# Reciprocal amygdala-prefrontal interactions in learning

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## Abstract

Animals constantly evaluate their environment in order to avoid potential threats and obtain rewards in the form of food, shelter and social interactions. In order to appropriately respond to sensory cues from the environment, the brain needs to form and store multiple cue-outcome associations. These can then be used to form predictions of the valence of sounds, smells and other sensory inputs arising from the surroundings. However, these associations must be subject to constant update, as the environment can rapidly change. Failing to adapt to such change can be detrimental to survival. Several systems in the mammalian brain have evolved to perform these important behavioral functions. Among these systems, the amygdala and prefrontal cortex are prominent players. While the amygdala has been shown to form strong cue-outcome associations, the prefrontal cortex is essential for modifying these associations through extinction and reversal learning. Synaptic plasticity occurring in the strong reciprocal connections between these structures is thought to underlie both adaptive and maladaptive learning. Here we review the synaptic organization of the amygdala-prefrontal circuit, and summarize the physiological and behavioral evidence for its involvement in appetitive and aversive learning.

## Anatomy of the prefrontal-amygdala network

The amygdala is a region deep within the temporal lobe that constitutes a major information crossroads. Amygdala neurons receive direct sensory input from all sensory modalities through projections arising both from the sensory cortices and from thalamic sensory regions [1,2]. These

inputs provide the amygdala with access to fine-scale sensory information [3]. Another set of important inputs to the amygdala arises from the hippocampal formation [2]. These inputs are thought to deliver processed sensory information in the form of contextual representations, supporting the integration of specific sensory cues with contextual information [4]. While the sources of sensory cue-related information to the amygdala is well-described, less is known about the circuits transmitting outcome-associated information. Amygdala responses to unexpected aversive stimuli [5,6] are thought to be carried by a distributed set of circuits including the periaqueductal gray [7], insular cortex [8] and habenula [9]. Together, these convergent inputs support the formation of defined cue-outcome associations in the lateral area of the amygdala [10].

In addition to these inputs, which provide it with sensory information at various degrees of processing, the amygdala also receives "top-down" inputs from several different subregions of the prefrontal cortex (PFC). The PFC plays a major role in the control of adaptive behavior and is involved in a wide range of behavioral control processes, from working memory and decision making to impulse control and emotional regulation. In primates, the PFC is highly-developed, constituting a major fraction of the frontal cortex [11]. In rodents, the location of homologous regions has been anatomically and functionally identified based on tracing, lesion studies and pharmacological manipulations [12,13]. While the rodent PFC lacks a granular zone (which encompasses the entire dorsolateral PFC in primates), its medial-wall regions are thought to correspond to medial PFC structures in the primate: the prelimbic (PL) and infralimbic (IL) sub-regions of the rodent medial PFC (mPFC), are considered to be homologous in their connectivity patterns and functional properties with the primate anterior cingulate and ventral medial prefrontal cortex, respectively [12,14,15].

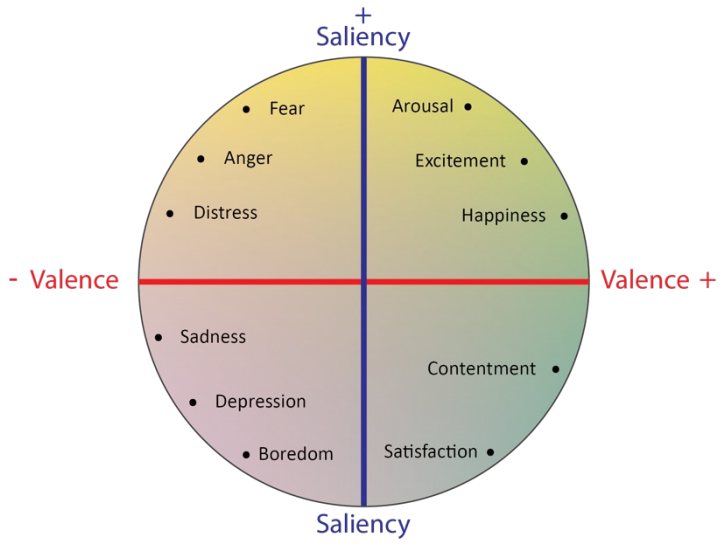


**Figure 1**. Modified from Russel (1980), this figure places representative affective states within a two-dimensional space defined by Valence (*X* axis) and Salience (*Y* axis).

The convergence of inputs from sensory, hippocampal and frontal regions allows the amygdala to produce an integrated output that can be regarded as an "annotated" version of sensory inputs from the animal's environment. Amygdala representations carry crucial information about the degree of relevance of a stimulus to the animal, which can be regarded as its saliency, and about its incentive value, or its valence [16,17]. These properties can be incorporated by the amygdala into a meaningful signal transmitted to downstream circuits and used to guide behavior. Such incorporated signals can be considered as including crucial characteristics of affective information [18]. Although the definition of emotions and their roles in behavior have been under much debate in the past century [19], one influential framework specifically highlights aspects related to the information carried by the amygdala-mPFC network. This framework describes affect in a two dimensional space, with arousal or saliency on one axis and valence on the other [18]. Saliency and valence can be regarded as the two major defining features of sensory stimuli, and are both features encoded by BLA and mPFC circuits (**Fig. 1**). By encoding these crucial variables, the mPFC-BLA axis can serve as a major channel providing affective information to top down control of adaptive, goal-directed behavior.

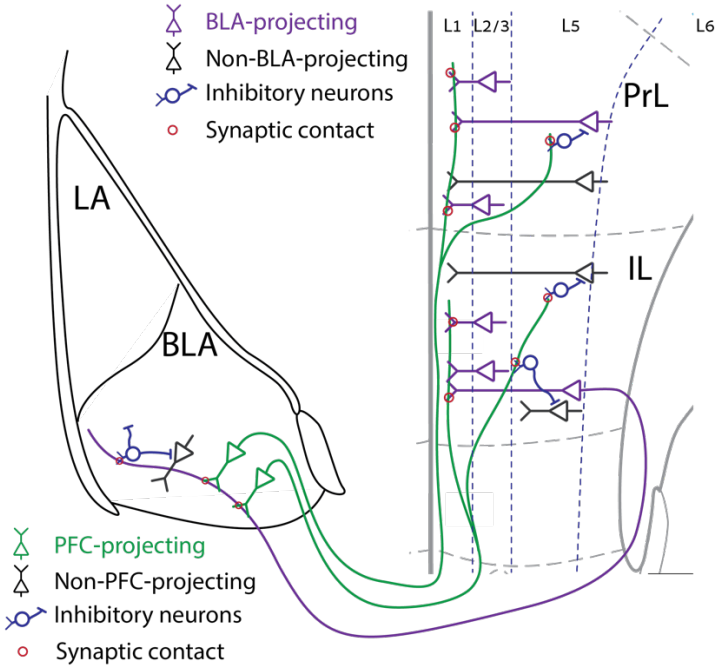


**Figure 2**. Reciprocal monosynaptic connectivity and local-circuit inhibition in the complex interplay between BLA and mPFC neurons. Excitatory projections from BLA pyramidal neurons drive both direct excitation and feed-forward inhibition in the different and functionally segregated mPFC subregions, with distinct populations of BLA neurons projecting to the infralimbic and prelimbic regions. Back-projections from the mPFC to the BLA follow similar logic with excitatory projections to BLA forming synaptic connections with higher probability onto mPFC-projecting neurons. Prelimbic (PL) and infralimbic (IL) depicted here, cingulate cortex not shown.

## Fine-scale synaptic connectivity in the prefrontal-amygdala network

While forming one of the major neocortical inputs to the amygdala, the PFC is also one of its major synaptic targets (**Fig. 2**). The basolateral nucleus of the amygdala (BLA) projects directly and forms monosynaptic excitatory connections with several sub-regions of the mPFC [20,21]. In rodents, the main targets of BLA input in the mPFC are the anterior cingulate (ACC), prelimbic (PL) and infalimbic (IL) cortices [22-25]. In primates, similarly robust and bidirectional connections were demonstrated between the amygdala and the medial pole of the prefrontal cortex, particularly in the caudal medial and orbitofrontal regions (areas 24, 25 and 32) [26,27]. This strong reciprocal connectivity suggests that information about learned associations is relayed from the BLA to the mPFC, where it is processed and redirected back into the amygdala in a manner that supports flexible responding to sensory cues. While the amygdala-mPFC network has been studied mostly

in the context of regulating fear behaviors, it is also emerging as a key player in emotional regulation in a wider variety of adaptive and maladaptive behaviors [28-33] .

At the macroscopic level, the long-range projections from mPFC to BLA and from the BLA to mPFC are anatomically dissociable [34]. Out of several main projection pathways leaving the BLA, the projections targeting the mPFC travel mainly laterally through the external capsule and adjacent deep cortical layers with minimal branching to additional targets along the pathway. The axons then diverge medially into and around the rostral pole of the accumbens, traversing toward the mPFC [34]. In the reciprocal direction, out of two descending pathways originating from the mPFC, the vast majority of projections towards the amygdala travel medially towards the medial part of the rostral-caudate putamen, branching from the bundle that crosses to the contralateral hemisphere in the corpus callosum towards the internal capsule. At the level of the sublenticular region, numerous fibers leave the internal capsule, diverge laterally across the sublenticular region and enter the amygdala [34].

Within the mPFC, BLA inputs diverge and innervate mostly layers 2 and 5, targeting the dendritic spines of post-synaptic pyramidal neurons, suggesting a direct feed-forward excitation of cells with dendrites in those layers [35]. Strikingly, BLA inputs were shown to preferentially target mPFC pyramidal cells projecting back to the BLA (**Fig. 2**; [36]), suggesting fine-scale recurrent wiring within this network. This recurrence is mirrored within the BLA, with similar specificity in the innervation of BLA cells projecting back to the mPFC [37]. However, despite this strong feedforward excitation, BLA stimulation suppresses firing in the mPFC [38]. Recent work has shown that this inhibition is mediated through excitation by BLA axons onto mPFC GABAergic interneurons of the parvalbumin (PV) and somatostatin (SOM) subtypes (Fig. 2; [35,39] [40]). Thus, BLA inputs to the mPFC can potentially both excite pyramidal neurons in this region and alter local-circuit dynamics through feed-forward inhibition. A recent study has provided fascinating insight into this local-circuit inhibition, demonstrating that a specific PV neuron subtype comprised mainly of chandelier-type inhibitory interneurons forms specific synaptic connections with layer 2 BLA-projecting pyramidal cells [41].

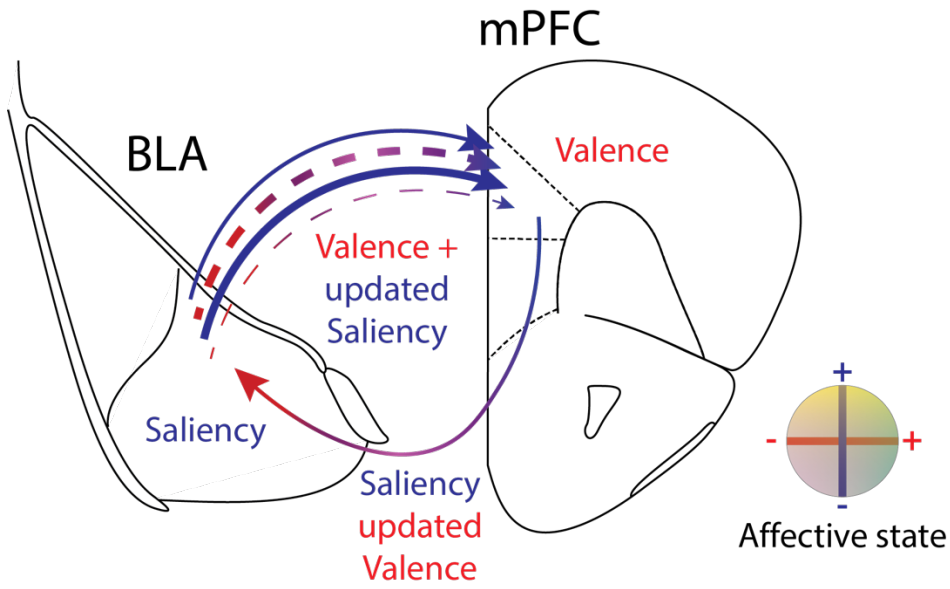


**Figure 3**: Schematic model of the propagation of information through the BLA-mPFC system in support of updating the valence and saliency of sensory stimuli during learning. The BLA signals the input's saliency to the mPFC where it is combined into an integrated saliency + valence signal which travels back to update the BLA representation, driving adaptive behavioral responses and regulating affective states.

## Fear and anxiety

The functions of the amygdala nuclei have been extensively studied in the context of fear and anxiety [42-44]. The lateral amygdala (LA) has been shown to be crucial for the formation of associations between aversive conditioned stimuli and unconditioned stimuli [45,46]. Newly-formed associations generated in the LA can control autonomic, reflexive fear behaviors through the projections to the central nucleus, a key output of the amygdala to brainstem nuclei controlling behavioral and visceral correlates of conditioned fear [10,47,48]. This associative fear response is controlled by inputs the mPFC. Within the mPFC, the pre-limbic and infra-limbic subregions were shown to play dissociable and often opposing roles in fear acquisition and extinction [49] (for reviews see [48,50]). The aforementioned recurrent network allows the same associations to modulate their own prefrontal top down control. It has been shown that the mPFC neural response (both PL and IL) to a stimulus associated with an emotionally salient event such as a foot shock highly depends on input from the BLA [51]. Directionality of information transfer between BLA and mPFC seems to play an important role in both fear and safety[52]. In primates it has been shown that adaptive-aversive learning depends on unsigned prediction error signal

developing in the amygdala transmitted to the ACC where a signed prediction error develops to guide learning [6,53]. However, the exact nature of the information carried by this network is still under debate. A recent study demonstrated that BLA neurons projecting to the PL and IL are differentially activated during fear and extinction learning, respectively [54]. This could imply that amygdala processing could not only provide the mPFC with information of relevant salient cues, but also bias mPFC output based on the antagonistic roles of PL and IL in fear expression. A more recent study provided support to a more general model in which fear-related information from the amygdala targets both PL and IL, while local-circuit processing combined with information from other nodes of the fear circuit transform this information to allow the differential contribution of these two regions to fear and extinction learning [55]. That is, while saliency is computed in the amygdala and introduced to the mPFC, the direction of behavioral control due to relevance or valence depends on information flow through the recurrent BLA-mPFC network. Information is subscribed through the differential connectivity of the BLA to the local circuitry within the mPFC. This process could potentially create a signal which encodes both saliency and valence in both the BLA and the mPFC and allow this integrated signal to modify the behavioral output through the BLA (**Fig. 3**).

**Action control**

Performance in various decision making tasks is thought to depend on two different behavioral control mechanisms, mostly related to the amount of training in the task. Restricted training leads to action control that is mediated by the association of the response to its outcome in a goal-directed manner. In contrast, prolonged training leads to action control through stimulus-response associations that are insensitive to the outcome, and therefore more habitual in nature [56,57]. Habit formation allows fast and efficient responding to pre-specified stimuli, while changes in circumstances call for re-evaluation and hence require the flexibility that characterizes the goal-directed behavioral control systems. Goal directed behavior is controlled by consequences, while habitual behavior is guided primarily through sensory stimuli activating a pre-programed behavior [58]. The ability to switch between these two control strategies is essential for adaptive behavior, and failure to do so was suggested to lie at the root of pathologies such as obsessive-compulsive disorder (OCD), obesity and addiction [59-63]. Mirroring their roles in fear learning and extinction, the PL and the IL have been suggested to exert opposing effects on habitual and goal directed behavior [58]. Whereas the PL supports goal-directed behavior

[64,65], the IL has been shown to be involved in habitual behavior [66,67]. As mentioned before, both subregions are highly innervated and influenced by BLA inputs. In fact it was shown that mPFC output to the ventral striatum, during responding to a conditioned cue, is highly influenced by BLA activation [68]. That same influence is how BLA projections to the mPFC affects drug seeking behavior [32]. However, more work will be needed to delineate the interactions of the BLA and mPFC in the formation and extinction of habitual behavior.

**Differential involvement of BLA to mPFC projections in aversive and appetitive learning**

The potential role of the BLA-mPFC circuit in routing emotional information during learning is especially evident in its differential contribution to appetitive and aversive learning. Two distinct spatially segregated populations of projection neurons were identified in the BLA which participate in valence-specific behaviors. These neurons seem to differentially target mPFC subregions, such that negative valence neurons project more densely to superficial layers in PL while the positive valence-encoding neurons more densely innervate deep-layer IL targets [69]. This corresponds with findings of the differential roles of the PL and IL in aversive [49] and appetitive behaviors [66]. This study implies a hard-wired system whereby amygdala neurons control both the valence and vigor of behavioral control exerted by the mPFC, where both saliency and valence are encoded in the amygdala and projected onwards. However, other evidence indicates that amygdala neurons included in fear memory engrams are not pre-defined, but rather result from a competitive process in which excitability dictates the recruitment of BLA neurons fear representations [70,71]. Indeed, a more recent work found that activating BLA to PL projections biases behavior towards defensive behavior (response to aversion) and that PL-projecting BLA cells were mainly active when responding to aversive rather than appetitive stimuli. However, some PL projecting BLA cells responded to appetitive stimuli and cross correlation analysis indicated inhibitory interactions between BLA and PL neurons during appetitive learning [72]. This could indicate a more nuanced picture, where BLA input widely targets the mPFC circuit, but local circuit interactions, driven through complex connectivity patterns described above (Fig. 2) is required in order to yield appropriate behavioral responses. Our recent work showing a reduction in response to aversive stimulus, when the BLA to both PL or IL projections are attenuated [55] is in line with this hypothesis, but more work is required to understand the detailed connectivity patterns and how individual circuit motifs are recruited during defined behavioral states.

## Summary

In this review, we summarize the anatomical, electrophysiological and behavioral evidence for the organization and functional roles of reciprocal BLA-mPFC interactions in appetitive and aversive learning. While the BLA is crucial for the formation of cue-outcome associations and for updating their value, the mPFC is required for the formation of adaptive, flexible behavioral responses. The tightly recurrent circuit linking the BLA and mPFC circuits might serve to continually update and refine both the saliency and valence of sensory stimuli in support of adaptive goal-directed behavior and regulation of affective states.

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