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Parsing Reward and Aversion in the Amygdala

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The basolateral amygdala (BLA) is critical for encoding the value of stimuli. [Beyeler et al. \(2016\)](#) now show that distinct populations of BLA neurons, which are defined by their efferent targets, code reward and aversion. This arrangement promotes parallel processing of biologically relevant events.

Learning to predict the occurrence of biologically relevant experiences, whether a painful bee sting or a tasty scoop of ice cream, is a brain function that is critical for survival. Pavlovian conditioning is one form of learning that contributes to our capacity to predict the pains and pleasures of life. Decades of research on the brain substrates of Pavlovian conditioning have revealed a central role for the amygdala, an almond-shaped collection of neurons buried deep within the medial temporal lobe. The evidence for the amygdala's contribution to emotional learning is broad and deep ([Duvarci and Paré, 2014](#); [LeDoux, 2000](#); [Orsini and Maren, 2012](#)) and extends to both aversive and appetitive conditioning processes ([Holland and Gallagher, 1999](#)).

Within the amygdala, neurons in the basolateral amygdala (BLA) have been implicated in representing the value of outcomes, whether good (e.g., a tasty food reward) or bad (e.g., an aversive electric shock). For example, BLA neurons represent both learned fear and safety ([Hobin et al., 2003](#); [Sangha et al.,](#)

[2013](#)), and code the value of appetitive and aversive outcomes ([Gore et al., 2015](#); [Paton et al., 2006](#)). This has led to the view that the BLA has a central role in representing the sensory features of rewarding and aversive outcomes and the stimuli that predict them ([Balleine and Killcross, 2006](#)).

But how does the BLA parse reward and aversion within its microcircuitry? Recent work on this question suggests a “salt and pepper” organization; that is, neurons encoding pain and pleasure appear to be randomly interspersed within the BLA ([Gore et al., 2015](#); [Herry et al., 2008](#)). This begs the question: how can an amalgam of aversion and reward cells direct adaptive behaviors involved in avoidance and approach, respectively? [Beyeler et al. \(2016\)](#) have now discovered an organizing principle for amygdalar coding of stimulus value: reward and aversion are parsed into discrete circuits defined by the efferent targets of BLA neurons.

To reveal this organizing principle, [Beyeler et al. \(2016\)](#) recorded from over 1,600

BLA neurons in awake, behaving mice that were conditioned to associate auditory conditioned stimuli (CSs) with appetitive (sweet sucrose) or aversive (bitter quinine) fluids (unconditioned stimuli or USs). These fluids were delivered to sipper tubes from which the animals could lick soon after the onset of the auditory CSs. After 1 week of training, animals showed robust anticipatory licking (a conditioned response or CR) to the sucrose-paired CS (CS_{sucrose}), but not to the quinine-paired CS (CS_{quinine}). Importantly, hundreds of BLA neurons in the conditioned mice responded to the CSs by either increasing or decreasing their firing rates to one or both of the stimuli. But what differentiated the valence coding among these neurons?

To address this question, [Beyeler et al. \(2016\)](#) examined whether the projection targets of the neurons they recorded from would segregate the population according to the CSs driving their activity. Three months prior to the recording experiments, the mice received intracranial injections of viral vectors to “phototag” BLA neurons

projecting to a particular efferent target. Using laser light pulses *in vivo*, the authors identified a subset of BLA neurons projecting to the nucleus accumbens (NAc), central nucleus of the amygdala (CeA), or ventral hippocampus (vHPC) in their electrophysiological recordings. These particular brain regions were targeted because they are known to organize CRs to rewarding (NAc) and aversive (CeA and vHPC) CSs. It should be noted that an important feature of [Beyeler et al. \(2016\)](#) phototagging strategy was the use of *in vitro* brain slice recordings to define pathway-specific latencies for light-induced responses in infected BLA neurons. This allowed the authors to discriminate specific BLA projection neurons from light-responsive “nearby neighbors” receiving collateral input from other infected neurons.

Having identified specific BLA “projectors” in their *in vivo* recordings, the authors could then ask how each subset of projection neurons responded to the sucrose- or quinine-paired CSs. They found that BLA neurons projecting to the NAc responded preferentially to the CS signaling reward (CS_{sucrose}), whereas BLA neurons projecting to the CeA responded preferentially to the CS signaling the aversive outcome (CS_{quinine}); BLA neurons projecting to the vHPC showed similar responses to the two CSs ([Figure 1](#)). In other words, whether a BLA neuron preferentially responded to a rewarding or aversive CS was determined, at least in part, by where the neuron projected. Indeed, over 80% of the tagged NAc-projecting BLA neurons had a “valence bias” for the CS_{sucrose}, whereas 69% of CeA-projecting neurons biased their responses to the CS_{quinine}. Interestingly, these response patterns were also found in neural activity evoked directly by the US, suggesting that projection-specific valence coding is a hardwired feature of BLA circuitry that is co-opted by conditioned stimuli during learning.

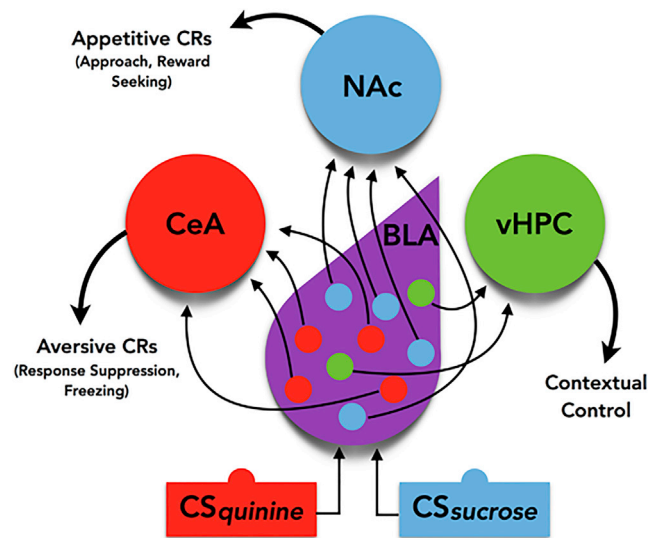


Figure 1. Projection-Specific Coding of Appetitive and Aversive CSs in the Basolateral Amygdala

Sensory information concerning auditory CSs paired with sucrose (CS_{sucrose}, blue) or quinine (CS_{quinine}, red) reaches the basolateral amygdala (BLA, purple). Neurons in the BLA exhibit preferential responses to aversive and appetitive CSs (blue, red “cells”; green “cells” do not prefer one CS over the other), and these firing preferences are related to the efferent projections to the central nucleus of the amygdala (CeA, red), nucleus accumbens (NAc, blue), and ventral hippocampus (vHPC, green). BLA→CeA and BLA→NAc microcircuits are involved in the production of aversive and appetitive conditioned responses (CRs), respectively; BLA→vHPC projections may be involved in contextual control of motivated behavior.

Discrete microcircuits for reward and aversion permit the BLA to influence efferent neural circuits involved in generating conditioned behavioral responses to appetitive or aversive CSs. Of course, a critical question is how information encoded in the BLA influences efferent structures in a behaviorally relevant manner. For example, although it is well-documented that BLA projections to the CeA are involved in conditioned fear responses, such as freezing and fear-potentiated startle ([Jimenez and Maren, 2009](#); [Namburi et al., 2015](#)), their role in lick suppression (or quinine avoidance) is less clear. In fact, there is reason to believe the CeA, rather than the BLA, is involved in the suppression of appetitive behavior (such as lever pressing for food) by Pavlovian CSs that predict aversive outcomes ([Balleine and Killcross, 2006](#); [Petrovich et al., 2009](#)). Hence, the specific function of CeA-projecting neurons in the BLA that encode quinine-paired CSs remains an open question.

Similarly, the function of BLA neurons encoding sucrose-paired CSs and projec-

ting to the NAc is also unclear. While it has recently been shown that animals will engage in instrumental behavior to receive photostimulation of BLA neurons projecting to the NAc, activating this pathway does not influence conditioned licking for a sucrose CS ([Namburi et al., 2015](#)). Hence, although stimulating NAc-projecting neurons in the BLA can positively reinforce instrumental responding, neither the BLA nor its projections to the NAc are required for appetitive CRs *per se* ([Holland and Gallagher, 1999](#)). Rather, reward-related representations established in the BLA during Pavlovian conditioning are involved in modulating instrumental responses for appetitive reinforcers via projections to the NAc (i.e., Pavlovian-instrumental transfer; [Balleine and Killcross, 2006](#)). It will be important to determine whether neuronal activity in CeA- and NAc-projecting neurons in the BLA is correlated with behaviors mediated by those circuits. Lastly, there was no particular bias in the valence coding of BLA neurons projecting to the vHPC; this pathway may integrate hedonic and aversive information from the amygdala to bring motivated behavior under contextual control ([Maren et al., 2013](#)).

The parsing of reward and aversion in BLA microcircuits does, however, reveal a novel anatomical organization by which valence coding in the BLA can bias appetitively or aversively motivated behavior via the NAc and CeA, respectively. Yet it raises an intriguing question concerning how the BLA projectors themselves come to respond preferentially to biologically significant outcomes. In other words, how do CeA- and NAc-projecting neurons come to respond preferentially to aversive and appetitive stimuli, respectively? Stated more simply, how do these neurons “know” where they project? Given that BLA neurons respond selectively to aversive and appetitive tastes, it is possible that afferent gustatory information to the

amygdala is parsed in such a way that CeA- and NAc-projecting neurons in the BLA are preferentially targeted by sensory pathways representing bitter and sweet tastes, respectively. If true, this organization would seem to require a feedback mechanism (perhaps early in development) by which CeA and NAc shape sensory inputs onto BLA neurons in a projection- and valence-specific manner. Because neither the CeA nor NAc projects directly to the BLA, this feedback might be mediated by descending projections to midbrain monoaminergic neurons which, in turn, modulate plasticity in forebrain circuits, including the BLA.

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Inhibition Patterns the Whisking Rhythm

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In this issue of *Neuron*, Deschênes et al. (2016) propose that rhythmic inhibition of whisker motor neurons is a key pattern generator underlying exploratory whisking. The inhibitory premotor neurons located in the brainstem reticular formation are synchronized by breathing-related oscillators.

Rodents actively scan their immediate facial environment through rhythmic forward and backward whisker movements at ~10 Hz. As a moving whisker encounters an object, the whisker bends, causing the opening of mechanogated ion channels depolarizing the nerve endings of sensory trigeminal neurons, which innervate the whisker follicle. Action potential firing in these whisker sensory neurons releases glutamate onto postsynaptic neurons in the trigeminal brainstem, forming the start of diverse sensory signaling pathways to downstream brain areas (Petersen, 2007). Whisker movements provide the drive for active sensing, and thus understanding whisker motor control

is of paramount importance for a mechanistic understanding of whisker sensory perception (Petersen, 2014). In this issue of *Neuron*, Deschênes et al. (2016) report important advances in whisker motor control, unexpectedly finding that rhythmic inhibitory, rather than excitatory, input controls important aspects of whisker motor neuron firing.

Whisker protraction is generated by contraction of intrinsic muscles within the mystacial pad (Dörfl, 1982), controlled by motor neurons located in the ventral lateral facial nucleus (Herfst and Brecht, 2008; Takatoh et al., 2013; Sreenivasan et al., 2015). Deschênes et al. (2016) recorded intracellularly from whisker motor

neurons during kainic acid-induced artificial whisking in anesthetized rats. They found that the whisker motor neurons gradually depolarize and fire action potentials during whisker protraction, and then rapidly hyperpolarize just before the onset of whisker retraction (Figure 1). The membrane potential dynamics of these whisker motor neurons is determined by convergent excitatory and inhibitory synaptic input from premotor neurons. By using transsynaptic rabies virus (Wickersham et al., 2007; Stepien et al., 2010), whisker premotor neurons have been mapped to a large number of brain regions including spinal trigeminal oralis nucleus (Sp5O), the vestibular

