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Amygdala-prefrontal interactions in (mal)adaptive learning

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Abstract

The study of neurobiological mechanisms underlying anxiety disorders has been shaped by learning models that frame anxiety as maladaptive learning. Pavlovian conditioning and extinction are particularly influential in defining learning stages that can account for symptoms of anxiety disorders. Recently, dynamic and task related communication between the basolateral complex of the amygdala (BLA) and the medial prefrontal cortex (mPFC) has emerged as a crucial aspect of successful evaluation of threat and safety. Ongoing patterns of neural signaling within the mPFCBLA circuit during encoding, expression and extinction of adaptive learning are reviewed. The mechanisms whereby deficient mPFC-BLA interactions can lead to generalized fear are discussed in learned and innate anxiety. Findings with crossspecies validity are emphasized.

Pavlovian conditioning, an enduring model of associative learning

Navigation through daily life depends on a blueprint of familiar stimulus-outcome associations and the ability to update them as circumstances change. The update is particularly important for tracking shifting sources of danger. Too little self-protection in the face of new threat risks bodily harm whereas indiscriminate fear is physically and psychologically debilitating, as evidenced in anxiety disorders such as Post-Traumatic Stress Disorder (PTSD) and Generalized Anxiety Disorder (GAD). In neurobiology, the most popular model of associative learning, first formalized by Pavlov in the early 20th century [1], continues to be a versatile tool for studying how the nervous system learns about the changing world in general and emotional learning in particular [2]. The model states that associations are learned by experiencing neutral stimuli predictive of physically arousing unconditioned stimuli (US), and as these experiences are paired, the former are converted to conditioned stimuli (CS) that elicit a similar physiological response as the anticipated US. Therefore the CS and US have to meet the criteria of *contingency* (predictability) and *contiguity* (temporal proximity) for associative learning to occur. Recently, dynamic

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communication between the medial prefrontal cortex (mPFC) and the basolateral amygdala (BLA) during behavior has emerged as a key mechanism for incorporating new information about danger and **safety** into the existing blueprint. In this review we first briefly present the amygdala's role in associative learning and then focus on mPFC-BLA signaling in the face of changing CS-US contingencies during acquisition, expression and extinction of associative learning. We discuss how maladaptive, circuit-level communication during different phases of acquisition and expression can model heightened anxiety. Finally, we suggest some outstanding questions for investigating the mPFC-BLA circuit, with the goal of building a more complete understanding of how these brain regions contribute to anxiety.

Associative learning in the amygdala: A preference for aversion

The amygdala, named for its almond shape by Karl-Friedrich Burdach in the early 19th century, is an evolutionarily conserved structure [3]. It is a collection of nuclei deep in the temporal lobe that together constitute a tightly knit microcircuit. Molecular mapping has shown that the amygdala shares its embryonic origins with several parts of the telencephalon, including the vomeronasal system, striatum and hypothalamus [4]. Overall, the amygdala is widely recognized as a centralized hub for processing information that is critical for threat assessment and emotional associative learning. Anatomically, it is reciprocally connected with a wide swath of sensory cortices and subcortical structures, receiving multiple streams of sensory input from olfactory, auditory and visual areas [5]. The amygdala is also well-innervated by midbrain neurotransmitter systems, including cholinergic, noradrenergic, serotonergic and dopaminergic input [6] and modulated by a wealth of neuropeptides, including neuropeptide S [7], cholecystokinin [8], pituitary adenylate cyclase-activating polypeptide [9, 10] and oxytocin [11]. Thus, the interplay of neurotransmitters and neuromodulators in the amygdala sets the stage for a complex modulatory milieu that regulates multi-modal integration during anxiety and threat processing. Indeed, depending on the activated receptor and cell type, the same neurotransmitter can promote or block synaptic plasticity and have opposite effects on anxiety [12, 13]. For example, serotonergic activation of the 5HT_{1A} receptor in the amygdala drives an inhibitory potassium current and has anxiolytic behavioral effects, whereas serotonergic activation of the 5HT_{2C} receptor results in increased concentrations of intracellular calcium, which leads to excitation and is associated with an anxiogenic phenotype [13]. Likewise, cholinergic activation stimulates both nicotinic and muscarinic receptors, which drive inhibitory and excitatory postsynaptic currents, respectively [14,15]. Increased cholinergic and noradrenergic transmission has long been implicated in enhanced attention and memory [6,16,17,18]. Midbrain innervation of the amygdala aids in stimulus detection and encoding, as well as facilitation of plasticity at thalamic and cortical inputs to pyramidal neurons of the amygdala [17,18,19, 20]. Furthermore, such modulation enables more reliable transfer of information to cortical regions [20, 21,22]. Thus, multiple transmitter systems contribute to intra-amygdala processing and amygdalo-cortical information transfer that is critical for memory storage.

Although traditionally the amygdala is well-known for aversive memory formation, recent work has demonstrated that activity in the BLA represents rewarding stimuli as well [23, 24, 25, 26, 27, 28, 29, 30, 31]. However, when both aversive and rewarding stimuli are

associatively trained, a bias develops toward representing aversive rather than pleasant information [29, 31]. For example, in one study a large proportion of BLA cells that fired more to a rewarding olfactory CS during training, switched during recall to represent an aversive olfactory CS [29]. Another study showed that once an aversive association is formed in the amygdala, the same neurons don't switch to encoding reward [31]. These findings are consistent with our understanding of the cellular and molecular mechanisms underlying aversive memory formation and plasticity in the amygdala, which largely come from work focusing on aversion rather than reward [32, 33, 34, 35]. Thus, although the amygdala encodes multiple valences, the evidence to date suggests that BLA plasticity and long term memory formation is preferentially driven by aversion.

One question of great interest has been to understand whether certain amygdala neurons are selectively recruited into an aversive memory over others. Recent work has uncovered a key role of the transcription factor cyclic AMP/ Ca^{2+} response-element binding protein (CREB, [36]) - a factor associated with protein synthesis during long term potentiation and memory [37] - for recruiting BLA neurons into an aversive association. BLA cells that express more CREB are slightly more depolarized, making it easier for inputs to drive their activity during associative learning [36,37]. Furthermore, ablating a portion of CREB-expressing amygdala neurons during training diminishes the animals' memory for fear conditioning at test [38, 39]. Since CREB is activity dependent [40], it's likely that active neurons are easier to incorporate into a new memory. This raises the question whether such active, CREB-expressing cells are prewired for emotional memory encoding. Amygdala neurons that participate in encoding tend to receive inputs from the ventral hippocampus and project to the mPFC [41]. It would be interesting to know if this pattern of innervation provides elevated spontaneous activity, activating intracellular cascades and CREB-expression, thereby predisposing these neurons for recruitment into memory formation. For a comprehensive understanding of cellular and molecular processes underlying amygdala plasticity during aversive associative learning, the reader is directed to several excellent recent reviews on these topics [22, 32, 33, 34, 35].

BLA-mPFC connectivity in stimulus discrimination: acquisition

To have an adequate representation of our surroundings, a systems-level mechanism must learn to discriminate threat from safety. For the purposes of this review, safety refers to the part of an environment or a task, which could be a stimulus or a zone, learned or innate, which is never associated with danger. An important feature of the safety signal is that it inhibits or diminishes threat-elicited behavioral responses. Indeed, in the case of conditioning, Pavlov described the CS- as a conditioned inhibitor because it inhibited subjects' physiological response to the CS+ [1]. In keeping with this idea, the influential experimental behaviorist Robert Rescorla developed two behavioral paradigms, summation and retardation [42], for determining whether a CS is inhibitory. These tests asked whether previous negative CS-US pairings results in (1) retardation of subsequent acquisition of the conditioned emotional response to the same CS, and (2) summation of its inhibitory properties with the excitatory properties of the CS+, such that the conditioned emotional response to the CS+ is acquired slower [42]. Indeed, it has been shown that a learned conditioned inhibitor (the CS- acquired during **differential fear conditioning**) serves as a

learned safety signal in an innately anxiogenic environment such as an open field, where its presence increases exploration of the anxiogenic center [43,44]. Thus, in this review the definition of a safety signal includes the conditioned inhibitor CS– in a differential conditioning task, an aversive CS after it has undergone **extinction** and no longer elicits threat-related responding, an explicitly learned safety signal and the safe zone in an innately anxiogenic environment.

The BLA has been shown to encode safety in a growing number of tasks, and across several species [45,46,47,48,49] (Figure 2). When animals are trained to discriminate between an aversive CS+ and a CS– that does not predict the arrival of danger, BLA neurons become responsive to the CS– as quickly and with as much variety (increased and decreased firing) as to the CS+ [45,46,50]. Indeed, after the association has been acquired, BLA neurons continue responding to the safe CS– during recall [46,48]. Notably, a large proportion of BLA neurons that respond to the CS– also fire to a CS predicting reward [46], indicating that safety and reward circuits may rely on the same cell populations in the BLA and that safety itself may be rewarding. Therefore, one intriguing line of inquiry is to establish the mechanisms of safety encoding in the amygdala (Box 2).

Box 2

Outstanding Questions

- How does the dACC combine stimulus-specific coding for averseness with tracking the valence of other available stimuli during fear discrimination?
- Determine whether mPFC responsiveness during differential conditioning and extinction is BLA dependent
- What are the interactions between the dorsal and ventral subdivisions of the mPFC in discriminative associative learning?
- Establish whether there are aspects of mPFC-BLA signaling that are universal across a range of paradigms probing discrimination (e.g. explicit safety, differential conditioning, extinction and innate anxiety).
- How do prefrontal inputs alter synaptic interactions within BLA microcircuit during safety discrimination?
- Gain an understanding of how prefrontal inputs interact with other cortical BLA afferents in shaping anxiety
- Identify the effects of mPFC inputs on molecular cascades in pyramidal cells and interneurons of the BLA
- Can better discrimination be trained by increasing baseline synchrony between the BLA and mPFC?
- Are there indirect routes via which mPFC and BLA communicate during adaptive learning?

The mPFC is a key region for various forms of adaptive learning [51], making this area the ideal candidate for interacting with the amygdala for successful discrimination between evolving predictors of threat and safety [48,52,53,54,55]. A working framework that has been established over the past decade suggests that fear expression and fear suppression are supported by different subdivisions of the mPFC. The more dorsal mPFC (called the prelimbic (PL) cortex in rodents and dorsal anterior cingulate (dACC) in primates) increases activity during fear conditioning and expression, whereas the ventral mPFC (called the infralimbic (IL) cortex in rodents and ventral mPFC (vmPFC) in primates) is active during expression of non-aversive associations or safety [56,57,58,59]. Accordingly, interactions of the more dorsal PFC with the BLA is suggested to support threat-related behavior [50,52,60,61], whereas the vmPFC is proposed to interact with the amygdala during fear suppression [61,62]. However, more recently it has become clear that this division of labor is not always the case. For instance, mice with compromised extinction have increased firing rates in both the PL and IL [63], suggesting that disrupted activity in one subregion affects activity in the other. Indeed, mice with impaired extinction due to ethanol exposure showed disrupted physiological responses in IL neurons and morphological changes in the dendritic arbor of PL cells [64].

Importantly, in addition to processing aversive stimuli, the dACC/PL is a prominent region for response adjustment in a broad range of circumstances when cues change their meaning [57,65,66]. Cue discrimination in the mPFC is likely shaped by convergent inputs from multiple cortical as well as subcortical structures [67,68]. Depending on CS modality, a wide range of cortical sites is active when associations are encoded, including the auditory, visual, gustatory and prefrontal cortices [20, 56, 68, 69, 70, 71]. Furthermore, cortices projecting to the mPFC have been shown to be crucial for aversive associative learning [71, 72], supporting the idea that they provide the mPFC with integrated information about the CS. Likewise, the amygdala is a prominent cortical input during encoding and consolidation of salient associations, when widely distributed BLA afferents are shaping plasticity at multiple cortical regions [20, 73]. Indeed, BLA inputs to distal sites have been shown to play a role in shaping activity in the gustatory cortex during conditioned taste aversion [68,74], the cerebellum, PL and dACC during fear conditioning [57,73,75], and the rhinal cortices during appetitive conditioning [22]. Simply pairing a tone with BLA activation, even in the absence of an aversive US, has been shown to shift the preferred frequency of neurons in the primary auditory cortex toward the frequency of the paired tone [73]. Thus through a convergence of cortical and subcortical inputs, dorsal prefrontal activity is likely to simultaneously encode the averseness of a stimulus and to track how it compares to other stimuli in the environment [57,60]. Notably, amygdala neurons that fire to the threatening CS+ have been shown to preferentially project to the PL [47,56] whereas those active after extinction of conditioned fear preferentially target the IL. This suggests that functional activation of amygdala afferents during encoding could be a determining factor for which mPFC subdivision is active during recall [60,61]. Interestingly, the dorsal mPFC in rats shows increased activity after trials with unexpected outcomes [76,77]. This activity could be driven by BLA inputs that are excited during an unexpected US [78,79]. Indeed, correlated mPFC-BLA firing persists throughout training on a partial reinforcement

schedule whereas it quickly diminishes during continuous reinforcement [60], suggesting that uncertainty or surprise related to upcoming reinforcements keeps this circuit engaged.

During differential conditioning, reciprocal connectivity between the mPFC and BLA supports bidirectional information transfer between the two structures. Simultaneous cell recordings during differential conditioning show that amygdala cells that go on to differentially encode the valence associated with each CS, fire before the mPFC to both CS types [57]. Indeed, BLA cells appear to have an attentional processing component, signaling new incoming associations irrespective of valence [78,79]. As training continues, valence-selective BLA cells, which fire to either an aversive or a rewarding CS, *follow* neural firing in the mPFC [57], suggesting that prefrontal gating of preferred valence in BLA cells develops with training. Thus the temporal development of activity in the BLA-mPFC circuit can underlie the differential acquisition of stimulus valence in a changing environment. First, amygdala activation to incoming stimuli functions as an attending signal to the mPFC, where the information is combined with other incoming input. Then, as training continues, the mPFC assigns valence to incoming stimuli and sends it to the amygdala as a way to modulate amygdala activity [57].

Given active engagement of the mPFC-BLA circuit and temporal development of mPFC-to-BLA directionality as associations are acquired, one would expect that diminished mPFC-BLA communication results in maladaptive learning. In keeping with this idea, a decrease in correlated firing in the BLA-mPFC has been observed in macaques that don't successfully learn to discriminate between different CS-US associations [57]. Likewise, simultaneously recorded BLA and mPFC local field potentials (LFPs) show that there is higher synchrony in mice that successfully learn to discriminate between an aversive CS+ and a neutral CS- than in mice that show fear **generalization** [48]. Critically, similar work in humans, assayed by resting state and functional imaging, shows that BLA-mPFC connectivity and co-activation is increased when subjects discriminate between stimuli and compromised during fear generalization (Figure 2) [53,80,81,82].

mPFC-BLA activity during recall of learned associations

Successful recall of learned associations is critical to using the established blueprint of familiar stimulus-outcome relationships. Simultaneous recordings of neural firing and oscillatory activity in the mPFC and BLA are used to investigate the dynamics of communication during recall of associative learning in real-time. In general, oscillations recorded in regions subcortical and cortical regions, reflect waves of synchronous membrane potential fluctuations in groups of cells, shaping firing patterns and creating temporal windows when neurons are receptive to input. Likewise, oscillations within one structure can synchronize with their downstream targets for long range communication [83,84]. Recordings have shown that direction of information transfer in the mPFC-BLA circuit determines the successful recall of differential CS-US associations [48,57]. In particular, mPFC-BLA oscillatory activity in the theta (4–12 Hz) and high gamma (70–120 Hz) range, each considered in turn below, have been associated with stimulus discrimination [48,57,85,86].

From rodents to humans theta power has been shown to increase in the mPFC and BLA with presentation of the aversive CS [48, 85, 87, 88, Box 1]. Interestingly, theta-range **synchrony** also increases between the two regions with successful recall of differential CS associations [48] (Figure 1a). Such similar increases in theta power with aversion and discrimination are likely to result from different circuit-level dynamics. The increased mPFC-BLA synchrony during discrimination likely reflects different inputs depending on subregion of the mPFC/dACC, CS valence and schedule of reinforcement (partial or continuous). Overall, increased communication between the two regions indicates an attempt at discrimination between the stimuli, whereas no changes in synchrony is associated with generalization [48,53,80–82].

Box 1

Studying how the mPFC-BLA circuit learns across species

The main impetus for research in prefrontal-amygdala computations during learning is to understand how we adapt to a world where circumstances change. A complete picture of adaptive learning in this circuit must include the dynamics of both bottom-up and top-down processing. To this end, a variety of techniques allows for windows into intracellular signaling cascades and synaptic interactions between prefrontal and amygdala neurons as a function of learning. Notably, most of these approaches allow for different temporal and spatial specificity and can only be used in particular species, complicating the road to clinical applications. For example, intracellular signaling, and receptor expression changes during adaptive learning have been most extensively studied in rodents. Different techniques give windows into subcellular events that occur at different points after learning, creating a mosaic that has to be pieced together. Electrophysiology, a technique that is used in rodents, primates and humans, shows ongoing changes in communication during and after learning, but the molecular identity of recorded cell types remains largely unknown. These shortcomings are alleviated by recent technological advances, such as genetic tagging of immediate early genes [107], in vivo monitoring of large number of cells with calcium imaging [108], chemogenetics [109], and optogenetics [110,111]. These techniques expand our ability to study the contribution of different cell types to behavior and physiology in a temporally and spatially precise manner. Moreover, chemogenetics and optogenetics allows for input-specific control [112, 113] during behavior, opening the door for a more detailed circuit-level analysis.

Learning paradigms (e.g. **reversal learning**, differential fear conditioning, extinction) used to study the mechanisms of adaptive learning offer two important benefits for integrating findings across species and techniques. First, these paradigms are successfully implemented in rodents, primates and humans with minimal species-specific alterations. Second, there is a clear separation of CS and US encoding and decoding stages. This allows for versatility in the question being asked and a bridge between species. Thus, there is good cross-species concordance in a range of findings (Figure 2), indicating that work in rodents, including protein and synaptic interactions relevant to plasticity during learning, is likely to reflect processing in humans. Advances in technology that allow for translational work, including magnetic resonance spectroscopy to study region-specific neurotransmitter release [114], algorithms for monitoring oscillatory activity at deeper

structures, such as the amygdala [115] and analyses of genetic and epigenetic changes will further unify our understanding of how this circuit functions during adaptive learning.

Synchronous spiking in the mPFC-BLA circuit increases when animals are trained on a partial reinforcement schedule –when the valence of a given CS is less clear– which results in prolonged conditioned emotional responding and resistance to extinction [60] (Figure 1b). With such training, synchronous firing in the dACC-BLA circuit is associated with a dACC lead [60]. Notably, during discrimination of associations that were learned on a continuous reinforcement schedule, BLA firing is entrained by or follows prefrontal theta only during the safe CS–, indicating that theta oscillations in the mPFC selectively organize BLA activity when fear is suppressed [48] (Figure 1c). Accordingly, when animals generalize fear, there is no engagement of mPFC-BLA synchrony with stimulus presentation and BLA firing is not entrained by prefrontal oscillations [48]. These findings indicate that the mPFC – to – BLA projection that is active when unambiguous valence is assigned to a CS during training [57] (Figure 1d), is then activated again during recall and that theta-oscillations are a likely mechanism for transferring such information between the two structures. At the same time, ongoing dACC-BLA communication is crucial for disambiguating the valence of a CS.

Gamma oscillations are known to increase in power and synchrony during successful performance of cognitive tasks [70]. In the BLA-mPFC circuit, fast gamma power and synchrony are higher during discrimination of the safe CS– [54]. Notably, this is the opposite of a lower-range BLA gamma oscillation (30–80 Hz), which was found to increase with fear [89]. A subset of BLA cells that are modulated by fast gamma oscillations also fire more during diminished fear [54], indicating that they play a role in generating local fast gamma and that they could be critical for mediating fear suppression. Given the role of inhibitory interneurons in generating gamma and pacing theta oscillations in other structures [90,91], it's likely that a set of amygdala interneurons generates the safety-related high gamma oscillation in the BLA. Moreover, inhibition in the amygdala plays a prominent role in suppressing fear-related behavior [32,92,93,94,95], and there is evidence that mPFC-to-BLA communication actively diminishes fear expression during recall of a CS– [57]. It's likely that such mPFC-to-BLA communication relies on theta-frequency oscillations. In keeping with this idea, BLA high gamma power is well modulated by mPFC theta [54], suggesting that mPFC inputs to the BLA feed into fast-gamma generating inhibitory circuits that modulate fear suppression. In a testament to the cross-species relevance of this circuit (Box 1), studies using fMRI show that when human subjects overcome their fear of an aversive stimulus, activity is increased in the mPFC and decreased in the amygdala (Figure 2) [95]. Furthermore, work in humans has demonstrated increased prefrontal gamma oscillations during presentations of the CS– [87].

A unified view of mPFC-BLA circuit function in adaptive learning

Our discussion of safety has thus far included training and recall of differential associations. However, mPFC-to-BLA directionality of information transfer and the impact of prefrontal

inputs on BLA microcircuits apply to extinction as well [96,97]. Increased activity in the mPFC, driven by prolonged potassium currents [98], glutamate receptor activity [99], and BDNF release [100,101], facilitates extinction. As during recall of a safe CS–, the mPFC is an important afferent that shapes post-extinction inhibition in the amygdala [62, 102, 103] likely via prefrontal inputs feeding into inhibitory microcircuits of the amygdala [32, 92, 93, 94, 103–105]. Indeed, the excitatory-inhibitory balance at prefrontal inputs to the BLA has been shown to shift toward inhibition after extinction of conditioned fear [62, 103]. Likewise, fast gamma oscillations increase in the mPFC and follow the same mPFC-to-BLA directionality after extinction of an aversive CS+ as during discrimination of a safe CS– [54]. Indeed, similar oscillatory changes and synaptic remodeling could underlie the mPFC-to-BLA signaling seen during discriminative training of a safe CS [57]. Given the clinical advantage of boosting discrimination in patients [106], it is important to identify the BLA microcircuit responsible for increasing high gamma oscillations in the BLA during safety [54] (Box 2).

In an expansion of the notion of safety beyond adaptive learning, data show that in a brightly lit open field, a test of innate anxiety for rodents, as animals head for the safer periphery of the enclosure, there develops an mPFC-to-BLA directionality in theta oscillations and fast gamma power increases in the BLA [48,54]. In addition, as mice leave the anxiogenic center of the field and go to the periphery, BLA neurons decrease their firing, suggesting that the mPFC-to-BLA shift may be functionally shutting down the BLA during safety in innate anxiety as well as in learned fear [48,62,105]. Thus, the mPFC-to-BLA mode of communication during safety occurs in a range of paradigms spanning learned and innate anxiety. To identify whether the mPFC-BLA circuit dynamic described here is a true signature of “safety”, future work will need to establish whether these mPFC-BLA interactions occur during explicit safety signaling— when a stimulus identifies a period of safety from the otherwise ubiquitously present danger [43]. Furthermore, experiments using spatiotemporally precise manipulation of this circuit will have to demonstrate causality across multiple paradigms.

Concluding Remarks

The formalization of associative learning is heading toward its 90th birthday. In this time tremendous strides have been made in our understanding of the cellular, molecular and circuit-level mechanisms involved in acquisition and expression of this behavior. Progress is also ongoing in understanding how associations are updated, reversed or become irrelevant. The importance of a functional mPFC-BLA circuit is evident in all aspects of adaptive learning, from initial stimulus encoding and response modulation, to recall and extinction of learned associations. The mPFC-BLA circuit is engaged in discriminative learning from the beginning, when BLA –to-mPFC directionality predominates, to later in training when mPFC-to-BLA directionality is more prominent. The mPFC-BLA circuit relies on theta and gamma oscillations to transmit information about discrimination and as a result BLA firing codes both safety and danger. Dysfunctional coordination within this circuit has been shown to result in maladaptive learning and fear generalization. The current phase of neuroscience research, which benefits from a number of novel techniques that allow for genetic mapping, large scale imaging of neurons in vivo, targeted molecular interference and temporally

precise and input-specific intervention, will be crucial for further developing our understanding of how this circuit defines our ability to adapt to a changing world.

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Glossary

Safety	a relatively non-anxious state initiated by either a stimulus or a place in an environment. The physical state is characterized by more activity in the para-sympathetic nervous system such as increased vasodilation, decreased blood pressure and fewer behavioral indications of threat assessment (such as fight or flight responses)
Differential fear conditioning	a form of Pavlovian fear conditioning where one CS (often referred to as the CS+) is paired with an aversive US and one CS (referred to as the CS−) is either unpaired or paired with a pleasant US, thereby setting up a differential valence of the two CSs
Extinction	a behavioral paradigm where a previously conditioned CS-US association is decoupled by presentations of the CS without the previously accompanying US. After extinction training, the CS ceases to elicit the same physiological responses as the US. Extinction is context specific and in the adult is conceived of as new learning about the CS rather than forgetting of the CS-US association because the memory of the association is retained if probed again later and in a different context. Extinction training can be used in combination with medication to treat PTSD
Generalization	manifestation of similar behavioral responses to conditioned stimuli that were and were not previously paired with a particular US. Usually, the response to a CS predicting an aversive outcome is transferred to a neutral CS. This mode of similar behavioral response to threatening and non-threatening stimuli models behavior seen in PTSD and GAD
Reversal learning	A paradigm that tests adaptive learning in which the subject simultaneously learns two different CS-US contingencies that reverse in valence after they have both been acquired. Thus, two different CSs that used to predict an aversive US and a pleasant US or an aversive US and no US will without warning become predictive of the opposite outcome. The subject learns to adapt to these new contingencies
Synchrony	In extracellular electrophysiology, a measure of how well signals simultaneously recorded in two structures align with one another. Any measure of synchrony is assumed to give information about changes in communication between two regions. Some measures look at the

fluctuations in phase and amplitude of an oscillation across the two structures. Others measure how well cell firing in one structure is aligned with the ongoing oscillation in another structure. Others look at whether cells tend to fire within close temporal proximity of each other in both structures

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Highlights

- Threat and safety encoding in the amygdala
- mPFC-BLA communication promotes better discrimination of stimulus valence
- BLA follows mPFC activity during safety and successful stimulus discrimination
- Role of oscillations in mPFC-BLA circuit during threat and safety processing

Figure 1.

mPFC – BLA engagement dynamically changes during training and recall of aversive learning. (A–B) Neurons in the BLA are synchronized with theta oscillations (4–12 Hz) in the mPFC during stimulus assessment (mouse). (A) Example of a simultaneously recorded local field potential (LFP) oscillation (black – raw trace; blue –theta filtered trace) and firing of a single unit. (B) Mice that discriminate between the CS+ and CS– during recall, show increased mPFC-BLA synchrony. In mice that generalize fear to both stimuli, mPFC-BLA synchrony does not increase above baseline during stimulus presentation. MRL- mean resultant length. (C–D) mPFC-BLA synchrony is higher during stimulus assessment (monkey). (C) Example of simultaneously recorded neural firing in the dACC and BLA during the end of training on a partial reinforcement schedule. After CS onset, neural firing in the two areas is highly correlated. (D) Whereas correlated neural firing in dACC-BLA remains high throughout training when monkeys are trained on a partial reinforcement schedule (red trace), correlated firing drops quickly during training on a continuous reinforcement schedule (green trace). (E–F) During discrimination of a safe CS–, BLA firing is predominantly coupled to prefrontal theta oscillations of the past. (E) BLA cells of mice that discriminate between an aversive CS+ and a safe CS– are more synchronized (phase-locked) to mPFC theta oscillations of the past only during the safe CS– (blue). During the aversive CS+ (red) and both the CS+ and CS– of mice that generalize fear (inset), there is no preferred direction of information flow between the BLA and mPFC. (F) Higher probability of prefrontal theta oscillations leading changes in amygdala theta

oscillations during the CS– correlates with better discriminated between the two stimuli (Discrimination Score). (G–H) Dynamic changes in BLA-dACC communication during adaptive learning in the macaque. (G) Histogram of the center-of-masses (CoMs) obtained from all significant cross-correlations of simultaneously recorded spikes in the BLA and dACC during learning. Cross-correlations of spiking activity shows that during learning (red) communication between the two regions increases and becomes more bidirectional than during the habituation period, when the dACC tends to lead the amygdala (blue). The variance of the distribution is significantly smaller during learning than habituation (Inset), indicating a tighter coupling of activity between the two areas. (H) Neurons in the amygdala fire before dACC (blue) when an amygdala cell fires to all stimuli, (ones that predict an upcoming stimulus and ones that do not). However, dACC neurons lead amygdala neural firing in cells that fire in response to stimuli that don't deliver an expected outcome. Figures adapted with authors' permission [57,48,60].

Figure 2.

Cross-species findings in mPFC-BLA circuit function during adaptive learning. Similar findings in more than one species are highlighted by boxes. The colored dots refer to the techniques used to obtain the described findings. Technique Key is found in the upper left. Images of brains are published with permission, courtesy of the University of Wisconsin and Michigan State Comparative Mammalian Brain Collections, and the National Museum of Health and Medicine (brainmuseum.org). All preparation of the specimens and images were funded by the NSF. Rat, Mouse, Primate silhouettes are Wikimedia images in the public domain. Human figure, drawing courtesy of P. Drubetskoy.