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Prefrontal control of fear: more than just extinction

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Abstract

While fear research has largely focused on the amygdala, recent findings highlight cortical control of the amygdala in the service of fear regulation. In rodent models, it is becoming well established that the infralimbic prefrontal cortex (IL) plays a key role in extinction learning, and recent findings are uncovering molecular mechanisms involved in extinction-related plasticity. Furthermore, mounting evidence implicates the prelimbic prefrontal cortex (PL) in the production of fear responses. Both IL and PL integrate inputs from the amygdala, as well as other structures to gate the expression of fear via projections to inhibitory or excitatory circuits within the amygdala. We suggest that dual control of the amygdala by separate prefrontal modules increases the flexibility of an organism's response to danger cues.

Keywords

infralimbic cortex; prelimbic cortex; amygdala; plasticity; emotion

Back to cortical control of fear

Over a century ago, the prevalent notion was that evolutionary recent cortical areas exert control over evolutionary older subcortical areas [1,2]. Later, the prefrontal cortex (PFC) emerged as a critical regulator of aversive conditioning [3,4]. More recently, focus shifted to the amygdala as a hub of emotions [5,6], when it was reported that interfering with activity in the PFC or other cortical areas did not prevent fear learning. A wealth of data supports the role of the amygdala in fear learning. Nonetheless, interest in the role of PFC in emotion re-emerged with the discovery that the medial PFC (mPFC) was necessary for extinction of conditioned fear [7,8]. In the last few years, it has become clear that mPFC contains different subregions, playing unique roles in fear learning and extinction. In particular, it was shown that the infralimbic region (IL) of the mPFC is a critical site of plasticity for inhibition of fear responses after extinction, and new findings are uncovering the mechanisms involved. In contrast, mounting evidence implicates the prelimbic (PL) region of the mPFC in the production of fear responses. Both IL and PL are thought to exert their influences via the amygdala, suggesting that the amygdala must work with mPFC to orchestrate fear responses. Here, we review these recent findings, and consider the possible significance of this dual cortical control of the amygdala-based fear responses.

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IL-mediated inhibition of fear after extinction

While previous recording and lesion studies have implicated IL in extinction [9], recent findings have identified specific molecular cascades in IL involved in extinction learning. While it is well established that *N*-methyl-D-aspartate receptors (NMDAR) within the amygdala are necessary for extinction [10,11], more recent reports implicate IL NMDAR in extinction, especially in the period immediately following extinction [12-14]. The role of IL in extinction consolidation is further supported by recent findings using post-extinction infusions into IL of the inactivating agent muscimol [15], a cannabinoid antagonist [16], or dopamine (D1) antagonist [17]. Several of these pathways are thought to interact with brain-derived neurotrophic factor (BDNF) to form long-term memory. Accordingly, histone acetylation of the BDNF gene promoter in IL was found to be correlated with extinction [18], and mice exhibiting a deficient BDNF gene showed impaired extinction and reduced IL volume [19]. Furthermore, mice with deficient 5-HT transporter activity showed poor extinction and shrunken IL dendrites [20], and similar behavioral findings were obtained for cAMP-responsive element-binding protein-mediated gene expression in IL [21]. Together, these molecular, pharmacological, and genetic studies suggest new targets in IL for facilitating extinction consolidation.

What might constitute a physiological signature of extinction learning in IL? The degree of extinction success is correlated with the level of high-frequency bursting in IL neurons immediately after extinction training [12]. Bursting in IL could increase local calcium currents as well as increase the depolarization and calcium entry in downstream targets of IL, which would favor the development of extinction-related plasticity at both sites. Extinction-related bursting could be due to potentiation of synaptic inputs, and/or increases in intrinsic excitability. In support of the latter possibility, it was recently shown that conditioning and extinction decreased and increased, respectively, the intrinsic excitability of IL neurons [22]. Interestingly, following extinction, IL neurons tended to burst in response to intracellularly injected current. This suggests that IL neurons are more responsive to their inputs following extinction. In support of this, studies using the activity marker *c-Fos* show that IL activity was increased in rodents that successfully retrieved extinction [23], but not in strains that are extinction-deficient [24,25]. In adolescent rats, where extinction does not require NMDAR, IL was not necessary for extinction, nor was IL activated by extinction [26]. Thus, NMDAR-mediated potentiation of fear inhibitory circuits appears to be a hallmark of adult extinction.

PL-mediated excitation of fear expression

While earlier studies suggested a role of PL in excitation of fear [27,28], new studies using pharmacological inactivation and unit recording have confirmed and extended that role. Inactivation restricted to PL reduced expression of conditioned fear to contextual and auditory stimuli, but had no effect on the expression of innate fears, or the development of plasticity related to conditioning or extinction [15,29]. In other words, PL activity is necessary for fear expression, but not for fear plasticity (in the amygdala or other structures). Consistent with such a role, PL neurons are activated by conditioned stimuli [23,30]. However, unlike neurons in lateral amygdala whose conditioned responses last only a few hundred milliseconds [31], PL neurons show sustained increases in activity that mirror the time course of freezing responses, lasting tens of seconds [30]. PL is the first site to show conditioned responses that model fear responses, and suggests that similar sites may be found in targets of PL such as the basal nucleus of the amygdala (BA). Furthermore, PL activity is increased in rats that fail to retrieve extinction memory [23,30], and decreased by pharmacological agents that reduce fear expression, such as propranolol [32] and cannabidiol [33]. Thus, to a large extent, PL output predicts the magnitude of a fear response.

Outputs and inputs of IL and PL

The opposite effects of IL and PL on fear expression are thought to be mediated by outputs to different targets within the amygdala [28,34]. IL projects to the intercalated cell masses (ITC) and lateral division of the central nucleus (CeL) both of which consist of GABAergic neurons that inhibit amygdala output neurons of the medial division of the central nucleus (CeM). In contrast, PL targets the BA. This suggests that ITC cells should be critical for extinction, whereas BA should be critical for fear expression. Due to the small size of ITC islands, it has been difficult to target them experimentally. Capitalizing on a unique distribution of receptor subtypes, however, it was recently observed that lesions or activation of ITCs impaired or facilitated extinction, respectively [35,36]. In contrast to ITCs, the situation with BA is more complex. Focal inactivation of BA prevented renewal of fear after extinction, but also prevented expression of extinction, depending on the time point of inactivation [37]. This suggests that BA is recruited only when it is necessary to switch from a high fear state to a low fear state, or vice versa. In support of this switching function, there exist separate classes of BA neurons encoding fear or extinction [37]. Such findings point toward the existence of a BA network, which interacts with an ITC-CeL network prior to modulating CeM output neurons. Also, non-amygdala outputs of PL and IL, such as the nucleus accumbens for appetitive behavior [38] and raphe nucleus for “controlability” [39] are emerging as important for emotional regulation.

IL and PL receive inputs from a number of sources that could facilitate fear regulation. An important fear-related input is the amygdala itself. Within the BA, both fear and extinction neurons project to mPFC [37], although it is unclear whether they project differentially to IL and PL. This suggests that the amygdala may recruit IL and PL [40-42], which in turn regulate amygdala output. Another key input is the ventral hippocampus (Hipp), which unlike the dorsal hippocampus, projects monosynaptically to PL, IL, and BA [43]. Extinction training is correlated with increases in the size of ventral Hipp – mPFC evoked potentials [44], suggesting potentiation of hippocampal inputs to IL. Weakening this pathway with low-frequency stimulation or stress impairs extinction [44,45]. It has been suggested that the hippocampus drives bursting in IL neurons, which may strengthen tone inputs from BA, leading to inhibition of fear expression to the tone [9]. PL and IL also receive a massive input from the mediodorsal nucleus of the thalamus (MD), which is potentiated for several days following (but not right after) extinction training [44]. In light of these connectivity findings, we are beginning to understand how PL and IL can integrate contextual information with emotional salience and other inputs, to regulate fear expression and extinction (see figure 1).

Why does the amygdala “need” the prefrontal cortex for fear?

Given that auditory fear conditioning can occur in the absence of cortical areas, one might be tempted to think that the amygdala, together with its subcortical connections, is sufficient for normal fear learning and expression. However, as reviewed above, PL and IL are required for fear expression and extinction, under normal circumstances. This suggests that the mPFC has access to information that the amygdala does not, which enables emotional regulation, such as the emotional history of a stimulus (amygdala), context and time (hippocampus), internal state (brainstem monoamines), and cognitive-mnemonic information (orbital and lateral PFC). These convergent signals are integrated by mPFC neurons and, if a threshold is exceeded, they drive fear. Indeed, the sustained conditioned responses of PL neurons may represent the outcome of such integration. The brief conditioned response of lateral amygdala neurons projecting to PL may provide a bias signal to mPFC that favors (but does not ultimately determine) the production of a fear response. In the same way, integration of diverse types of information in IL may be needed to determine whether or not to express extinction to a given stimulus, in a given context, at a given time, etc. In addition, PL excitatory and IL inhibitory

networks could interact via reciprocal inhibitory connections [46]. Consequently, prefrontal control of the amygdala increases the flexibility of an organism's response to danger cues.

In addition to diverse inputs, mPFC also has divergent outputs capable of orchestrating dissociable and sometimes competing brain systems [47,48]. During extinction, for example, at the same time that the mPFC is terminating a fear response (via amygdala ITC neurons), it may also be triggering an appetitive approach response (via nucleus accumbens), and learning controllability (via the raphe nucleus). During renewal of fear, the excitatory drive emanating from mPFC would converge with amygdala projections to the periaqueductal grey, to produce defensive responses, while at the same time suppressing approach behaviors, via the midbrain dopaminergic system [49]. Studies within the next few years are likely to focus on how PFC interacts with the amygdala and other areas during competition between aversive and appetitive behaviors.

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*special interest

**outstanding interest

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Figure 1. Prefrontal control of fear expression and extinction

During fear expression (left) and extinction (right) of auditory fear conditioning, tone responses from the amygdala (amyg) get integrated by the prelimbic (PL) or infralimbic (IL) prefrontal cortex with converging information from diverse sources such as hippocampus (Hipp), brainstem monoamines (Bstm), mediodorsal thalamus (MD), and orbital prefrontal cortex (OFC) to determine whether or not to produce a fear response. Fear excitation involves PL projections back to basal amygdala (BA), whereas fear inhibition involves IL projections to amygdala intercalated cells (ITC). In turn, BA excites neurons in the medial division of the central nucleus of the amygdala (CeM) to produce fear responses, while ITCs inhibit these amygdala output neurons thereby inhibiting fear responses. Thus, the same conditioned stimulus (e.g. a tone) signals either high fear (red) or low fear (green) states in the appropriate circumstances.