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Fear from the bottom up: amygdala inputs to the prefrontal cortex

Joseph M. Stujenske¹ and Ekaterina Likhtik^{2,3}

¹Dept. of Psychiatry, Weill Cornell Medical College, New York, NY, USA.

²Dept. Biological Sciences, Hunter College, CUNY, New York, NY, USA.

³Neuroscience Collaborative, The Graduate Center, CUNY, New York, NY, USA.

Abstract

In this issue, two groups demonstrate the important role of amygdala inputs to the medial prefrontal cortex for signaling aversion across a range of behaviors.

In introductory neuroscience classes, it is often taught that the amygdala is the seat of emotion, but as we now well know, there is a distributed network--sometimes loosely referred to as the limbic circuit--that works in concert with the amygdala to mediate emotional processing. In particular, neural signatures encoding threat and safety are found in the prefrontal cortex and amygdala, forming a critical bidirectional highway for encoding complex emotional information¹. To investigate this reciprocal pathway, one approach in the field has been to divide and conquer by studying top-down communication of threat-evoked fear expression, and suppression of threat -related memories through extinction of conditioned aversion. This approach has shown that the prelimbic region (PL) of the medial prefrontal cortex (mPFC) is involved in signaling fear expression², whereas neurons in the infralimbic (IL) region signal fear decrement seen during extinction³. Information from the PL and IL is sent to the basolateral amygdala (BLA), driving aversion- or safety-related amygdala microcircuits, respectively⁴. However, the amygdala rapidly fires to incoming sensory cues⁵, and integration of the BLA message to the mPFC is crucial to understanding communication along this information superhighway. With this in mind, two groups--Klavir et al.⁶ and Burgos Robles et al.⁷--specifically investigated the direction of information flow from the BLA to the mPFC. Together, they show that amygdala inputs to both PL and IL, irrespective of behavioral paradigm, convey the association between a stimulus and aversion. This association is then likely further processed within the mPFC in order to either strengthen or extinguish fearful associations back in the amygdala.

Klavir et al. developed a novel technique of optogenetic high frequency stimulation (HFS) to reversibly depress BLA input to the mPFC in mice, allowing for temporally-specific downregulation in BLA drive of either the PL or IL. Surprisingly, despite data suggesting a regional segregation of top-down function in the PL and IL^{2,3}, Klavir et. al. found that suppressing BLA input to either region was sufficient to degrade fearful associations, when applied before fear learning or fear extinction. BLA-to-PL or BLA-to-IL HFS before acquisition weakened consolidation of subsequent defensive behavior to the aversive stimulus, while BLA-to- PL or BLA-to-IL HFS before fear extinction training hastened

extinction of defensive behavior. These data suggest that amygdala inputs to both the PL and IL convey aversive information, which, when impaired, result in decreased vigilance to threat. Interestingly, the fear-diminishing effect of depressing BLA input to the PL was most pronounced early in subsequent defensive behavior, whereas depressing BLA input to the IL had a stronger and longer lasting impact on behavior. This suggests different time courses for BLA-evoked network effects in the PL and IL, with a faster BLA-mediated drive of the PL network, and slower, longer-term and BLA-driven changes in the IL.

Burgos Robles et al. probed the role of BLA input to the PL using a combined electrophysiological and optogenetic approach during a task that created competition between appetitive and aversive associations. When aversive stimuli were presented alone, BLA inputs showed pronounced excitatory recruitment of downstream PL cells. Similarly, optogenetic activation of BLA inputs to the PL was sufficient to promote defensive behavior during aversive stimuli without altering responses to rewarding stimuli. Furthermore, when both stimulus types were present, activation of BLA-to-PL input was sufficient to bias behavior towards defensive responding, even in the presence of a competing reward. Likewise, silencing amygdala inputs had the opposite effect, indicating that BLA inputs to the PL selectively convey aversive but not appetitive associations. Consistent with this hypothesis, PL-projecting BLA cells were primarily active in response to aversive but not appetitive stimuli. Burgos-Robles et al. also provide evidence that during appetitive stimulus processing, there is pronounced recruitment of inhibition by amygdala inputs to the PL, suggesting that amygdala inputs signal aversion via PL excitation and selective inhibition of the PL when other modes of behavior are more appropriate.

Recent in vitro data suggest that despite the primarily excitatory projection from the amygdala to the mPFC, there is also recruitment of strong feedforward inhibition specifically onto cortico-amygdala neurons with reciprocal projections back to the amygdala⁸. This circuit may be active during reward processing, as suggested by data in Burgos-Robles et al. Critically, prefrontal projections have also been shown to recruit inhibition in addition to excitation in the amygdala⁹. Thus, there is both bottom-up and top-down control occurring in the mPFC-BLA circuit, which underlies dynamic alterations in the directionality of information transfer between these structures⁴. This view is consistent with recent work in primates¹⁰ that implicated the amygdala in signaling purely “unsigned” information to the prefrontal cortex, which then became “signed” by prefrontal processing, assigning either positive or negative valence through training. This signed information is then transmitted back to the BLA¹⁰. As Klavir et al. and Burgos-Robles et al. demonstrate in this issue of the journal, amygdala inputs to the prefrontal cortex also play an important role in shaping neural activity upstream. Thus, proper reciprocal excitation and inhibition between the prefrontal cortex and amygdala is a critical step for altering these circuits during stimulus processing in a changing environment, for instance as defensive behavior is extinguished to a previously aversive stimulus.

Previous investigation of the bottom-up roadway showed that separate cell groups in the BLA are active during fear expression and fear suppression seen during extinction, termed “fear” and “extinction” cells¹¹, respectively, which we will refer to as “On” and “Off” cells. Since the BLA directly projects to the central amygdala --which then orchestrates such

physiological and behavioral responses as changes in heart rate and freezing -- a simplistic model for the induction of defensive responses would have On cells promoting sympathetic responses while Off cells would suppress them. The role of the prefrontal cortex in this model is unclear, although from lesions¹² to finer optogenetic manipulations¹³, we know that changing activity in the mPFC directly impacts fear learning and expression. On and Off cells are differentially connected with the PL and the IL^{11,14}, suggesting that the formation of On and Off responses may require recurrent activity between these two regions. Previous work has shown that the BLA is an important contributor to PL activity during fear expression¹⁵, but the degree to which this input guides behavioral output was unknown. Now, Klavir et al., show that BLA projections to the IL and PL participate in consolidating and maintaining aversive associations, and Burgos-Robles et al., show that aversive signaling from the BLA to PL prevails in the face of competing rewards (Figure 1).

It is likely that BLA inputs to the PL and IL shape the dialogue between these subregions, which contributes to behavioral output. Klavir et al. in particular suggest that this input engages both the PL and IL in the acquisition and extinction of fear memories with roles that are not as clearly distinct as found in previous studies. BLA input to both structures seems to be involved in the short-term encoding and maintenance of fear memories, while BLA inputs to the IL were also required for the long-term maintenance of memory for threat. Contrary to the conclusions drawn in a previous study, in which activity of PL- and IL-projecting BLA cells were suggested to be associated with fear and extinction, respectively¹⁴, the data in Klavir et al. and Burgos Robles et al. suggest that aversive information is transferred by both PL- and IL- projecting BLA cells. Indeed, it is likely that manipulation of aversive information that is instrumental for extinguishing fear associations occurs primarily in the prefrontal cortex, which then projects back to the BLA. Thus, the extinction-related pattern of activity in IL-projecting cells of the BLA may emerge due to reciprocal connectivity from the IL back down onto these cells.

Together, these two papers suggest that amygdala projections to the prefrontal cortex convey the identity of aversive stimuli. This has important implications for our understanding of psychiatric disease. Post traumatic stress disorder, in particular, is associated with hyperactivity in the amygdala, which may indicate unconstrained output of aversive associations. Hyperactive inputs into the prefrontal cortex could underlie resistance of fear memories to extinction in patients, which possibly reinforces persistent hyperactivity downstream in the amygdala. Finding and fine-tuning the most appropriate circuit-breakers in this loop could constitute an important step forward in developing treatment.

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Figure 1.

Amygdala inputs to the mPFC tilt behavior toward fearful responding, even in the face of competing rewards and extinction. When presented with aversive stimuli (orange circle), BLA activity drives neural firing in both the PL and IL. Amygdala inputs boost fear expression during associative threat conditioning, during extinction (thick black arrows) and when an animal faces competing appetitive stimuli. The amygdala may also actively suppress PL activity (dashed arrow) when an animal faces rewarding stimuli (yellow circle).