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Basolateral amygdala circuitry in positive and negative valence

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Abstract

All organisms must solve the same fundamental problem: they must acquire rewards and avoid danger in order to survive. A key challenge for the nervous system is therefore to connect motivationally salient sensory stimuli to neural circuits that engage appropriate valence-specific behavioral responses. Anatomical, behavioral, and electrophysiological data have long suggested that the amygdala plays a central role in this process. Here we review experimental efforts leveraging recent technological advances to provide previously unattainable insights into the functional, anatomical, and genetic identity of neural populations within the amygdala that connect sensory stimuli to valence-specific behavioral responses.

The amygdala and valence-specific behavior

Sensory stimuli can be described by both their salience (how arousing a stimulus is) and their valence (how good or bad a stimulus is). Salient sensory stimuli elicit behavioral responses that can be either specific to the valence of a stimulus, such as approach towards a reward, or valence non-specific, such as increases in autonomic reactivity in the presence of both rewarding and aversive stimuli. The notion that the amygdala plays a central role in connecting motivationally salient sensory stimuli to behavioral output was first suggested by the observation that removal of the temporal lobes caused profound motivational disturbances in primates [1–3]. This finding inspired many other groups to investigate the role of the amygdala in motivated behavior, typically by employing a Pavlovian fear-conditioning paradigm. In this paradigm, an aversive stimulus (unconditioned stimulus, US)

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is contingently paired with a neutral stimulus (conditioned stimulus, CS) such that an animal learns that the CS predicts the US [4]. Subsequent presentation of the CS alone elicits defensive responses similar to those evoked by the US. Lesions of either the basolateral or central nuclei of the amygdala prevent the acquisition and expression of learned defensive responses to a CS, while lesions of the basolateral amygdala impair innate responses to an aversive US [5–9]. These data have profoundly influenced the study of the neurobiology of motivated behavior, and have firmly established the importance of the amygdala in mediating behavioral and physiological responses to aversive stimuli.

In addition to the amygdala's well-established role in defensive behaviors, converging evidence has implicated the amygdala in specific forms of appetitive behavior. Lesions of the basolateral nucleus of the amygdala impair behaviors that depend on both the sensory qualities and the value of a stimulus (such as reinforcer devaluation, second-order conditioning, and outcome-specific Pavlovian-instrumental transfer) [10–13], while lesions of the central nucleus of the amygdala produce deficits in behaviors that depend on the more general motivational properties of a stimulus (such as Pavlovian conditioned approach and generalized Pavlovian-instrumental transfer) [11, 14–16]. Since appetitive and aversive behavioral responses are often distinct, and even opposing, it follows that rewarding and aversive stimuli may engage distinct amygdala circuits to elicit valence-specific behavioral responses. In accord with this premise, converging lines of evidence have identified functionally distinct neural circuits in the amygdala that mediate appetitive and aversive behavioral responses, and recent studies have begun to delineate how these circuits might be defined at the anatomical and genetic levels.

Evidence for distinct positive and negative networks in the amygdala

Electrophysiological recordings of neural activity have consistently identified neural representations of both appetitive and aversive stimuli in the amygdala [17–36]. Some neurons have been shown to respond to CSs [17, 18, 25, 31, 33, 35, 37–39], others to USs [18, 19, 21, 29, 38, 40], and others to both CSs and USs [20–22, 24, 30, 32, 41]. Notably, neural responses to a CS change as a function of learning, with some neurons increasing their firing rate, and other neurons decreasing their firing rate, an observation recently confirmed by using calcium imaging to assess neural activity during fear learning [22–25, 30, 32, 33, 41]. The specific neurons that remain CS-responsive after learning may be dictated by their relative excitability at the time of conditioning [36, 42, 43].

Electrophysiological recordings in monkeys performing a trace conditioning task have shown that CSs of each valence elicit higher levels of activity in largely distinct, but anatomically intermingled, populations of neurons; this signal about CS valence is distinct from a neural signal that represents CS identity [32]. In these studies “valence preference” is termed “value coding”, and is defined by the differential activity of a neuron in response to a CS associated with either rewarding or aversive reinforcement. Neurons that exhibit higher activity in response to a CS when it predicts a rewarding US than to the same CS when it predicts an aversive US are classified as ‘positive value-coding’, and neurons with higher activity in response to a CS when it predicts an aversive US than when it predicts a rewarding US are classified as ‘negative value-coding’ (Figure 1A). Notably, simultaneously

recorded neurons that prefer CSs with the same valence have been shown to exhibit short latency peaks in cross-correlograms, consistent with direct connectivity [44] and have been observed to update their responses to a CS upon a reversal in reinforcement contingencies at different rates depending upon the valence-preference of recorded neurons [45]. More recent studies in rodents have observed that CSs and USs of each valence differentially engage largely distinct yet anatomically intermingled neuronal populations [35, 41, 46–48]. Taken together, these results suggest that neurons within the amygdala display valence selectivity and exist in functionally discrete appetitive and aversive circuits [29, 30, 32, 44, 45]

Through learning, neural representations of appetitive and aversive CSs becomes more similar to the representation of appetitive and aversive USs that entrained learning, at both the population and single-cell levels (Figure 1B) [29, 30, 41, 46] (but note that the response to USs themselves change as a function of learning, since amygdala neurons modulate their responses to a CS as a function of expectation [29, 49])

In principle, the valence-specific neural responses evoked by a learned CS in the amygdala may represent information about the sensory qualities of the US associated with a CS, rather than its valence per se. However, positive value-coding neurons have been shown to fire more in response to multiple stimuli of the same valence, including to a fixation point (itself a mildly positive CS), CSs predicting large rewards, and to multiple distinct rewarding USs [30, 47]. Negative value-coding neurons have been shown to exhibit the opposite response profile, decreasing their firing rate to a fixation point, and increasing their firing rate to CSs predicting aversive stimuli, and to multiple distinct aversive USs [30, 41]. Strikingly, on average positive value-coding neurons not only increase their firing in response to rewarding stimuli, but also decrease their firing rate to a CS predicting an aversive air-puff; negative value-coding neurons exhibit the opposite response profile [30]. In addition, while negative value coding neurons respond most strongly to a CS predicting an aversive air-puff, these cells also tend to respond more strongly to a CS predicting a small reward compared to a CS predicting a large reward [30]. These data indicate that individual amygdala neurons are capable of integrating information about different types of associated USs. Taken together, these findings demonstrate that amygdala neurons do not merely represent the sensory quality of an associated US; instead, they track the moment-to-moment value of stimuli that can span sensory modality and valence. This observation has led to the proposition that the amygdala represents state value; how good or bad a stimulus is at any given moment in time, given an animal's internal and external situation.

Additional support for the proposition that the amygdala represents state value has been provided by a recent report utilizing a contrast revaluation procedure to demonstrate that amygdala neurons encode the relative value of a stimulus compared to other stimuli presented to an animal in the same experimental session [50]. In these experiments, the amount of reward associated with a CS remained constant, but its relative value was manipulated by changing the amount of reward associated with a second CS. Monkeys and amygdala neurons tracked the change in relative value of the first CS, indicating that even when a CS-US contingency does not change, an internal evaluative process can alter state value and the representation in the amygdala [50]. Similar observations have been made regarding amygdala neural responses to USs [19].

The extensive evidence linking the amygdala to valence-specific processing does not imply that the amygdala lacks neural signals related to other aspects of motivation. In addition to encoding the perceived value of motivationally salient stimuli, the amygdala also encodes signals related to motivational salience, irrespective of valence. Electrophysiological studies have demonstrated that neural responses in the amygdala are enhanced when unconditioned stimuli are unexpected [29, 49]; some studies have also reported amygdala neurons that respond to CSs that predict either rewarding or aversive USs [35]. Neurons activated by stimuli of either valence may play a role in orchestrating valence non-specific responses to motivationally salient stimuli, such as increases in arousal or attention [51]

The identification of discrete neural circuits that respond to rewarding and aversive stimuli in the amygdala suggests that these circuits may play a central role in connecting sensory stimuli to valence-specific behavioral output. To explicitly test this hypothesis requires asking whether activating amygdala neurons that respond to either a rewarding or an aversive stimulus is capable of eliciting valence-specific behavioral responses. Unfortunately, the absence of obvious gross anatomical segregation between positive and negative networks within the amygdala (but see [52]) has made it difficult to perform causal manipulations to assay the function of each network independently using classical lesion, pharmacological, electrical, or even optical techniques to manipulate neural activity. To circumvent this, rodent researchers have recently developed several different approaches that utilize immediate early gene (IEG) promoters to drive expression of reporter proteins in an activity-dependent manner, facilitating genetic access to neurons that are activated by an array of different stimuli [46, 53–64].

Two recent studies utilized this approach to induce expression of the photoactivatable cation channel, channelrhodopsin, in cells that respond to either rewarding or aversive stimuli in the basolateral amygdala (BLA) [46, 64]. It should be noted that since neurons in the amygdala display mixed-selectivity [39], it is unlikely that these neurons respond exclusively to rewarding or aversive stimuli, but instead are likely to respond to multiple stimuli, potentially even of opposing valence. In support of this, an electrophysiology study in monkeys showed that “positive” valence preferring neurons often respond to both rewarding and aversive USs, an observation also made for “negative” valence preferring neurons [32]. This notwithstanding, in both studies, subsequent photoactivation of neurons in appetitive networks elicited reward-related behaviors, and photoactivation of neurons in aversive networks elicited defensive behavioral responses. In addition, photoactivation of US representations was capable of driving valence-specific learning, while photoinhibition of an aversive US representation prevented the expression of previously learned defensive responses [46]. These data suggest that CSs generate learned behavioral responses through the activity of the entraining US representation. Finally, consistent with prior electrophysiological studies [29, 30, 32, 44, 45], the activity of neurons from appetitive and aversive networks in the amygdala could not be entrained to the opposite valence [64], indicating that valence-specific networks in the amygdala may be fixed. This observation raises the interesting possibility that appetitive and aversive networks in the amygdala are predetermined to elicit valence-specific behavioral responses by virtue of their anatomical connectivity, their genetic identity, or both.

Defining positive and negative networks

Anatomical Connections

One mechanism by which the distinct appetitive and aversive networks within the amygdala might coordinate opposing behavioral responses is through differential connectivity to downstream brain regions. Anatomical tracing studies have demonstrated that the amygdala sends projections to numerous cortical and subcortical structures that have been implicated in the generation of an array of different motivated behaviors [65, 66]. The advent of optogenetics, a strategy with which to express light-sensitive channels and pumps in genetically defined populations of neurons in order to make their activity controllable by light [67], has enabled researchers to ask whether the activity of specific efferent projections from the amygdala can drive different motivated behaviors. Photoactivation of BLA axon terminals in the prelimbic cortex, ventral hippocampus, and central amygdala elicits defensive and anxiety-related behaviors [68–71], while photoactivation of BLA axon terminals in the nucleus accumbens elicits appetitive behaviors, and supports instrumental responding [70, 72]. These studies demonstrate that distinct anatomical projections from the amygdala are capable of eliciting valence-specific behavioral responses. Yet, the extent to which these projections are engaged during natural behavior has remained somewhat unclear.

Recent studies have begun to examine the physiological function of amygdala neurons that project to distinct brain regions. In one study, investigators employed retrograde labeling strategies to identify BLA neurons that project to either the nucleus accumbens or the central nucleus of the amygdala [70]. The authors demonstrated that photoactivation of these neurons could serve as a positive or negative reinforcer, respectively. Moreover, electrophysiological recordings in *ex vivo* slice preparations revealed that these neural populations undergo opposite changes in synaptic plasticity following reward or fear learning. In a subsequent study, the same group conducted *in vivo* electrophysiological recordings of BLA neurons that project to either the nucleus accumbens or central nucleus of the amygdala during the performance of an appetitive or aversive conditioning paradigm [48]. BLA neurons projecting to the nucleus accumbens preferentially responded to an auditory cue predicting an appetitive sucrose US; by contrast, BLA neurons that project to the central nucleus of the amygdala preferentially responded to an auditory cue predicting an aversive quinine US. These data suggest that positive and negative networks in the BLA may be segregated in their outputs to the nucleus accumbens and central amygdala (Figure 2). However, the use of tastants as unconditioned stimuli means that the ‘correct’ behavioral response to the quinine predictive cue was to stop licking in order to avoid the quinine. As a consequence, avoidance of the quinine punishment may itself be rewarding, complicating interpretation of neural responses to the ‘aversive CS’. In addition, the authors observed substantial collateralization of BLA projection neurons to both the nucleus accumbens and central amygdala [48]. This collateralization may help to explain why a recent study reported that BLA neurons that respond to either reward or punishment project to both the nucleus accumbens and central nucleus of the amygdala [52]. Furthermore, photoactivation of the nucleus accumbens projections from a genetically defined subset of BLA neurons can elicit defensive behaviors [52]. It is therefore possible that appetitive and aversive networks

in the BLA send projections to both the nucleus accumbens and central amygdala to mediate different elements of valence-specific behavioral responses (Figure 2).

Although the activity of amygdala axonal projections to specific brain regions is capable of eliciting valence-specific behavioral responses, the biological function of many of these projections may be more nuanced. Indeed, some behavioral responses to rewarding and aversive stimuli are clearly distinct; liquid rewards induce licking, whereas the presence of a predator may induce micturition. These behavioral responses are likely mediated through specific neural circuitry mediating distinct functions. However some behavioral responses to rewarding and aversive stimuli are less distinct: approach to a reward and avoidance of an aversive stimulus likely both engage motor circuits involved in action planning and execution. This might explain why the BLA projection to the nucleus accumbens, which has extensive connectivity with motor circuits [73], is capable of eliciting both appetitive and aversive behavioral responses. Overall, specific anatomical connectivity must underlie the expression of appetitive and aversive behavior, but the anatomical scale – whether at the local circuit or brain area level – may vary depending upon the behavioral or physiological response.

Genetic Identity

Recent advances in activity-dependent labeling of neurons and genetic sequencing technologies permit rapid and comprehensive genetic characterization of neurons that respond to different stimuli. One group combined this approach with screening on the Allen Mouse Brain Atlas to identify two genes, protein phosphatase 1 regulatory inhibitor subunit 1B (*Ppp1r1b*) and R-spondin 2 (*Rspo2*), that are selectively enriched in amygdala neurons that respond to rewarding and aversive stimuli, respectively (Figure 2) [52]. In contrast to prior studies demonstrating that neurons responding to rewarding and aversive stimuli are anatomically intermingled, the researchers observed an anterior to posterior segregation of *Ppp1r1b*+ and *Rspo2*+ neurons, with *Ppp1r1b* expressed predominantly in the posterior BLA, and *Rspo2* expressed predominantly in the anterior BLA. The authors replicated this finding using c-Fos immunohistochemistry to demonstrate that other rewarding stimuli, including sucrose and water, primarily activate the posterior BLA, while other aversive stimuli, such as quinine and trimethylthiazoline (TMT), primarily activate the anterior BLA. The discrepancy between this finding and prior reports may be due to the fact that prior studies have mainly sampled from the medial portion of the BLA, where both rewarding and aversive stimuli induce comparable levels of c-Fos expression.

In the same set of studies, the group then examined the functional role of *Ppp1r1b*+ and *Rspo2*+ neurons in the generation of valence-specific behavioral responses. Optogenetic activation and inactivation experiments demonstrated that the activity of *Ppp1r1b*+ and *Rspo2*+ neurons was both necessary and sufficient for appetitive and aversive behavioral responding, respectively. Moreover, photoactivation of *Ppp1r1b*+ neurons inhibited *Rspo2*+ neurons and disrupted aversive behavior, while activation of *Rspo2*+ neurons inhibited *Ppp1r1b*+ neurons and disrupted reward-seeking behavior. These data suggest that in addition to eliciting valence-specific responses directly, these genetically defined subsets of neurons also mutually inhibit each other, potentially favoring binary behavioral responses. In

addition, subsequent analyses in the central nucleus of the amygdala have suggested that Ppp1r1b+ and Rspo2+ BLA neurons may have genetically distinct post-synaptic targets capable of facilitating and suppressing appetitive responding [74].

While the behavioral results of this study are compelling, it should be noted that only a small fraction of either Rspo2+ or Ppp1r1b+ neurons are activated (based on c-fos expression) by either footshock or female presentation, respectively. It therefore remains to be determined whether neurons within each genetically defined population that are not activated by these reinforcers respond to other stimuli of the same valence, or not. Future experiments conducting single cell RNA sequencing of neurons activated by a range of rewarding or aversive stimuli or events are therefore critical to furthering our understanding of the extent to which appetitive and aversive networks are defined by genetic identity.

Conclusions and Future Directions

The amygdala plays a central role in connecting sensory stimuli to appropriate valence-specific behavioral output. The studies outlined in this review suggest that inherently reinforcing unconditioned stimuli (USs) activate populations of amygdala neurons predetermined to elicit appetitive or aversive behavioral responses via a combination of their genetic identity and anatomical connectivity. Since neutral sensory stimuli only acquire valence through experience, it follows that absent learning, neutral CSs do not robustly activate valence-specific behavioral outputs [48, 70]. However, after learning a CS can drive valence-specific behavior, likely through mechanisms that require reactivation of US representations in the BLA [46]. The capacity of a CS to drive valence-specific behavior, however, often depends upon rapidly evolving contextual information; in blackjack the presentation of a king can be highly rewarding or highly aversive depending upon the other cards in a player's hand. Recent recordings in monkeys have shown that both behavioral and neural responses to a CS can switch when subjects use inference to adjust predictions of reinforcement outcomes [39]. This flexible adjustment of responses to a CS cannot be attributed to learning-related plasticity but instead must be due to the implementation of a rule. How rule-based tasks rapidly engage appropriate appetitive and aversive networks in the amygdala is unclear. It therefore remains to be established how appetitive and aversive networks are dynamically regulated to mediate complex goal-directed behaviors.

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Highlights

Neurons in the amygdala respond to rewarding and aversive stimuli and provide a representation of state value

Neurophysiological, anatomical and genetic methods have characterized distinct neural circuits in the amygdala that preferentially process appetitive and aversive stimuli

Valence-specific behavioral responses to reinforcing stimuli are mediated by these distinct neural circuits in the amygdala

Figure 1. Positive and negative value-coding neurons in the amygdala

A. Response profiles of two representative value-coding neurons in the primate amygdala recorded during a reversal learning task. A positive value-coding neuron (left) increases its firing rate to a CS that predicts an appetitive US (blue lines) while a negative value-coding neuron (right) responds to a CS that predicts an aversive US (red lines). Note that these neurons reflect the value of a CS rather than its identity, as they maintain value-coding after reinforcement contingencies are switched (solid lines, pre-reversal, dashed lines, postreversal). For details, see [44]. **B.** CS and US response profiles in a population of positive value-coding (left) or negative value-coding (right) neurons across 20 trials following a reversal in reinforcement contingencies. The color code plots the average normalized difference in activity on rewarding and aversive trials where a z-score of 0 means there is no difference in response to an appetitive vs aversive CS. Immediately after reversal (trial 1), there is discordance between CS and US selectivity (different colors after CS and

US appearance on trial 1 for both populations). With learning, CS responses, at the population level, come to match US responses (same color after CS and US). For details, see [29]. Reproduced with permission from [29] and [44].

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Figure 2. Anatomical connectivity and genetic identity of positive and negative value-coding BLA neurons

A model, based on the integration of findings from [48, 52, 70, 74], in which genetic markers and anatomical connections from the BLA to the nucleus accumbens and central amygdala determine valence-specific behaviors. Green = neurons activated by rewarding stimuli. Red = neurons activated by aversive stimuli. Solid line = excitatory connection. Dashed line = inhibitory connection. Ppp1r1b = protein phosphatase 1 regulatory inhibitor subunit 1B. Rspo2 = R-spondin 2. Sst = somatostatin. Nts = neurotensin. Tac2 = tachykinin

2. *Note that the activity of somatostatin-expressing neurons in the central amygdala has also been shown to be able to elicit defensive behaviors [75].