HHS Public Access

Author manuscript

Curr Opin Behav Sci. Author manuscript; available in PMC 2020 August 20.

Published in final edited form as:

Curr Opin Behav Sci. 2019 April ; 26: 97–106. doi:10.1016/j.cobeha.2018.10.010.

Valence coding in amygdala circuits

Michele Pignatelli[1], **Anna Beyeler**[2]

[1]Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, 02139 MA, USA

[2]Neurocentre Magendie, INSERM 1215, Université de Bordeaux, 146 Rue Léo Saignat, 33000 Bordeaux, France

Abstract

The neural mechanisms underlying emotional valence are at the interface between perception and action, integrating inputs from the external environment with past experiences to guide the behavior of an organism. Depending on the positive or negative valence assigned to an environmental stimulus, the organism will approach or avoid the source of the stimulus. Multiple convergent studies have demonstrated that the amygdala complex is a critical node of the circuits assigning valence. Here we examine the current progress in identifying valence coding properties of neural populations in different nuclei of the amygdala, based on their activity, connectivity, and gene expression profile.

Neural substrate of valence

The concept of valence

Across the animal kingdom, environmental stimuli can elicit a repertoire of behavioral responses ranging from approach to avoidance. Valence is the *subjective value* assigned to sensory stimuli which determines subsequent behavior. Positive valence leads to approach and consummatory behaviors while negative valence leads to defensive and avoidance behaviors [1,2]. For many sensory stimuli the assigned valence is innate, however, valence is weighted by the internal state of the organism and by its previous experiences [3,4] (Box 1). A simple example of state-dependence of valence is the value assigned to food, which strongly depends on the homeostatic needs of the animal [5]. Another internal state regulating valence assignment is basal anxiety. Indeed, high anxiety levels can induces a bias towards negative valence, even for stimuli that are normally rewarding [6].

Despite the fundamental role of valence on animal survival and well-being, the underlying neurobiological substrate remains partially understood. One of the main working hypothesis postulates that specific neural circuits assign valence to stimuli in order to activate defined motor patterns and ensure an adaptive behavioral response [3,7]. In line with this hypothesis, human brain imaging has identified divergent networks activated in response to stimuli of

Corresponding author: Beyeler, Anna (anna.beyeler@inserm.fr).

Conflict of interest statement

Nothing declared.

positive or negative valence [8–10]. Multiple animal models including non-human primates [11], rodents [12••], drosophila [13] and bees [14] have been used to decipher how neuronal populations composing these networks encode valence.

Defining valence circuits – role of the amygdala

A vast body of literature reporting gain and loss of function experiments, as well as correlative measures of neuronal activity, has identified the amygdala complex as a central node to drive specific motor patterns in response to external stimuli [4,15–17]. The amygdala complex includes three main groups of nuclei: the basolateral amygdala (BLA), the central amygdala (CeA) and the medial amygdala (MeA) (Figure 1). Developmentally, the CeA and MeA arise from the same cell lineage, presenting a striatal-like organization compared to the BLA which originates from a different lineage and presents a cortical-like organization [18,19] (Figure 1a–b). Thus, the CeA is composed almost exclusively of inhibitory neurons, and the MeA is mainly composed of GABAergic neurons but contains one third of glutamatergic cells [20]. In contrast, the BLA is mainly composed of excitatory projection neurons (~85%) and of a small proportion of local inhibitory interneurons (~15%) [18,19]. Together with fast amino acid neurotransmitters, neurons of amygdala nuclei also produce numerous neuropeptides and express several neuromodulator receptors (Figure 1c). Despite increasing knowledge of anatomical and molecular properties of amygdala neurons, we are just starting to unravel their contribution to valence.

Neural coding of valence

The role of neuronal populations in assigning valence has been studied using gain and loss of function experiments, and through analysis of neural activity recorded during tasks of opposite valences. Valence coding has been defined in terms of neural firing in response to at least two conditioned stimuli (CS), one of positive and one of negative valence [12••,21–23]. Depending on their changes in firing rate in response to both CSs, neurons can be classified into nine coding populations [12••,24] (Figure 2a). Among these nine classes, two include neurons responding similarly to cues of both positive and negative valence which could in principle support an arousal response. In addition, valence can also be defined as the differential response to positive and negative stimuli [21,25•,26,27•] (Figure 2b). In this case, neurons excited (or inhibited) by both positive and negative stimuli may still encode valence as they display a stronger response for one specific stimulus. In this framework, valence coding is rather defined by a coding preference or bias, than by an on/off coding pattern.

Recent advances in neurotechnologies allow us to analyze valence coding properties of single neurons in specific populations defined by other features including connectivity (inputs and outputs) and gene expression. This expands the experimental possibilities from local recordings within single brain regions, to circuit dissection at synaptic and molecular scales (Figure 3). The scope of this review is to synthesize the latest findings and future directions in identifying hallmarks of amygdala populations depending on their valence coding properties.

Valence coding in populations of the central amygdala (CeA)

The CeA is the main output of the amygdala and has primarily been studied in the context of fear-related behaviors [28]. However, the CeA has also repeatedly been reported to promote appetitive behaviors [29●●,30,31]. Although contradictory, these results could be supported by divergent activity of distinct neural populations. Extensive research has been dedicated to identify the function of gene-defined and projection-defined populations within the capsular, lateral, and medial areas of the CeA (CeC, CeL and CeM, Figure 1). Pharmacological inhibition of CeL as well as optogenetic activation of CeM both induce unconditioned freezing suggesting that these different subregions differentially encode valence [32]. Subregions of CeA express selective genetic markers such as protein kinase-Cδ (PKCδ), somatostatin (SOM), corticotropin-releasing factor (CRF), tachykinin 2 (Tac2), neurotensin (Nts) or serotonin 2A receptor (5-HT2$_A$, Figure 1c) [29●●,33●,34], and a complex microcircuit connectivity characterizes the interaction among these cells [35,36●].

PKCδ$^+$ cells represent a prominent subpopulation in both CeC and CeL. Optogenetic inhibition of this population can suppress defensive behavior [29●●,37]. Nevertheless, while optogenetic activation of PKCδ$^+$ cells in CeC can drive defensive behaviors, activation of CeL PKCδ$^+$ cells does not drive valence-related behaviors and their suppression does not inhibit defensive behavior, but instead enhances drinking behavior [29●●] (Table 1). Consistently, it has been reported that neurons inhibited by a cue predicting a footshock (CeL$_{OFF}$ neurons) [32] largely overlap with PKCδ$^+$ cells [35]. However, optogenetic activation of PKCδ$^+$ cells in CeL can increase fear-cue generalization and can be anxiogenic [38]. Lastly, optogenetic activation of PKCδ$^+$ cells in CeL suppresses food intake [39] whereas activation of 5HT2$_a^+$ cells, a marker for PKCδ$^-$ cells in CeL, promotes food intake [33●].

As the PKCδ$^+$ population, the SOM$^+$ population represents about 40% of the neurons in CeL and the two populations interact through mutual inhibition [36●]. Optogenetic activation of SOM$^+$ neurons in CeL and in CeM can drive appetitive behaviors [29●●], and their inhibition in CeL promotes defensive behaviors [40]. Consistent with this finding, activation of SOM$^+$ neurons can decrease conditioned flight responses [41] but can also initiate passive freezing [41,42]. Finally, CRF$^+$ cells are necessary for defensive behaviors [43], can increase conditioned flight responses, and the balance between conditioned flight and freezing behaviors is regulated by local inhibitory connections between CRF$^+$ or activation of SOM$^+$ neurons [41]. Altogether, activation of PKCδ$^+$ and SOM$^+$ neurons are able to drive both appetitive and defensive behaviors depending on the experimental conditions (Table 1).

This discrepancy might stem from divergent connectivity of genetically defined populations, including synaptic inputs and outputs. For example, PKCδ$^+$ cells of CeC receive direct inputs from neurons of the parabrachial nucleus expressing calcitonin gene-related peptide (PBN$_{cgRP}$) [44], and optogenetic activation of those inputs suppresses appetite and drives defensive responses [45,46]. On the other hand, inhibition of inputs from the paraventricular nucleus of the thalamus (PVT), which mainly targets SOM$^+$ cells in CeL, strongly reduces fear conditioning [47]. Furthermore, inputs from the intermediate insular cortex (i.e. bitter

gustatory cortex) in CeA promote avoidance behaviors [48]; however, the genetic identity of the CeA target population remains unknown. Further, projection neurons of CeL and CeM targeting the ventrolateral periaqueductal grey (vlPAG) strongly drive hunting behavior [49●]. Finally, a recent functional mapping study has shown that inhibitory projection form CeA suppresses activity of vlPAG local interneurons disinhibiting the excitatory cells, which in turn project to the cholinergic cells of the magnocellular nucleus of the medulla driving a defensive response [50●●]. Overall, despite in depth knowledge of genetic populations of the CeA, few studies have analyzed their single-unit activity in response to both positive and negative valence, leaving their valence coding properties elusive (Table 1).

Valence coding in populations of the basolateral amygdala (BLA)

Multiple studies have performed single-unit recordings in the BLA during stimuli of both positive and negative valence. Although direct optogenetic stimulation of the lateral amygdala (LA) can elicit a defensive response in a naïve mouse [51], recordings of BLA neurons in monkeys, rats and mice have shown that around 50% of the units respond to predictive cues of positive or negative valence [12●●,21,27●], with an overrepresentation of neurons responding to positive valence in monkeys [21] and mice [12●●], and an even distribution of neuron responding to both valences in rats [27●]. Additionally, pioneering work has shown that some BLA neurons track the value of a sensory stimulus during reversal of the CS-US association [21,22] emphasizing the critical role of the BLA in valence coding. Finally, a recent study has also identified that even if relatively few cells in the BLA cells encode valence, the valence assigned to a stimulus can be decoded at the population level of neural activity [27●].

As the BLA is mainly composed of glutamatergic projection neurons, the search for neuronal features defining the polarity of valence has been predominantly focused on post-synaptic targets (Table 1). Optogenetic activation has shown that projections to CeA (BLA-CeA) [52], medial prefrontal cortex (BLA-mPFC) [53–55] and ventral hippocampus (BLA-vHPC) [56] can drive defensive behaviors. On the contrary, optogenetic activation of projections to the nucleus accumbens (BLA-NAc) has repeatedly been shown to support reinforcement [52,57,58] (Figure 3a). This accumulation of results reporting regulation of valence-related behavior by BLA projections supports the hypothesis that anatomically divergent populations of the BLA differentially encode valence. Moreover, recordings combined with optogenetic photoidentification of specific neural subpopulations have shown that BLA-NAc units are preferentially excited by a positive CS and BLA-CeA units are preferentially excited by a negative one [12●●]. Further, synaptic inputs on BLA-NAc and BLA-CeA neurons are regulated in an opposite manner after learning associations of positive and negative valence [52]. Importantly, *in vivo* recordings have also revealed heterogeneity of single neuron activity within projection-defined populations [12●●,53,59]. This supports a model where valence coding of a projector population can be inferred from the projection target of its neurons, but the projection target of a single neuron is not sufficient to infer its valence coding properties (Figure 2).

BLA projection neurons are segregated in large neurons in the anterior part (magnocellular) and smaller neurons in the posterior part (parvocellular) [60]. Activity-dependent profiling

combined with extensive gene screening [61,62••] has shown that the magno-cellular and parvocellular populations are defined by the expression of the *Rspo2* and *Ppp1r1b* genes, respectively. Interestingly, optogenetic stimulation of $Rspo2^+$ cells elicits a defensive response in naive mice whereas stimulation of $Ppp1r1b^+$ cells promotes an appetitive response [62••]. Both populations send projections to the NAc and CeA, $Rspo2^+$ cells monosynaptically contacting $PKC\delta^+$ cells of the CeC whereas $Ppp1r1b^+$ cells innervate the other cellular subtypes of the CeM and CeL (Figure 3b) [29••]. The anteroposterior topography of the *Rspo2* and *Ppp1r1b* gene markers does not overlap with the distribution of BLA-NAc and BLA-CeA populations which are intermingled with mediolateral and dorsoventral gradients [25•]. The ability of genetically defined and anatomically defined populations to drive polarized behaviors combined with the coding heterogeneity recorded in BLA projectors raises the interesting possibility that defining populations using a combination of anatomical and genetic approaches may be instrumental in selecting populations sharply tuned to a specific valence.

Populations of local inhibitory interneurons of the BLA expressing SOM or parvalbumine (PV) have been shown to differentially drive behavioral responses to aversive cues [63]. However, their role in positive valence coding remains unexplored. Similarly, oscillatory activity, which is generated by local inhibitory interneurons [64], is known to causally regulate behaviors driven by negative valence [65•], but has not been investigated with positive valence (Box 2). In addition, the BLA receives inputs from a vast array of regions also involved in valence, including the mPFC, anterior cingulate cortex (ACC), auditory cortex and multiple nuclei of the thalamus — all of which have been almost exclusively analyzed during aversive states [55,66–69]. Albeit essential to understand the functional role of local interneurons and inputs to the BLA in fear and defensive behaviors, the studies leave their implication in reward processing uncharted.

Valence in other amygdala nuclei

Most studies analyze the origin of valence in the CeA and BLA but surrounding amygdaloid nuclei also regulate valence. For example, direct optogenetic activation of the basomedial amygdala (BMA, Figure 1) is anxiogenic, as the optogenetic activation of the vmPFC inputs to this nucleus [70]. Interestingly, the BMA directly projects to the ventromedial hypothalamus (VMH) which regulates defensive and social behaviors [71].

Neurons in the medial amygdala (MeA, Figure 1) have repeatedly been shown to regulate social behaviors [20,72] and GABAergic neurons of the posterodorsal MeA promote social behaviors of both negative (e.g. aggression) and positive valence (e.g. mating and social grooming) [73]. Neurons in the MeA can be genetically identified by the unique marker laminin $\beta 3$ [74] and express numerous receptors including oxytocin receptors [72], estrogen receptors and the CRF receptor 2 [75]. MeA cells expressing CRF-2 receptor mRNA are active during a social experience of negative valence (social defeat stress) [76]. In addition, a subpopulation of MeA neurons expressing kisspeptin protein modulates anxiety and sexual partner preference in male mice [77], whereas neurons expressing the alpha-estrogen receptor controls body weight [78]. When analyzed independently of projection or gene markers, neurons of the cortical amygdala (CoA, Figure 1) represent odor objects of both

valences using distributive population codes [79]. Optogenetic inhibition of CoA reduces innate responses to odors of both positive and negative valence [80]. Interestingly, neurons activated by odors of positive or neutral valence are mainly recruited in the posterior section of the CoA, compared to neurons activated by an odor of negative valence which are equally distributed in the antero-posterior axis [80].

Importantly, the intercalated cells (ITC), which are clusters of GABAergic interneurons (Figure 1), were shown to relay negative valence to the BLA, including fear and pain information [81–84].

Moving forward to crack the valence code

Gain and loss of function experiments have demonstrated that neuronal subpopulations of the amygdala defined by their projection targets or gene expression can drive behaviors of opposite valence (Figure 3). Activity-dependent markers and electrophysiological recordings have revealed that average activity of a population is generally consistent with the driven behaviors (Figure 3c). Yet, recordings revealing single-unit heterogeneity in valence coding within populations [12●●,53] suggest the presence of functional subpopulations. Increasing the level of specificity by integrating multiple cell features, such as genetic identity and anatomical connectivity, could promote the identification of more uniform populations selectively encoding one valence [85●] (Figure 2c-d).

Anatomical complexity

Although the activity of BLA projection-defined populations can predict valence, these cells send collaterals to multiple brain regions [12●●]. The distribution of collaterals at a single cell level and its correlation with valence coding properties remains unexplored (Figure 3b). Projection collaterals, topography, and post-synaptic cell identity in the downstream region represent critical points that could reconcile conflicting results. For example, the NAc and the CeA both contain neurons expressing both dopamine D1 and D2 receptors, which have been shown to induce behaviors of opposite valence in the dorsal striatum [86]. Moreover it was shown that depending on the dorsal-to-ventral axis, optogenetic stimulation of NAc neurons induces preference or avoidance respectively [87]. To circumvent these limitations, systematic mapping of projection-defined, activity-defined or genetically defined populations in whole brain samples [88] will provide a greater level of understanding of the anatomo-functional organization of the amygdala. Micro-circuit connectivity including feedforward, feedback, and mutual inhibition also appears as a mechanism of population selection. For instance, optogenetic activation of the BLA-CeA population induces a stronger inhibition of neighboring neurons than activation of other projector populations [25●,89]. Moreover, mutual inhibition was described between functionally divergent populations such as PKCδ^{+} and SOM^{+} neurons in CeA [35], as well as Rspo2 and Ppp1rb1 neurons in BLA [62●●].

Genetic complexity

Unique transcriptional signatures of multiple immediate early genes have been identified in the amygdala after experiences of positive and negative valence [90]. Similarly, neurons with

an increased expression of cyclic adenosine monophosphate response element-binding protein (CREB) in the LA are preferentially recruited to encode a memory of negative valence compared to neurons with a lower expression of CREB [91]. These studies highlight that beyond stable gene markers, dynamic gene expression is also a defining feature of neural populations encoding valence. Importantly, genetic identification of multiple genes is now possible in 'intact' fixed samples using new technologies such as MERFISH [92] or STARmap [93]. Interestingly, these techniques might also allow to identify the contribution of glial cells in valence coding which has so far only been described in CeM, for negative valence [94]. We expect the combination of these approaches with anatomical tracing and mapping of cellular activation to potentiate the progress of our understanding of valence coding in amygdala nuclei.

Conclusions

Over the last decade, the study of valence coding in the amygdala has made unprecedented progress by revealing elaborate genetic and anatomical circuits differentially involved in positive and negative valence (Figure 3). This exceptional leap forward is the fruit of technological advancements combined with the spread of systematic behavioral testing of both positive and negative valence in the same experiment. Beyond this experimental prerequisite, recent studies have even started to combine recordings in response to both positive and negative valence with recordings during anxiety-related behaviors [95], providing crucial data to understand the role of valence circuits in state anxiety. Future investigations into valence coding in animal models of neuropsychiatric disorders, might further advance our understanding of valence circuit dysregulations in the physiopathology of diseases including post-traumatic stress disorders, anxiety, depression, and addiction.

Acknowledgements

We thank Joanna Dabrowska, Mario Martin-Fernandez, Sebastien Delcasso, Xavier Leinekugel, Gwendolyn Calhoon, Caitlin Vander Weele and Praneeth Namburi for critical reading of the manuscript. We acknowledge support by the Région Nouvelle-Aquitaine and INSERM-Avenir to the Beyeler Lab and by the Brain and Behavior Research Foundation NARSAD young investigator grant to AB.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

● of special interest

●●of outstanding interest

1. Lewin K: The Conceptual Representation and the Measurement of Psychological Forces. Duke University Press; 1938.
2. Russell JA: A circumplex model of affect. J Pers Soc Psychol 1980, 39:1161–1178.
3. Anderson DJ, Adolphs R: A framework for studying emotions across species. Cell 2014, 157:187–200. [PubMed: 24679535]
4. Morrison SE, Salzman CD: Re-valuing the amygdala. Curr Opin Neurobiol 2010, 20:221–230. [PubMed: 20299204]
5. Tinbergen N: The Study of Instinct. Clarendon Press; 1951.

6. Samuels BA, Hen R: Novelty-suppressed feeding in the mouse In Mood and Anxiety Related Phenotypes in Mice, vol. 63 Edited by Gould TD. Humana Press; 2011:107–121.
7. Hebb DO: The Organization of Behavior: A Neuropsychological Theory. Psychology Press; 2002.
8. Borchardt V et al.: Echoes of affective stimulation in brain connectivity networks. Cereb Cortex 2017:1–14 10.1093/cercor/bhx290. [PubMed: 28365777]
9. Kragel PA, LaBar KS: Decoding the nature of emotion in the brain. Trends Cogn Sci 2016, 20:444–455. [PubMed: 27133227]
10. Pessoa L: Understanding emotion with brain networks. Curr Opin Behav Sci 2018, 19:19–25. [PubMed: 29915794]
11. Zhang W et al.: Functional circuits and anatomical distribution of response properties in the primate amygdala. J Neurosci 2013, 33:722–733. [PubMed: 23303950]
12. Beyeler A et al.: Divergent routing of positive and negative information from the amygdala during memory retrieval. Neuron 2016, 90:348–361. [PubMed: 27041499] ●● This study analyzes the firing response of three subpopulations of BLA projector neurons to positive and negative associated auditory stimuli in head restrained behaving mice. Neurons are classified into nine groups according to the response to sounds associated to sucrose or quinine. The study suggests that a population code may determine the correct attribution of a specific valence.
13. Yamazaki D et al.: Two parallel pathways assign opposing odor valences during Drosophila memory formation. Cell Rep 2018, 22:2346–2358. [PubMed: 29490271]
14. Roussel E, Sandoz J-C, Giurfa M: Searching for learning-dependent changes in the antennal lobe: simultaneous recording of neural activity and aversive olfactory learning in honeybees. Front Behav Neurosci 2010, 4. [PubMed: 20179788]
15. Bucy PC, Kluver H: An anatomical investigation of the temporal lobe in the monkey (Macaca mulatta). J Comp Neurol 1955, 103:151–251. [PubMed: 13271593]
16. Janak PH, Tye KM: From circuits to behaviour in the amygdala. Nature 2015, 517:284–292. [PubMed: 25592533]
17. Weiskrantz L: Behavioral changes associated with ablation of the amygdaloid complex in monkeys. J Comp Physiol Psychol 1956, 49:381–391. [PubMed: 13345917]
18. Sah P, Faber ESL, Lopez De Armentia M, Power J: The amygdaloid complex: anatomy and physiology. Physiol Rev 2003, 83:803–834.
19. Swanson LW, Petrovich GD: What is the amygdala? Trends Neurosci 1998, 21:323–331. [PubMed: 9720596]
20. Li Y et al.: Neuronal representation of social information in the medial amygdala of awake behaving mice. Cell 2017, 171:1176–1190. e17. [PubMed: 29107332]
21. Paton JJ, Belova MA, Morrison SE, Salzman CD: The primate amygdala represents the positive and negative value of visual stimuli during learning. Nature 2006, 439:865–870. [PubMed: 16482160]
22. Schoenbaum G, Chiba AA, Gallagher M: Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning. J Neurosci 1999, 19:1876–1884. [PubMed: 10024371]
23. Shabel SJ, Janak PH: Substantial similarity in amygdala neuronal activity during conditioned appetitive and aversive emotional arousal. Proc Natl Acad Sci U S A 2009, 106:15031–15036. [PubMed: 19706473]
24. Namburi P, Al-Hasani R, Calhoon GG, Bruchas MR, Tye KM: Architectural representation of valence in the limbic system. Neuropsychopharmacology 2016, 41:1697–1715 10.1038/npp.2015.358. [PubMed: 26647973]
25. Beyeler A et al.: Organization of valence-encoding and projection-defined neurons in the basolateral amygdala. Cell Rep 2018, 22:905–918. [PubMed: 29386133] ● This study maps the location of more than a 1000 BLA cells recorded during a Pavlovian discrimination task. Furthermore, by using triple retrograde tracing, the study reveals the three-dimensional location of BLA cells projecting to NAc, CeA and vHPC.
26. O'Neill P-K, Gore F, Salzman CD: Basolateral amygdala circuitry in positive and negative valence. Curr Opin Neurobiol 2018, 49:175–183. [PubMed: 29525574]

27. Kyriazi P, Headley DB, Pare D: Multi-dimensional coding by basolateral amygdala neurons. Neuron 2018, 99:1315–1328 e5. [PubMed: 30146300] ● Using a task where rats can produce different behaviors in response to the same CS, the authors identified similarities at the population level between valence coding for CS and behavioral response.
28. Duvarci S, Pare D: Amygdala microcircuits controlling learned fear. Neuron 2014, 82:966–980. [PubMed: 24908482]
29. Kim J, Zhang X, Muralidhar S, LeBlanc SA, Tonegawa S: Basolateral to central amygdala neural circuits for appetitive behaviors. Neuron 2017, 93:1464–1479 e5. [PubMed: 28334609] ●● By using a genetic screening this study demonstrates the presence of several segregated populations in the CeA, controlling negative or positive attribution of valence.
30. Robinson MJF, Warlow SM, Berridge KC: Optogenetic excitation of central amygdala amplifies and narrows incentive motivation to pursue one reward above another. J Neurosci 2014, 34:16567–16580. [PubMed: 25505310]
31. Tom RL, Ahuja A, Maniates H, Freeland CM, Robinson MJF: Optogenetic activation of the central amygdala generates addiction-like preference for reward. Eur J Neurosci 2018 10.1111/ejn.13967.
32. Ciocchi S et al.: Encoding of conditioned fear in central amygdala inhibitory circuits. Nature 2010, 468:277–282. [PubMed: 21068837]
33. Douglass AM et al.: Central amygdala circuits modulate food consumption through a positive-valence mechanism. Nature Neurosci 2017, 20:1384–1394. [PubMed: 28825719] ● This study shows that GABAergic 5HT2A+ cells of the CeA modulate food consumption, promote positive reinforcement and are active in vivo during eating.
34. McCullough KM, Morrison FG, Hartmann J, Carlezon WA, Ressler KJ: Quantified coexpression analysis of central amygdala subpopulations. eNeuro 2018, 5.
35. Haubensak W et al.: Genetic dissection of an amygdala microcircuit that gates conditioned fear. Nature 2010, 468:270–276. [PubMed: 21068836]
36. Hunt S, Sun Y, Kucukdereli H, Klein R, Sah P: Intrinsic circuits in the lateral central amygdala. eNeuro 2017, 4.● By combining patch clamp recordings in acute slices with immunostaining of specific cell markers, this study analyzes the monosynaptic connectivity among different neuronal types in the CeL.
37. Yu K et al.: The central amygdala controls learning in the lateral amygdala. Nat Neurosci 2017, 20:1680–1685. [PubMed: 29184202]
38. Botta P et al.: Regulating anxiety with extrasynaptic inhibition. Nat Neurosci 2015, 18:1493–1500. [PubMed: 26322928]
39. Cai H, Haubensak W, Anthony TE, Anderson DJ: Central amygdala PKC-δ neurons mediate the influence of multiple anorexigenic signals. Nat Neurosci 2014, 17:1240–1248. [PubMed: 25064852]
40. Yu K, da Silva PG, Albeanu DF, Li B: Central amygdala somatostatin neurons gate passive and active defensive behaviors. J Neurosci 2016, 36:6488–6496. [PubMed: 27307236]
41. Fadok JP et al.: A competitive inhibitory circuit for selection of active and passive fear responses. Nature 2017, 542:96–100. [PubMed: 28117439]
42. Li H et al.: Experience-dependent modification of a central amygdala fear circuit. Nat Neurosci 2013, 16:332–339. [PubMed: 23354330]
43. Sanford CA et al.: A central amygdala CRF circuit facilitates learning about weak threats. Neuron 2017, 93:164–178. [PubMed: 28017470]
44. Lu Y-C et al.: Neurochemical properties of the synapses between the parabrachial nucleus-derived CGRP-positive axonal terminals and the GABAergic neurons in the lateral capsular division of central nucleus of amygdala. Mol Neurobiol 2015, 51:105–118. [PubMed: 24794145]
45. Carter ME, Soden ME, Zweifel LS, Palmiter RD: Genetic identification of a neural circuit that suppresses appetite. Nature 2013, 503:111–114. [PubMed: 24121436]
46. Han S, Soleiman MT, Soden ME, Zweifel LS, Palmiter RD: Elucidating an affective pain circuit that creates a threat memory. Cell 2015, 162:363–374. [PubMed: 26186190]
47. Penzo MA et al.: The paraventricular thalamus controls a central amygdala fear circuit. Nature 2015, 519:455–459. [PubMed: 25600269]

48. Wang L et al.: The coding of valence and identity in the mammalian taste system. Nature 2018, 558:127–131. [PubMed: 29849148]
49. Han W et al.: Integrated control of predatory hunting by the central nucleus of the amygdala. Cell 2017, 168:311–324 e18. [PubMed: 28086095] This unique study shows that optogenetic and chemogenetic stimulation of CeA of mice can elicit predatory attacks on insects.
50. Tovote P et al.: Midbrain circuits for defensive behaviour. Nature 2016, 534:206–212. [PubMed: 27279213] ●● This study identify an inhibitory pathway from the CeA to the ventrolateral periaqueductal grey that elicits freezing though disinhibition of ventrolateral periaqueductal grey excitatory outputs to pre-motor cells in the magnocellular nucleus of the medulla.
51. Johansen JP et al.: Optical activation of lateral amygdala pyramidal cells instructs associative fear learning. Proc Natl Acad Sci U S A 2010, 107:12692–12697. [PubMed: 20615999]
52. Namburi P et al.: A circuit mechanism for differentiating positive and negative associations. Nature 2015, 520:675–678. [PubMed: 25925480]
53. Burgos-Robles A et al.: Amygdala inputs to prefrontal cortex guide behavior amid conflicting cues of reward and punishment. Nat Neurosci 2017, 20:824–835. [PubMed: 28436980]
54. Felix-Ortiz AC, Burgos-Robles A, Bhagat ND, Leppla CA, Tye KM: Bidirectional modulation of anxiety-related and social behaviors by amygdala projections to the medial prefrontal cortex. Neuroscience 2015, 79:658–664 10.1016/j.neuroscience.2015.07.041.
55. Yizhar O, Klavir O: Reciprocal amygdala-prefrontal interactions in learning. Curr Opin Neurobiol 2018, 52:149–155. [PubMed: 29982085]
56. Felix-Ortiz AC et al.: BLA to vHPC inputs modulate anxiety-related behaviors. Neuron 2013, 79:658–664. [PubMed: 23972595]
57. Britt JP et al.: Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. Neuron 2012, 76:790–803. [PubMed: 23177963]
58. Stuber GD et al.: Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. Nature 2011, 475:377–380. [PubMed: 21716290]
59. Senn V et al.: Long-range connectivity defines behavioral specificity of amygdala neurons. Neuron 2014, 81:428–437. [PubMed: 24462103]
60. Hall E: The amygdala of the cat: a Golgi study. Z Zellforsch Mikrosk Anat 1972, 134:439–458. [PubMed: 4638299]
61. Allen Brain Atlas: Allen Brain Atlas: Mouse Connectivity, Projections. . Available at: 2016 (Accessed 17 October 2016) http://connectivity.brain-map.org/.
62. Kim J, Pignatelli M, Xu S, Itohara S, Tonegawa S: Antagonistic negative and positive neurons of the basolateral amygdala. Nat Neurosci 2016, 19:1636–1646. [PubMed: 27749826] ●● By using a genetic screening this study demonstrates the presence of two segregated populations in the basal amygdala. The Rspo2+ and the Ppp1rb1+ cells are located in the BLA and BLP and control negative and positive attribution of valence respectively. A mutual inhibition characterizes their synaptic relationship.
63. Wolff SBE et al.: Amygdala interneuron subtypes control fear learning through disinhibition. Nature 2014, 509:453–458. [PubMed: 24814341]
64. Buzsaki G: Neuronal oscillations in cortical networks. Science 2004, 304:1926–1929. [PubMed: 15218136]
65. Karalis N et al.: 4-Hz oscillations synchronize prefrontal-amygdala circuits during fear behavior. Nat Neurosci 2016, 19:605–612.● By using multiple extracellular recordings in behaving mice this study shows that freezing coincided with internally generated 4-Hz oscillations in prefrontal-amygdala circuits. 4-Hz oscillations predict freezing onset and offset and optogenetic induction of prefrontal 4-Hz oscillations can elicit fear behavior.
66. Allsop SA et al.: Corticoamygdala transfer of socially derived information gates observational learning. Cell 2018, 173:1–14 10.1016/j.cell.2018.04.004. [PubMed: 29570990]
67. Mátyás F, Lee J, Shin H-S, Acsády L: The fear circuit of the mouse forebrain: connections between the mediodorsal thalamus, frontal cortices and basolateral amygdala. Eur J Neurosci 2014, 39:1810–1823. [PubMed: 24819022]
68. McGarry LM, Carter AG: Prefrontal cortex drives distinct projection neurons in the basolateral amygdala. Cell Rep 2017, 21:1426–1433. [PubMed: 29117549]

69. Nabavi S et al.: Engineering a memory with LTD and LTP. Nature 2014, 511:348–352. [PubMed: 24896183]
70. Adhikari A et al.: Basomedial amygdala mediates top-down control of anxiety and fear. Nature 2015, 527:179–185. [PubMed: 26536109]
71. Yamamoto R, Ahmed N, Ito T, Gungor NZ, Pare D: Optogenetic study of anterior BNST and basomedial amygdala projections to the ventromedial hypothalamus. eNeuro 2018, 5.
72. Yao S, Bergan J, Lanjuin A, Dulac C: Oxytocin signaling in the medial amygdala is required for sex discrimination of social cues. eLife 2017, 6.
73. Hong W, Kim D-W, Anderson DJ: Antagonistic control of social behaviors by inhibitory and excitatory neurons in the medial amygdala. Cell 2014, 158:1348–1361. [PubMed: 25215491]
74. Zirlinger M, Kreiman G, Anderson DJ: Amygdala-enriched genes identified by microarray technology are restricted to specific amygdaloid subnuclei. Proc Natl Acad Sci U S A 2001, 98:5270–5275. [PubMed: 11320257]
75. Frankiensztajn LM, Gur-Pollack R, Wagner S: A combinatorial modulation of synaptic plasticity in the rat medial amygdala by oxytocin, urocortin3 and estrogen. Psychoneuroendocrinology 2018, 92:95–102. [PubMed: 29674171]
76. Fekete ÉM et al.: Social defeat stress activates medial amygdala cells that express type 2 CRF receptor mRNA. Neuroscience 2009, 162:5–13. [PubMed: 19358876]
77. Adekunbi DA et al.: Kisspeptin neurones in the posterodorsal medial amygdala modulate sexual partner preference and anxiety in male mice. J Neuroendocrinol 2018, 30 e12572. [PubMed: 29356147]
78. Xu P et al.: Estrogen receptor-a in medial amygdala neurons regulates body weight. J Clin Invest 2015, 125:2861–2876. [PubMed: 26098212]
79. Iurilli G, Datta SR: Population coding in an innately relevant olfactory area. Neuron 2017, 93:1180–1197 e7. [PubMed: 28238549]
80. Root CM, Denny CA, Hen R, Axel R: The participation of cortical amygdala in innate, odour-driven behaviour. Nature 2014, 515:269–273. [PubMed: 25383519]
81. Asede D, Bosch D, Lüthi A, Ferraguti F, Ehrlich I: Sensory inputs to intercalated cells provide fear-learning modulated inhibition to the basolateral amygdala. Neuron 2015, 86:541–554. [PubMed: 25843406]
82. Bienvenu TCM et al.: Large intercalated neurons of amygdala relay noxious sensory information. J Neurosci 2015, 35:2044–2057. [PubMed: 25653362]
83. Kuerbitz J et al.: Loss of intercalated cells (ITCs) in the mouse amygdala of Tshz1 mutants correlates with fear, depression, and social interaction phenotypes. J Neurosci 2018, 38:1160–1177. [PubMed: 29255003]
84. Strobel C, Marek R, Gooch HM, Sullivan RKP, Sah P: Prefrontal and auditory input to intercalated neurons of the amygdala. Cell Rep 2015, 10:1435–1442 10.1016/j.celrep.2015.02.008. [PubMed: 25753409]
85. Cui Y et al.: A central amygdala-substantia innominata neural circuitry encodes aversive reinforcement signals. Cell Rep 2017, 21:1770–1782. [PubMed: 29141212] ● This study demonstrates the role of the projections from PKCδ neurons of CeA projecting to the substantia innominata in the modulation of negative reinforcement learning.
86. Kravitz AV, Tye LD, Kreitzer AC: Distinct roles for direct and indirect pathway striatal neurons in reinforcement. Nat Neurosci 2012, 15:816–818. [PubMed: 22544310]
87. Al-Hasani R et al.: Distinct subpopulations of nucleus accumbens dynorphin neurons drive aversion and reward. Neuron 2015, 87:1063–1077. [PubMed: 26335648]
88. Ye L et al.: Wiring and molecular features of prefrontal ensembles representing distinct experiences. Cell 2016, 165:1776–1788. [PubMed: 27238022]
89. Calhoon GG et al.: Acute food deprivation rapidly modifies valence-coding microcircuits in the amygdala. bioRxiv 2018, 285189 10.1101/285189.
90. Mukherjee D et al.: Salient experiences are represented by unique transcriptional signatures in the mouse brain. eLife 2018, 7.

91. Han J-H et al.: Selective erasure of a fear memory. Science 2009, 323:1492–1496. [PubMed: 19286560]
92. Moffitt JR et al.: High-performance multiplexed fluorescence in situ hybridization in culture and tissue with matrix imprinting and clearing. PNAS 2016, 113:14456–14461. [PubMed: 27911841]
93. Wang X et al.: Three-dimensional intact-tissue sequencing of single-cell transcriptional states. Science 2018, 361.
94. Martin-Fernandez M et al.: Synapse-specific astrocyte gating of amygdala-related behavior. Nat Neurosci 2017, 20:1540–1548. [PubMed: 28945222]
95. Lee S-C, Amir A, Haufler D, Pare D: Differential recruitment of competing valence-related amygdala networks during anxiety. Neuron 2017, 96:81–88 e5. [PubMed: 28957678]
96. Tye KM et al.: Amygdala circuitry mediating reversible and bidirectional control of anxiety. Nature 2011, 471:358–362. [PubMed: 21389985]
97. Lowery-Gionta EG et al.: Chronic stress dysregulates amygdalar output to the prefrontal cortex. Neuropharmacology 2018, 139:68–75. [PubMed: 29959957]
98. Kim S-Y et al.: Diverging neural pathways assemble a behavioural state from separable features in anxiety. Nature 2013, 496:219–223. [PubMed: 23515158]
99. Redondo RL et al.: Bidirectional switch of the valence associated with a hippocampal contextual memory engram. Nature 2014, 513:426–430. [PubMed: 25162525]
100. Gore F et al.: Neural representations of unconditioned stimuli in basolateral amygdala mediate innate and learned responses. Cell 2015, 162:134–145. [PubMed: 26140594]
101. Isosaka T et al.: Htr2a-expressing cells in the central amygdala control the hierarchy between innate and learned fear. Cell 2015, 163:1153–1164. [PubMed: 26590419]
102. Paré D, Collins DR, Pelletier JG: Amygdala oscillations and the consolidation of emotional memories. Trends Cogn Sci 2002, 6:306–314. [PubMed: 12110364]
103. Amir A, Headley DB, Lee S-C, Haufler D, Paré D: Vigilance-associated gamma oscillations coordinate the ensemble activity of basolateral amygdala neurons. Neuron 2018, 97:656–669 e7. [PubMed: 29420934]
104. Girardeau G, Inema I, Buzsáki G: Reactivations of emotional memory in the hippocampus-amygdala system during sleep. Nat Neurosci 2017, 20:1634–1642. [PubMed: 28892057]
105. Stujenske JM, Likhtik E, Topiwala MA, Gordon JA: Fear and safety engage competing patterns of theta-gamma coupling in the basolateral amygdala. Neuron 2014, 83:919–933. [PubMed: 25144877]
106. Taub AH, Perets R, Kahana E, Paz R: Oscillations synchronize amygdala-to-prefrontal primate circuits during aversive learning. Neuron 2018, 97:291–298 e3. [PubMed: 29290553]
107. Seidenbecher T, Laxmi TR, Stork O, Pape H-C: Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. Science 2003, 301:846–850. [PubMed: 12907806]
108. Bocchio M, Nabavi S, Capogna M: Synaptic plasticity, engrams, and network oscillations in amygdala circuits for storage and retrieval of emotional memories. Neuron 2017, 94:731–743. [PubMed: 28521127]

Box 1 Innate versus learned valence in the amygdala.

Innate valence is attributed without requirement of learning and guides innate behavioral responses which have been selected during species evolution [5]. A clear example of innate valence is the unconditioned approach and avoidance exhibited by mice in presence of odorants of peanut oil and trimethylthiazoline (TMT), respectively. Neural ensembles in the BLA active during stimuli of positive or negative valence, also named *'engrams*' [91,99], can drive behavioral responses such as approach for a *'positive engram'* or avoidance for a *'negative engram'* [99,100]. In the dentate gyrus of the hippocampus, the valence of a *'positive engram'* (neurons in a male mouse activated during interaction with a female) can be reversed by reactivating this *'engram'* during exposure to an experience of negative valence (electric footshock) [99]. Interestingly, the engram cells of the BLA do not exhibit such behavioral plasticity [99]. Nevertheless, pairing the activation of an innate *positive or negative engram* in the BLA with an olfactory stimulus can support learning and drive conditioned behaviors to the stimulus, even though it has not been paired with an aversive or rewarding experience [100]. This observation suggests that learned valence can be encoded by the same populations encoding innate valence. However, studies in projection-defined populations suggest that BLA-vHPC neurons specifically encode innate negative valence and not learned valence [12●●,56]. Similarly, in the CeA, direct electrophysiological recordings from neurons expressing the 5HT2A-R indicate that their activity is suppressed during innate fear but not during learned-fear, and that their inactivation upregulates innate-freezing response while downregulating learned-freezing response [101].

Box 2 Oscillatory synchronization.

Cortical regions of the mammalian brain generate patterns of rhythmic oscillations of the local field potential (LFP) covering frequencies from 0.05 to 500 Hz [64]. Selective frequency bands are associated with different brain states and behaviors. Originally described in the neocortex and hippocampus, oscillations have also been observed in the rodent BLA [102], where changes in power of specific LFP frequencies have been correlated with learning of associations of negative valence [103,104]. Interestingly, it was shown that local oscillations can have different impact on neurons depending on their downstream target [103]. Consistent with the existence of distributed brain states, synchronous oscillations in the theta (7–12 Hz) and gamma (40–120 Hz) bands between the BLA and interconnected regions occur during consolidation and retrieval of emotional memories [104–106]. For example during retrieval of a fear memory, the hippocampus and amygdala are synchronized in the theta band [107], whereas prefrontal-amygdala circuits display synchronized 4-Hz oscillations [65•]. Interneurons are powerful regulators of this synchronized activity and are tightly controlled by several neuromodulators providing a gating mechanism for synaptic plasticity [108]. Whether oscillations of different frequencies, including gamma and theta display valence specific modulation remains unknown.

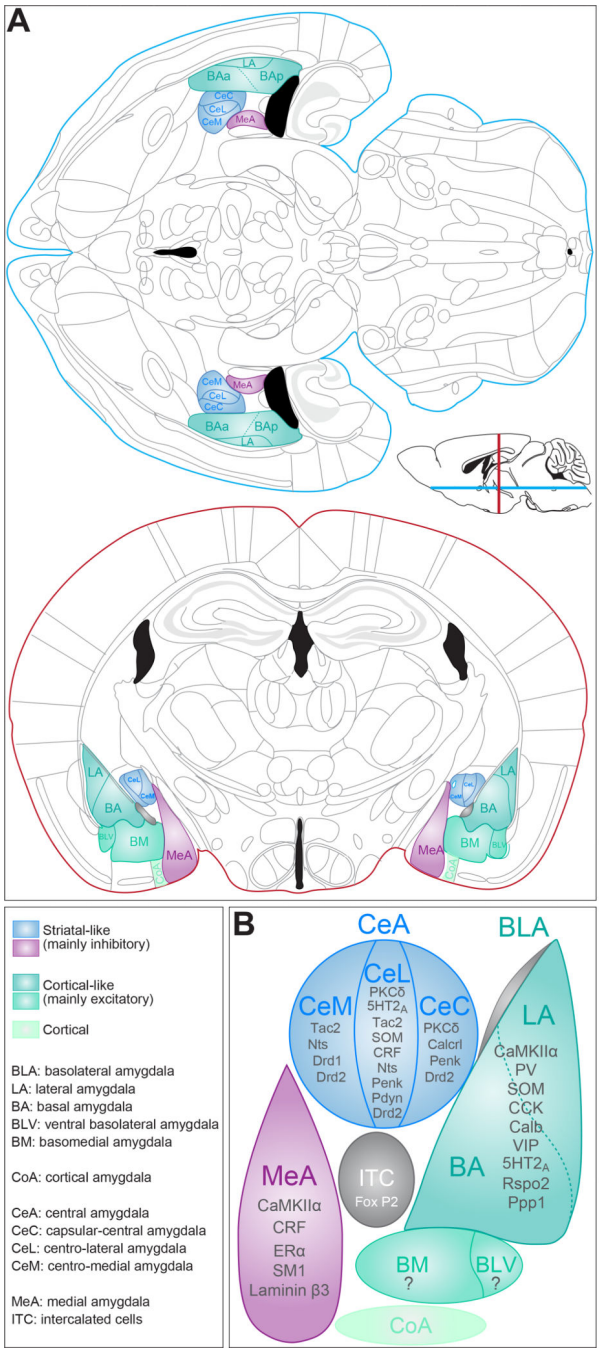

Figure 1.

The amygdala complex and genetically identified populations. (**a**) Atlas of horizontal and coronal sections of the adult mouse brain highlighting the different nuclei of the amygdala. (**b**) Schematic of the different amygdala nuclei and identified genetic markers.

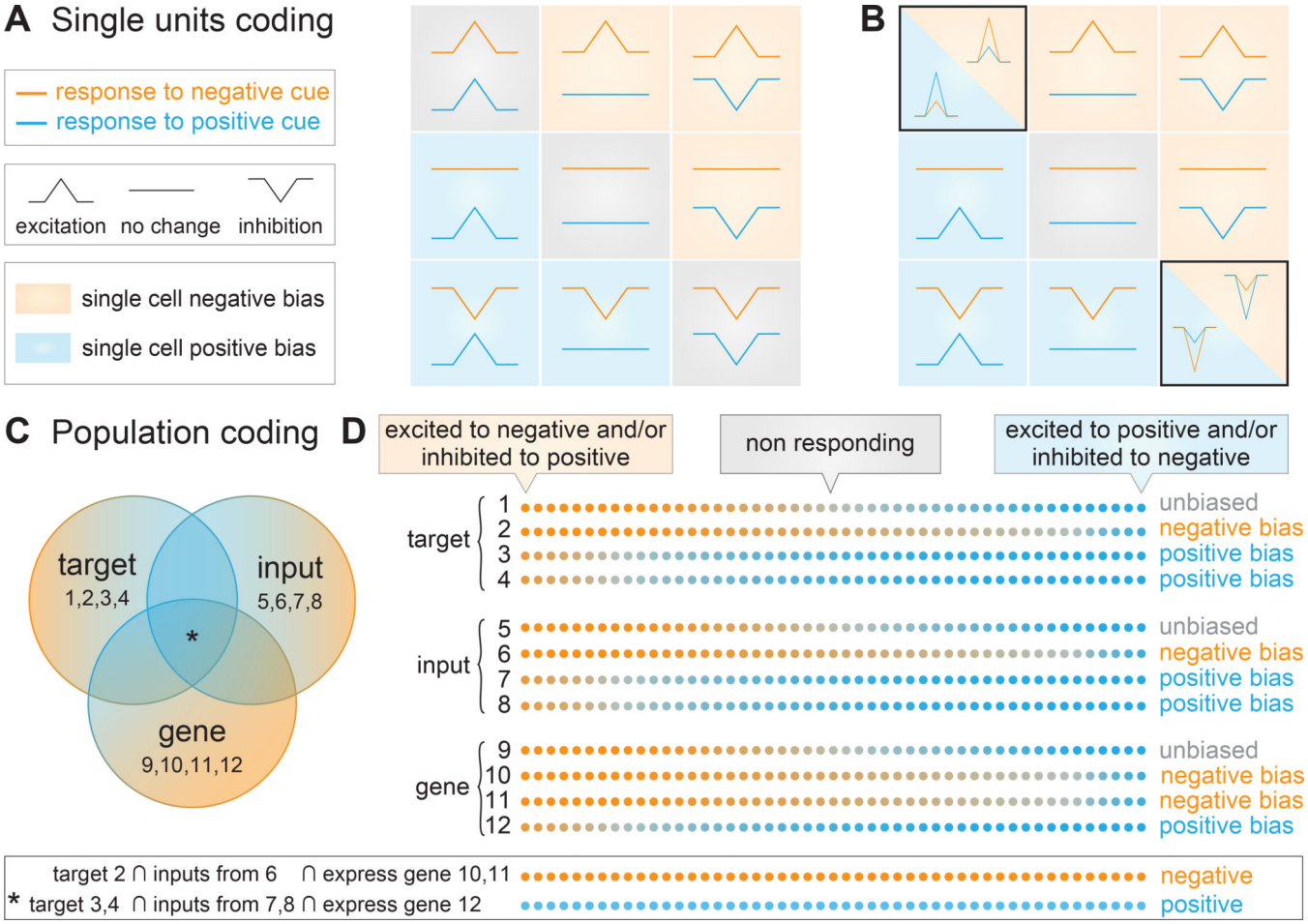

Figure 2.

Valence coding and population biases. (**a**) Definition of nine classes of neurons depending on their response to stimuli of positive and negative valence [12●●]. In this classification neurons responding to both stimuli in a similar way (excitation or inhibition to both stimuli) do not encode valence. (**b**) Alternative classification of units including the amplitude of the response. In this case, neurons responding to both stimuli in a similar way also encode valence as they exhibit a stronger response to one valence [12●●,21]. (**c**) Multidimensional definition of neurons encoding valence. (**d**) Each line represents a neuronal population and every dot corresponds to a single neuron. A single feature defines populations with valence coding biases, and combining multiple features could potentially reveal valence selective populations.

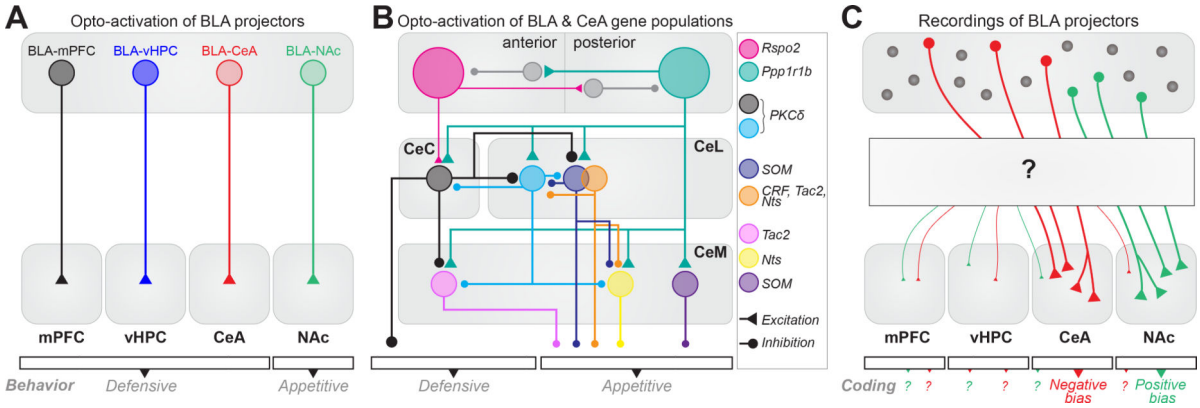

Figure 3.

Circuit diagram illustrating valence biases in BLA and CeA. (**a**) Optogenetic activation of three projection-defined BLA populations induces defensive behaviors [52,53,56] and activation of the last population induces appetitive behaviors [52,57,58] (**b**) Intra-amygdala circuit diagram of genetic populations in the anterior (a) and posterior (p) BLA, and CeA. Anterior BLA *Rspo2+* and posterior BLA *Ppp1r1b+* neurons drive opposite behavioral responses and reciprocally inhibit each other [62••]. *Rspo2+* neurons innervate CeC *PKC*δ^{+} neurons driving a defensive response. CeC PKCδ^{+} neurons inhibit CeL PKCδ^{+} neurons and *Tac2*+ CeM neurons, which mediate appetitive responses. *Ppp1r1b*+ neurons innervate all CeA neurons driving appetitive responses. CeC and CeL *PKC*δ^{+} neurons antagonize each other [29••] (**c**) Recordings of BLA neurons defined by their projection have revealed coding biases for learned positive and negative valence. Although collateralization has been described at a population level, the relationship between collateralization pattern and valence coding at a single neuron level remains unknown.

Table 1

Studies manipulating and recording neural activity in gene-defined, input-defined and projection-defined populations.

			Experiment	Behavior or neural response	Bidirectional*	Valence	Reference
Cental amygdala (CeA)							
Gene	PKCd+	CeL	single-unit	inhibited by CS-shock (CeL_{OFF})	x	+?	Haubensak 2010[35]
		CeL	ChR2	no valence-related behavior	yes	+/−	Kim 2017[29]
		CeC	ChR2	freezing	yes	−	Kim 2017[29]
		CeL	ChR2	anxiogenic	yes	−	Botta 2015[38]
		CeL	ChR2	anxiolytic	x	+	Cai 2014[39]
		CeL	ChR2	food intake supression	yes	−?	Cai 2014[39]
		CeL-SI	ChR2	avoidance (CPA)	x	−	Cui 2017[85]
	SOM	CeL	ChR2	decrease CS avoidance	yes	+	Yu 2016[40]
		CeL	ChR2	self-stimulation	yes	+	Kim 2017[29]
		CeM	ChR2	self-stimulation	yes	+	Kim 2017[29]
		CeL	ChR2	freezing	yes	−	Li 2013[42]
		CeL	ChR2	decrease CS-flight	no	+	Fadok 2017[41]
		CeL	ChR2	CS-freezing	no	−	Fadok 2017[41]
		CeL	single-unit	excited during CS-shock and freezing	x	−	Fadok 2017[41]
	CRF	CeL	ChR2	CS flight	yes	−	Fadok 2017[41]
		CeL	ChR2	decrease CS-freezing	no	−	Fadok 2017[41]
		CeL	single-unit	excited during CS-flight	x	−	Fadok 2017[41]
	5HT2A	CeA	ChR2	increase food intake	yes	+	Douglass 2017[33]
		CeA	ChR2	decrease freezing to aversive US	yes	−	Isosaka 2015[102]
Input	insula-CeA		ChR2	avoidance (RTPA)	x	−	Wang 2018[48]
	PBN_{CGRP}-CeC/L		ChR2	appetite suppression	no	−	Carter 2013[45]
	PBN_{CGRP}-CeC/L		ChR2	defensive behaviors	no	−	Han 2015[46]
	$PVT\text{-}CeL_{SOM}$		ChR2	inhibition decrease FC	no	−	Penzo 2015[47]
	BLA_{Rspo2}-CeC_{PKCd}		ChR2	defensive response	yes	−	Kim 2017[29]

		Experiment	Behavior or neural response	Bidirectional*	Valence	Reference
Output	CeA-vIPAG	ChR2	hunting (prey approach)	no	+	Han 2017[49]
	CeL-SI PKCd+	ChR2	avoidance (CPA)	x	−	Cui 2017[85]
Basolateral amygdala (BLA)						
Gene	Rspo2 (anterior)	ChR2	freezing	yes	−	Kim 2016[62]
	Ppp1 (posterior)	ChR2	self-stimulation	yes	+	Kim 2016[62]
	PV	ChR2	increase CS-shock freezing	yes	−	Wolff 2014[63]
		single-unit	excited to the CS-shock	x	−	Wolff 2014[63]
	SOM	ChR2	decrease CS-shock freezing	yes	+	Wolff 2014[63]
		single-unit	inhibited to the CS-shock	x	+	Wolff 2014[63]
Input	insula-BLA	ChR2	approach (RTPP)	x	+	Wang 2018[48]
	ACC-BLA	NpHR	decrease observational fear retrieval	no	−	Allsop 2018[66]
Output	BLA-NAc	ChR2	self-stimulation	x	+	Namburi 2015[52], Britt 2012[57], Stuber 2011[58]
		single-unit	preferentially excited to CS-sucrose	x	+	Beyeler 2016[12]
	BLA_{Rspo2}-NAc	ChR2	freezing & stimulation avoidance (RTPA)	x	−	Kim 2017[29]
	BLA-CeL	ChR2	anxiolytic	yes	+	Tye 2011[96]
	BLA-CeM	ChR2	place aversion	x	−	Namburi 2015[52]
	BLA-CeA	single-unit	preferentially excited to CS-quinine	x	−	Beyeler 2016[12]
	BLA-vHPC	ChR2	anxiogenic	yes	−	Felix-Ortiz 2013[54]
		single-unit	unbiased	x	+/−	Beyeler 2016[12]
	BLA-mPFC	ChR2	anxiogenic	yes	−	Felix-Ortiz 2015[56], Lowery-Gionta 2018[97]
		ChR2	increase CS-shock freezing	yes	−	Burgos-Robles 2017[53]
		single-unit	preferentially excited to CS-shock	x	−	Burgos-Robles 2017[53]
	BLA-PL	single-unit	active during CS-shock (early extinction)	x	−	Senn 2014[59]
	BLA-IL	single unit	active during CS-shock after extinction	x	+	Senn 2014[59]
	BLA-adBNST	ChR2	anxiogenic	x	−	Kim 2013[98]

*: study reporting bidirectional manipulation of the tested behavior/s

'x': not tested, RTPP/A: real time place preference/avoidance, CPA: conditioned place avoidance, PL: prelimbic, IL: infralimbic, adBNST: anterodorsal part of the bed nucleus of the stria terminalis [12••,29••,33•,35,38–42,45–48,49•,52–54,56–59,62••,63,66,85•,96–98,102]