brain Research Centre and Department of Biology, Southern University of Science and Technology, Shenzhen, China

v1 **First published:** 28 Jan 2020, 9(F1000 Faculty Rev):53 (<https://doi.org/10.12688/f1000research.21201.1>)
Latest published: 28 Jan 2020, 9(F1000 Faculty Rev):53 (<https://doi.org/10.12688/f1000research.21201.1>)

Abstract




Fear is a response to impending threat that prepares a subject to make appropriate defensive responses, whether to freeze, fight, or flee to safety. The neural circuits that underpin how subjects learn about cues that signal threat, and make defensive responses, have been studied using Pavlovian fear conditioning in laboratory rodents as well as humans. These studies have established the amygdala as a key player in the circuits that process fear and led to a model where fear learning results from long-term potentiation of inputs that convey information about the conditioned stimulus to the amygdala. In this review, we describe the circuits in the basolateral amygdala that mediate fear learning and its expression as the conditioned response. We argue that while the evidence linking synaptic plasticity in the basolateral amygdala to fear learning is strong, there is still no mechanism that fully explains the changes that underpin fear conditioning.

Keywords

learning, memory storage, associative learning, anxiety, long term potentiation

Open Peer Review

Reviewer Status 

	Invited Reviewers		
	1	2	3
version 1 28 Jan 2020			

F1000 Faculty Reviews are written by members of the prestigious **F1000 Faculty**. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

- 1 **Nathan M Holmes**, University of New South Wales, Sydney, Australia
- 2 **Roger L Clem**, Icahn School of Medicine at Mount Sinai, New York, USA
- 3 **Benedetto Sacchetti**, University of Turin, Turin, Italy

Any comments on the article can be found at the end of the article.

Corresponding author: Pankaj Sah (pankaj.sah@uq.edu.au)

Author roles: Sun Y: Writing – Original Draft Preparation; Gooch H: Writing – Original Draft Preparation; Sah P: Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work is supported by the National Health and Medical Research Council and Australian Research Council. *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

Copyright: © 2020 Sun Y *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Sun Y, Gooch H and Sah P. **Fear conditioning and the basolateral amygdala [version 1; peer review: 3 approved]** F1000Research 2020, 9(F1000 Faculty Rev):53 (<https://doi.org/10.12688/f1000research.21201.1>)

First published: 28 Jan 2020, 9(F1000 Faculty Rev):53 (<https://doi.org/10.12688/f1000research.21201.1>)

Introduction

Fear is a response to impending threat that prepares a subject to make appropriate defensive responses. Conserved across species, it describes a physiological state preparing the animal to freeze, fight, or flee to safety and, in humans, is accompanied by affective feelings of dread and anticipation. Our physiological understanding of fear and the neural circuits that underpin it have largely been studied using the Pavlovian paradigm of fear conditioning¹. In this paradigm, subjects, typically laboratory rodents, are exposed to a neutral sensory stimulus, such as a light, odor, or tone (the conditioned stimulus [CS]) that is contingently paired with an aversive one (the unconditioned stimulus [US]), typically a footshock. Following a number of pairings, sometimes just one, subjects exhibit defensive responses when exposed to the CS alone (the conditioned response [CR]). This learning is rapid and long lasting: presentation of the same CS days, weeks, or months after its conditioning continues to evoke defensive responses. Thus, fear conditioning is a form of associative learning in which pairing the CS with the US forms a memory trace that is later retrieved by the CS alone. As such, understanding the biology that underpins fear learning will not only help us understand fear but also provide insight into memory formation, storage, and retrieval. While there are differences between the subjective state of fear and anxiety², there are similarities in the accompanying physiological response, and the two states share neural circuits^{3–5}. Thus, understanding the neural circuits that mediate fear may also help to unravel those that underpin anxiety disorders.

Like all learning, fear conditioning has three phases: acquisition, during which a sensory input; the CS, becomes associated with an aversive outcome; storage, in which a memory trace is formed; and retrieval, when the memory trace is retrieved and initiates defensive responses. Early lesion experiments established that the amygdala, a region in the mid-temporal lobe, is an essential component of the circuits that mediate fear learning^{6,7}. The amygdala is a heterogeneous structure made of a number of nuclei that receive input from a host of cortical and subcortical areas and have extensive internuclear connectivity⁸. Of these, the best understood are the basolateral amygdala (BLA) and central amygdala (CeA), which form the main input and output structures of the amygdala, respectively^{8–10}. CS and US information converge in the BLA^{8–11}, and contingent activation of these inputs forms a memory trace that may even be stored there^{12–14}. Subsequent presentation of the CS activates circuits in the BLA, and projections from the BLA to the CeA drive defensive behaviors. While it is becoming increasingly clear that the CeA also plays a role in fear learning^{15,16}, much work has gone into understanding the acquisition and processing of information in the BLA during fear learning and expression. In this brief review, we focus on the BLA and its role in a commonly studied form of associated learning: cued auditory fear conditioning.

The basolateral amygdala

The BLA is located in the mid-temporal pole and anatomically divided into the lateral (LA) and basal (BA) nuclei. The

LA is situated dorsal to the BA and is subdivided into the dorso-lateral (LAdl), ventrolateral (LAvl), and ventromedial nuclei¹⁷, while the BA consists of the basolateral nucleus (BL) and the basomedial nuclei (BM), also known as the accessory BA (AB)^{8,18–20}. These divisions within the BLA are cytoarchitectonically different and have different internuclear and extranuclear connections^{18,19,21}. For example, the BL is subdivided into the rostral magnocellular subdivision and the more caudal intermediate and parvicellular subdivisions, while the AB comprises the magnocellular subdivision and the more medial and caudal parvicellular subdivision^{8,20}.

Fear conditioning: acquisition

Associative fear learning has an absolute requirement for CS–US contingency—that is, a temporal relationship between the two stimuli, and learning is weakened when this contingency is broken¹. In auditory fear conditioning, the CS (tones) and US (footshock) inputs converge on to single neurons in the LA^{22–24}. The prevailing model for associative learning is that conjunction of CS and US input results in long-term potentiation (LTP)^{25,26} of synapses carrying CS information, and this underpins the memory of the aversive nature of the CS^{9,11,27–29}. CS and US inputs use glutamate as the excitatory transmitter, and these inputs form classical dual-component glutamatergic synapses that express postsynaptic AMPA and N-methyl-D-aspartate (NMDA) receptors^{30,31}. NMDA receptors are calcium-permeable, cationic ion channels that are open only when the glutamate site on the receptor is occupied and the membrane potential is depolarised^{32,33}. Thus, these receptors are coincidence detectors³⁴, and cytosolic calcium delivered by their activity is required for many forms of synaptic plasticity^{35,36}. Fear conditioning requires NMDA receptor activity in the BLA^{37–39}, and CS inputs are known to undergo plasticity following fear learning^{40,41}. Thus, it is generally accepted that NMDA receptor-dependent LTP underpins Pavlovian fear conditioning^{11,28,42–44}. In this model, the CS engages glutamatergic synapses, and the US provides the coincident depolarizing signal that drives NMDA receptor activity, triggering LTP of inputs carrying CS information^{11,39,43,45}.

While this model is compatible with much of the literature and provides a plausible model for fear learning, how CS–US pairings result in LTP of synapses carrying CS input is not clear. In most auditory fear conditioning protocols, the CS lasts several seconds and then co-terminates with the US (known as delay fear conditioning). Typically, a 10-second CS is used, with the US being presented in the last 1 second and co-terminating with the CS. However, in LA principal neurons, the response to prolonged auditory stimulation is transient, lasting at most several hundred milliseconds^{22,46,47}. Whole cell recordings *in vivo* also show auditory evoked synaptic activity to last only a short period of time²³, suggesting that synapses carrying CS information are not active at the time the US signal arrives in the BLA. Moreover, when the CS and US are separated by a brief period of time, a procedure called trace conditioning, fear conditioning can still be induced⁴⁸. While trace conditioning with a long trace interval (>5 seconds) engages the hippocampus^{48,49}, perhaps indicating a different form of learning, this does not happen

with short (<3 seconds) trace intervals. In these experiments, although the interval between the CS and US is short, the offset time constant of synaptic NMDA receptors in the BLA is much shorter (in the order of ~100 milliseconds)^{50,51}, meaning that with trace intervals of >1 second, ionotropic glutamate receptors mediating CS information are again not engaged when the US signal arrives. Thus, one requirement for NMDA receptor-dependent LTP, receptor engagement by glutamate, is not met. Furthermore, while neurons in the BLA receive both CS and US input, some neurons that change their response to the CS appear to not respond to the US⁵², an observation that challenges the requirement of contingent input onto single neurons.

Finally, it is well established that the recent history of the CS is an important determinant in learning. One example is the blocking effect¹, in which a compound CS (light + tone) is paired with the US. If one of the CSs (e.g. the tone) has previously been paired with the US, subjects do not develop defensive responses to the light^{53,54}. This result suggests that factors other than a close temporal relationship between the CS and US are required in fear associative learning. Interestingly, the US has been found to activate several ascending systems that release neuromodulators such as noradrenaline⁵⁵ and acetylcholine⁵⁶, and these systems are known to be involved in fear learning. However, how activation of these neuromodulatory systems modulates NMDA receptor-driven plasticity evoked during acquisition is not currently clear. In summary, in cued fear conditioning, it is clear that CS-US contingency is necessary for associative learning, and while the idea that synaptic plasticity (LTP) within the BLA underpins learning is very compelling, how this plasticity is evoked is still not clear.

Fear conditioning: the role of inhibition

The BLA is a cortical-like structure, with the majority of neurons (principal or pyramidal) being glutamatergic and the rest (~20%) being GABAergic inhibitory interneurons⁵⁷⁻⁵⁹.

Although relatively a smaller population, interneurons powerfully regulate the excitability of principal cells^{15,60-63}. Thus, within the BLA, principal cells have very low resting firing rates⁶⁴ and single interneurons can block their activity⁶³. The importance of inhibition in fear learning was established early with experiments showing that pharmacologically enhancing inhibition in the BLA is anxiolytic and can block fear learning^{65,66}, and *in vitro* studies show that plasticity of thalamic and cortical input to BLA principal cells is strongly modulated by inhibition^{60,67,68}.

Similar to the cortex, interneurons are divided into distinct families based on expression of cytosolic markers and synaptic connections^{15,59,69-72}. Of these, the major population are interneurons that express calbindin and those that express calretinin^{73,74}. These groups can be further subdivided based on their expression of neuropeptides such as somatostatin (SOM) or the calcium-binding protein parvalbumin (PV)^{15,59,69,72}, with PV interneurons being more numerous in the BA as compared to the LA⁷⁴. Recent work has focused on these latter two families, which have distinct subcellular targets on principal neurons^{15,59,75}.

PV interneurons innervate the somatic and proximal dendritic compartment, as well as the axon initial segment⁷⁶⁻⁷⁹, the likely site of action potential generation, while SOM interneurons target the distal dendritic tree. Both PV and SOM interneurons provide feedforward as well as feedback inhibition. In the LA, fast spiking interneurons (likely PV interneurons) have been found to receive cortical and thalamic inputs, again indicating a role in feedforward inhibition⁸⁰⁻⁸². While the exact source of afferent inputs to these interneuron types has not been fully characterized, PV interneurons in the BA have been suggested to have both feedforward⁸³ and feedback connections⁷⁵.

More recently, *in vivo* recordings are beginning to establish how local interneuron circuits modulate learning. During auditory fear conditioning, PV interneurons in the BLA are excited by auditory input (CS) while SOM interneurons are inhibited²⁴. In contrast, PV interneurons are inhibited by footshocks (US)²⁴. Since SOM interneurons in the BLA receive inhibitory input from PV interneurons²⁴, the inhibition of SOM interneurons during CS presentation is proposed to be mediated by PV cells driven by the CS²⁴. Functionally, the CS is thought to support principal neuron dendritic depolarization by disinhibition of SOM interneurons. Finally, input to interneurons can also undergo synaptic plasticity^{82,84}, and there are clear changes to inhibitory circuitry following fear conditioning^{84,85}. In summary, inhibition in the BLA is a strong regulator of principal cell activity, and it is clear that inhibitory microcircuits play crucial and cell type-specific roles in fear conditioning⁸⁶. However, how the activity of these microcircuits establishes CS-US contingency is not clear.

Fear conditioning: expression

Within the BLA, auditory input is concentrated in the LA⁸⁷ and behavioral tests found that pretraining lesions of the LA⁸⁸, but not the BL^{88,89}, BM⁸⁸, or entire BA⁹⁰, blocks auditory fear conditioning. As described above, this learning is thought to result from the plasticity of synapses made by CS input to principal neurons in the LA. Consistent with this result, inhibition of pyramidal neurons in the LA, but not the BA, impairs fear learning⁹¹. Following associative learning, fear memory is thought to be stored as a network of excitatory neurons that has been called the engram⁹². Individual neurons within the network appear to be allocated by their excitability during fear acquisition⁹³, and inactivation of this network of neurons disrupts memory retrieval⁹⁴. This engram has been associated with pyramidal neurons in the LA⁹⁴. However, following fear conditioning, a network of neurons driven by the CS has also been identified in the BA⁵².

The primary target of auditory input is the LA, and the main target for LA pyramidal neurons is the BA^{95,96}, which in turn send afferents to the CeM⁹⁷, the main output station of amygdala to hypothalamus and brainstem^{8,98}. As expected, single unit recordings show selective increase of CS evoked spike firing after auditory fear conditioning in the LA^{10,46,99,100}. In agreement with the anatomy, a significant number of neurons in the BL and BM also acquire CS responsiveness following fear conditioning^{47,52,101}. Inactivation of either the BL or the BM individually has little impact on fear expression, but inactivation of the entire BA

abolishes fear expression⁴⁷. These results have led to a model of fear conditioning in which learning requires the LA, fear expression is gated by BLA projections to the central amygdala, and downstream projections from the central amygdala initiate the physiological responses underlying the defensive responses elicited by the CS⁴⁷.

Conclusions

In summary, the BLA is a complex structure that plays a central role in cued auditory fear conditioning. During learning, CS and US inputs converge in the LA, and the acquisition of fear memory is driven by contingent CS–US activity that results in an enhanced CS input by a mechanism that requires local inhibitory

circuits and activation of NMDA receptors. This enhanced CS activity results in the formation of a memory trace or engram within the BLA. Following fear conditioning, subsequent presentation of the CS retrieves the memory trace by activating a network of neurons in the BA, and the resultant output drives the CeA, initiating the conditioned response. While the evidence for this general model is compelling, the details of the mechanisms that initiate synaptic plasticity, how this plasticity establishes the engram, and the role of local inhibition are not fully understood, and indeed the current literature provides some conflicting observations. With the rapid development of new techniques to interrogate neural function, we have no doubt that these issues are ripe to be settled.

References



- Fanselow MS, Wassum KM: **The Origins and Organization of Vertebrate Pavlovian Conditioning.** *Cold Spring Harb Perspect Biol.* 2015; **8**(1): a021717. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- F** LeDoux J: **Rethinking the emotional brain.** *Neuron.* 2012; **73**(4): 653–76. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Davis M, Walker DL, Miles L, et al.: **Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety.** *Neuropsychopharmacology.* 2010; **35**(1): 105–35. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- F** Shackman AJ, Fox AS: **Contributions of the Central Extended Amygdala to Fear and Anxiety.** *J Neurosci.* 2016; **36**(31): 8050–63. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Sah P: **Fear, Anxiety, and the Amygdala.** *Neuron.* 2017; **96**(1): 1–2. [PubMed Abstract](#) | [Publisher Full Text](#)
- Fendt M, Fanselow MS: **The neuroanatomical and neurochemical basis of conditioned fear.** *Neurosci Biobehav Rev.* 1999; **23**(5): 743–60. [PubMed Abstract](#) | [Publisher Full Text](#)
- LeDoux J: **Fear and the brain: where have we been, and where are we going?** *Biol Psychiatry.* 1998; **44**(12): 1229–38. [PubMed Abstract](#) | [Publisher Full Text](#)
- Sah P, Faber ES, Lopez De Armentia M, et al.: **The amygdaloid complex: anatomy and physiology.** *Physiol Rev.* 2003; **83**(3): 803–34. [PubMed Abstract](#) | [Publisher Full Text](#)
- Maren S: **Neurobiology of Pavlovian fear conditioning.** *Annu Rev Neurosci.* 2001; **24**: 897–931. [PubMed Abstract](#) | [Publisher Full Text](#)
- Maren S, Quirk GJ: **Neuronal signalling of fear memory.** *Nat Rev Neurosci.* 2004; **5**(11): 844–52. [PubMed Abstract](#) | [Publisher Full Text](#)
- Pape HC, Pare D: **Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear.** *Physiol Rev.* 2010; **90**(2): 419–63. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Paré D: **Mechanisms of Pavlovian fear conditioning: has the engram been located?** *Trends Neurosci.* 2002; **25**(9): 436–7. [PubMed Abstract](#) | [Publisher Full Text](#)
- Josselyn SA: **Continuing the search for the engram: examining the mechanism of fear memories.** *J Psychiatry Neurosci.* 2010; **35**(4): 221–8. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- F** Josselyn SA, Köhler S, Frankland PW: **Finding the engram.** *Nat Rev Neurosci.* 2015; **16**(9): 521–34. [PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
- Ehrlich I, Humeau Y, Grenier F, et al.: **Amygdala inhibitory circuits and the control of fear memory.** *Neuron.* 2009; **62**(6): 757–71. [PubMed Abstract](#) | [Publisher Full Text](#)
- F** Fadok JP, Markovic M, Tovote P, et al.: **New perspectives on central amygdala function.** *Curr Opin Neurobiol.* 2018; **49**: 141–7. [PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
- Pitkänen A, Savander V, LeDoux JE: **Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala.** *Trends Neurosci.* 1997; **20**(11): 517–23. [PubMed Abstract](#) | [Publisher Full Text](#)
- McDonald AJ: **Neuronal organization of the lateral and basolateral amygdaloid nuclei in the rat.** *J Comp Neurol.* 1984; **222**(4): 589–606. [PubMed Abstract](#) | [Publisher Full Text](#)
- Krettek JE, Price JL: **A description of the amygdaloid complex in the rat and cat with observations on intra-amygdaloid axonal connections.** *J Comp Neurol.* 1978; **178**(2): 255–79. [PubMed Abstract](#) | [Publisher Full Text](#)
- Pitkänen A: **Connectivity of the rat amygdaloid complex.** In *The Amygdala: A functional analysis*, (ed J. P. Aggleton). Oxford University Press, 2000; 31–115. [Reference Source](#)
- McDonald AJ: **Neurons of the lateral and basolateral amygdaloid nuclei: a Golgi study in the rat.** *J Comp Neurol.* 1982; **212**(3): 293–312. [PubMed Abstract](#) | [Publisher Full Text](#)
- Romanski LM, Clugnet MC, Bordi F, et al.: **Somatosensory and auditory convergence in the lateral nucleus of the amygdala.** *Behav Neurosci.* 1993; **107**(3): 444–50. [PubMed Abstract](#) | [Publisher Full Text](#)
- Windels F, Yan S, Stratton PG, et al.: **Auditory Tones and Foot-Shock Recapitulate Spontaneous Sub-Threshold Activity in Basolateral Amygdala Principal Neurons and Interneurons.** *PLoS One.* 2016; **11**(5): e0155192. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- F** Wolff SB, Gründemann J, Tovote P, et al.: **Amygdala interneuron subtypes control fear learning through disinhibition.** *Nature.* 2014; **509**(7501): 453–8. [PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
- Bliss TV, Collingridge GL: **A synaptic model of memory: long-term potentiation in the hippocampus.** *Nature.* 1993; **361**(6407): 31–9. [PubMed Abstract](#) | [Publisher Full Text](#)
- Mayford M, Siegelbaum SA, Kandel ER: **Synapses and memory storage.** *Cold Spring Harb Perspect Biol.* 2012; **4**(6): pii: a005751. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Davis M: **The role of the amygdala in fear and anxiety.** *Annu Rev Neurosci.* 1992; **15**: 353–75. [PubMed Abstract](#) | [Publisher Full Text](#)
- Fanselow MS, LeDoux JE: **Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala.** *Neuron.* 1999; **23**(2): 229–32. [PubMed Abstract](#) | [Publisher Full Text](#)
- LeDoux J: **The emotional brain, fear, and the amygdala.** *Cell Mol Neurobiol.* 2003; **23**(4–5): 727–38. [PubMed Abstract](#) | [Publisher Full Text](#)
- Hestrin S, Perkel DJ, Sah P, et al.: **Physiological properties of excitatory synaptic transmission in the central nervous system.** *Cold Spring Harb Symp Quant Biol.* 1990; **55**: 87–93. [PubMed Abstract](#) | [Publisher Full Text](#)
- Mahanty NK, Sah P: **Excitatory synaptic inputs to pyramidal neurons of the lateral amygdala.** *Eur J Neurosci.* 1999; **11**(4): 1217–22. [PubMed Abstract](#) | [Publisher Full Text](#)
- Nowak L, Bregestovski P, Ascher P, et al.: **Magnesium gates glutamate-activated**

- channels in mouse central neurones. *Nature*. 1984; **307**(5950): 462–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Mayer ML, Westbrook GL, Guthrie PB: **Voltage-dependent block by Mg²⁺ of NMDA responses in spinal cord neurones.** *Nature*. 1984; **309**(5965): 261–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
34. McBain CJ, Mayer ML: **N-methyl-D-aspartic acid receptor structure and function.** *Physiol Rev*. 1994; **74**(3): 723–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Collingridge GL, Bliss TVP: **NMDA receptors - their role in long-term potentiation.** *Trends Neurosci*. 1987; **10**(7): 288–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Malenka RC, Nicoll RA: **NMDA-receptor-dependent synaptic plasticity: Multiple forms and mechanisms.** *Trends Neurosci*. 1993; **16**(12): 521–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Miserendino MJ, Sananes CB, Melia KR, *et al.*: **Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala.** *Nature*. 1990; **345**(6277): 716–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. Kim JJ, DeCola JP, Landeira-Fernandez J, *et al.*: **N-methyl-D-aspartate receptor antagonist APV blocks acquisition but not expression of fear conditioning.** *Behav Neurosci*. 1991; **105**(1): 126–33.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Goosens KA, Maren S: **NMDA receptors are essential for the acquisition, but not expression, of conditional fear and associative spike firing in the lateral amygdala.** *Eur J Neurosci*. 2004; **20**(2): 537–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. McKernan MG, Shinnick-Gallagher P: **Fear conditioning induces a lasting potentiation of synaptic currents *in vitro*.** *Nature*. 1997; **390**(6660): 607–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Tsvetkov E, Carlezon WA, Benes FM, *et al.*: **Fear conditioning occludes LTP-induced presynaptic enhancement of synaptic transmission in the cortical pathway to the lateral amygdala.** *Neuron*. 2002; **34**(2): 289–300.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Sah P, Westbrook RF, Lüthi A: **Fear conditioning and long-term potentiation in the amygdala: what really is the connection?** *Ann N Y Acad Sci*. 2008; **1129**: 88–95.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Blair HT, Schafe GE, Bauer EP, *et al.*: **Synaptic Plasticity in the Lateral Amygdala: a Cellular Hypothesis of Fear Conditioning.** *Learn Mem*. 2001; **8**(5): 229–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
44. Maren S: **Long-term potentiation in the amygdala: a mechanism for emotional learning and memory.** *Trends Neurosci*. 1999; **22**(12): 561–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
45. Johansen JP, Cain CK, Ostroff LE, *et al.*: **Molecular mechanisms of fear learning and memory.** *Cell*. 2011; **147**(3): 509–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
46. Quirk GJ, Repp JC, LeDoux JE: **Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat.** *Neuron*. 1995; **15**(5): 1029–39.
[PubMed Abstract](#) | [Publisher Full Text](#)
47. Amato T, Duvarci S, Popa D, *et al.*: **The fear circuit revisited: contributions of the basal amygdala nuclei to conditioned fear.** *J Neurosci*. 2011; **31**(43): 15481–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. Chowdhury N, Quinn JJ, Fanselow MS: **Dorsal hippocampus involvement in trace fear conditioning with long, but not short, trace intervals in mice.** *Behav Neurosci*. 2005; **119**(5): 1396–402.
[PubMed Abstract](#) | [Publisher Full Text](#)
49. Quinn JJ, Wied HM, Ma QD, *et al.*: **Dorsal hippocampus involvement in delay fear conditioning depends upon the strength of the tone-footshock association.** *Hippocampus*. 2008; **18**(7): 640–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
50. Delaney AJ, Sedlak PL, Autuori E, *et al.*: **Synaptic NMDA receptors in basolateral amygdala principal neurons are triheteromeric proteins: physiological role of GluN2B subunits.** *J Neurophysiol*. 2013; **109**(5): 1391–402.
[PubMed Abstract](#) | [Publisher Full Text](#)
51. Lopez de Armentia M, Sah P: **Development and subunit composition of synaptic NMDA receptors in the amygdala: NR2B synapses in the adult central amygdala.** *J Neurosci*. 2003; **23**(17): 6876–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
52. **F** Grewe BF, Gründemann J, Kitch LJ, *et al.*: **Neural ensemble dynamics underlying a long-term associative memory.** *Nature*. 2017; **543**(7647): 670–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
53. Kamin L: **Predictability, surprise, attention, and conditioning.** (Appleton-Century-Crofts.). 1969.
[Reference Source](#)
54. Sengupta A, McNally GP: **A role for midline and intralaminar thalamus in the associative blocking of Pavlovian fear conditioning.** *Front Behav Neurosci*. 2014; **8**: 148.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
55. **F** Giustino TF, Maren S: **Noradrenergic Modulation of Fear Conditioning and Extinction.** *Front Behav Neurosci*. 2018; **12**: 43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. **F** Knox D: **The role of basal forebrain cholinergic neurons in fear and extinction memory.** *Neurobiol Learn Mem*. 2016; **133**: 39–52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
57. McDonald AJ: **In The Amygdala: Neurobiological Aspects of Emotion, Memory and Mental Dysfunction.** (ed J. P. Aggleton) 67-96 (Wiley Liss, 1992).
58. Smith Y, Par JF, Par D: **Cat intraamygdaloid inhibitory network: ultrastructural organization of parvalbumin-immunoreactive elements.** *J Comp Neurol*. 1998; **391**(2): 164–79.
[PubMed Abstract](#) | [Publisher Full Text](#)
59. Spanpanato J, Polepalli J, Sah P: **Interneurons in the basolateral amygdala.** *Neuropharmacology*. 2011; **60**(5): 765–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
60. **F** Bissière S, Humeau Y, Lüthi A: **Dopamine gates LTP induction in lateral amygdala by suppressing feedforward inhibition.** *Nat Neurosci*. 2003; **6**(6): 587–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
61. Lang EJ, Paré D: **Similar inhibitory processes dominate the responses of cat lateral amygdaloid projection neurons to their various afferents.** *J Neurophysiol*. 1997; **77**(1): 341–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
62. Li XF, Armony JL, LeDoux JE: **GABA_A and GABA_B receptors differentially regulate synaptic transmission in the auditory thalamo-amygdala pathway: an *in vivo* microiontophoretic study and a model.** *Synapse*. 1996; **24**(2): 115–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
63. Woodruff AR, Sah P: **Inhibition and synchronization of basal amygdala principal neuron spiking by parvalbumin-positive interneurons.** *J Neurophysiol*. 2007; **98**(5): 2956–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Gaudreau H, Pare D: **Projection neurons of the lateral amygdaloid nucleus are virtually silent throughout the sleep-waking cycle.** *J Neurophysiol*. 1996; **75**(3): 1301–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
65. Harris JA, Westbrook RF: **Benzodiazepine-induced amnesia in rats: reinstatement of conditioned performance by noxious stimulation on test.** *Behav Neurosci*. 1998; **112**(1): 183–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
66. Pesold C, Treit D: **The central and basolateral amygdala differentially mediate the anxiolytic effects of benzodiazepines.** *Brain Res*. 1995; **671**(2): 213–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
67. Shaban H, Humeau Y, Herry C, *et al.*: **Generalization of amygdala LTP and conditioned fear in the absence of presynaptic inhibition.** *Nat Neurosci*. 2006; **9**(8): 1028–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
68. Tully K, Li Y, Tsvetkov E, *et al.*: **Norepinephrine enables the induction of associative long-term potentiation at thalamo-amygdala synapses.** *Proc Natl Acad Sci U S A*. 2007; **104**(35): 14146–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. McDonald AJ, Mascagni F, Zaric V: **Subpopulations of somatostatin-immunoreactive non-pyramidal neurons in the amygdala and adjacent external capsule project to the basal forebrain: evidence for the existence of GABAergic projection neurons in the cortical nuclei and basolateral nuclear complex.** *Front Neural Circuits*. 2012; **6**: 46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. Mascagni F, Muly EC, Rainnie DG, *et al.*: **Immunohistochemical characterization of parvalbumin-containing interneurons in the monkey basolateral amygdala.** *Neuroscience*. 2009; **158**(4): 1541–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
71. Mascagni F, McDonald AJ: **Parvalbumin-immunoreactive neurons and GABAergic neurons of the basal forebrain project to the rat basolateral amygdala.** *Neuroscience*. 2009; **160**(4): 805–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
72. Sosulina L, Meis S, Seifert G, *et al.*: **Classification of projection neurons and interneurons in the rat lateral amygdala based upon cluster analysis.** *Mol Cell Neurosci*. 2006; **33**(1): 57–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
73. Kemppainen S, Pitknen A: **Distribution of parvalbumin, calretinin, and calbindin-D(28k) immunoreactivity in the rat amygdaloid complex and colocalization with gamma-aminobutyric acid.** *J Comp Neurol*. 2000; **426**(3): 441–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
74. McDonald AJ, Mascagni F: **Colocalization of calcium-binding proteins and GABA in neurons of the rat basolateral amygdala.** *Neuroscience*. 2001; **105**(3): 681–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
75. Woodruff AR, Sah P: **Networks of parvalbumin-positive interneurons in the basolateral amygdala.** *J Neurosci*. 2007; **27**(3): 553–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. McDonald AJ, Muller JF, Mascagni F: **GABAergic innervation of alpha type II calcium/calmodulin-dependent protein kinase immunoreactive pyramidal neurons in the rat basolateral amygdala.** *J Comp Neurol*. 2002; **446**(3): 199–218.
[PubMed Abstract](#) | [Publisher Full Text](#)
77. McDonald AJ, Betette RL: **Parvalbumin-containing neurons in the rat basolateral amygdala: morphology and co-localization of Calbindin-D(28k).** *Neuroscience*. 2001; **102**(2): 413–25.
[PubMed Abstract](#) | [Publisher Full Text](#)

78. Muller JF, Mascagni F, McDonald AJ: **Pyramidal cells of the rat basolateral amygdala: synaptology and innervation by parvalbumin-immunoreactive interneurons.** *J Comp Neurol.* 2006; **494**(4): 635–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
79. Woodruff AR, Monyer H, Sah P: **GABAergic excitation in the basolateral amygdala.** *J Neurosci.* 2006; **26**(46): 11881–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
80. Szinyei C, Heinbockel T, Montagne J, *et al.*: **Putative cortical and thalamic inputs elicit convergent excitation in a population of GABAergic interneurons of the lateral amygdala.** *J Neurosci.* 2000; **20**(23): 8909–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
81. Polepalli JS, Sullivan RK, Yanagawa Y, *et al.*: **A specific class of interneuron mediates inhibitory plasticity in the lateral amygdala.** *J Neurosci.* 2010; **30**(44): 14619–29.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
82. Mahanty NK, Sah P: **Calcium-permeable AMPA receptors mediate long-term potentiation in interneurons in the amygdala.** *Nature.* 1998; **394**(6694): 683–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
83. Smith Y, Paré JF, Paré D: **Differential innervation of parvalbumin-immunoreactive interneurons of the basolateral amygdaloid complex by cortical and intrinsic inputs.** *J Comp Neurol.* 2000; **416**(4): 496–508.
[PubMed Abstract](#) | [Publisher Full Text](#)
84. Szinyei C, Narayanan RT, Pape HC: **Plasticity of inhibitory synaptic network interactions in the lateral amygdala upon fear conditioning in mice.** *Eur J Neurosci.* 2007; **25**(4): 1205–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
85. **F** Lucas EK, Jegarl AM, Morishita H, *et al.*: **Multimodal and Site-Specific Plasticity of Amygdala Parvalbumin Interneurons after Fear Learning.** *Neuron.* 2016; **91**(3): 629–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
86. **F** Lucas EK, Clem RL: **GABAergic interneurons: The orchestra or the conductor in fear learning and memory?** *Brain Res Bull.* 2018; **141**: 13–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
87. Doron NN, LeDoux JE: **Organization of projections to the lateral amygdala from auditory and visual areas of the thalamus in the rat.** *J Comp Neurol.* 1999; **412**(3): 383–409.
[PubMed Abstract](#) | [Publisher Full Text](#)
88. Nader K, Majidishad P, Amorapanth P, *et al.*: **Damage to the lateral and central, but not other, amygdaloid nuclei prevents the acquisition of auditory fear conditioning.** *Learn Mem.* 2001; **8**(3): 156–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
89. Amorapanth P, LeDoux JE, Nader K: **Different lateral amygdala outputs mediate reactions and actions elicited by a fear-arousing stimulus.** *Nat Neurosci.* 2000; **3**(1): 74–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
90. Anglada-Figueroa D, Quirk GJ: **Lesions of the basal amygdala block expression of conditioned fear but not extinction.** *J Neurosci.* 2005; **25**(42): 9680–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
91. **F** Tipps M, Marron Fernandez de Velasco E, Schaeffer A, *et al.*: **Inhibition of Pyramidal Neurons in the Basal Amygdala Promotes Fear Learning.** *eNeuro.* 2018; **5**(5): pii: ENEURO.0272-18.2018.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
92. **F** Josselyn SA, Frankland PW: **Memory Allocation: Mechanisms and Function.** *Annu Rev Neurosci.* 2018; **41**: 389–413.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
93. **F** Han JH, Kushner SA, Yiu AP, *et al.*: **Neuronal competition and selection during memory formation.** *Science.* 2007; **316**(5823): 457–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
94. **F** Han JH, Kushner SA, Yiu AP, *et al.*: **Selective erasure of a fear memory.** *Science.* 2009; **323**(5920): 1492–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
95. Smith Y, Paré D: **Intra-amygdaloid projections of the lateral nucleus in the cat: PHA-L anterograde labeling combined with postembedding GABA and glutamate immunocytochemistry.** *J Comp Neurol.* 1994; **342**(2): 232–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
96. Pitkänen A, Stefanacci L, Farb CR, *et al.*: **Intrinsic connections of the rat amygdaloid complex: projections originating in the lateral nucleus.** *J Comp Neurol.* 1995; **356**(2): 288–310.
[PubMed Abstract](#) | [Publisher Full Text](#)
97. Savander V, Go CG, LeDoux JE, *et al.*: **Intrinsic connections of the rat amygdaloid complex: projections originating in the basal nucleus.** *J Comp Neurol.* 1995; **361**(2): 345–68.
[PubMed Abstract](#) | [Publisher Full Text](#)
98. Duvarci S, Pare D: **Amygdala microcircuits controlling learned fear.** *Neuron.* 2014; **82**(5): 966–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
99. Quirk GJ, Armony JL, LeDoux JE: **Fear conditioning enhances different temporal components of tone-evoked spike trains in auditory cortex and lateral amygdala.** *Neuron.* 1997; **19**(3): 613–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
100. Goosens KA, Hobin JA, Maren S: **Auditory-evoked spike firing in the lateral amygdala and Pavlovian fear conditioning: mnemonic code or fear bias?** *Neuron.* 2003; **40**(5): 1013–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
101. **F** Herry C, Ciocchi S, Senn V, *et al.*: **Switching on and off fear by distinct neuronal circuits.** *Nature.* 2008; **454**(7204): 600–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

Open Peer Review

Current Peer Review Status: 

Editorial Note on the Review Process

F1000 Faculty Reviews are written by members of the prestigious F1000 Faculty. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

- Benedetto Sacchetti**
Department of Neuroscience, University of Turin, Turin, Italy
Competing Interests: No competing interests were disclosed.
- Roger L Clem**
Fishberg Department of Neuroscience and the Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, USA
Competing Interests: No competing interests were disclosed.
- Nathan M Holmes**
School of Psychology, University of New South Wales, Sydney, Australia
Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research