Neural Circuits Underlying Innate Fear

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Abstract

Fear is defined as a fundamental emotion promptly arising in the context of threat and when danger is perceived. Fear can be innate or learned. Examples of innate fear include fears that are triggered by predators, pain, heights, rapidly approaching objects, and ancestral threats such as snakes and spiders. Animals and humans detect and respond more rapidly to threatening stimuli than to non-threatening stimuli in the natural world. The threatening stimuli for most animals are predators, and most predators are themselves prey to other animals. Predatory avoidance is of crucial importance for survival of animals. Although humans are rarely affected by predators, we are constantly challenged by social threats such as a fearful or angry facial expression. This chapter will summarize the current knowledge on brain circuits processing innate fear responses to visual stimuli derived from studies conducted in mice and humans.

Keywords

Innate fear · Looming · Amygdala · Pulvinar

1.1 Introduction

Animals promote their survival by avoiding rapidly approaching objects that indicate threats. Looming stimulus-induced fear responses are conserved across species. For instance, expanding shadows specifying an impending collision can induce an avoidance response and upset in both infants and adults (Ball and Tronick 1971; King et al. 1992). In response to an expanding dark disk on a screen mimicking a predator, laboratory mice exhibit fear behaviors with either escape or freezing patterns (Yilmaz and Meister 2013). Given the robustness of looming stimuli-evoked fear behaviors, it is crucial to dissect the neural circuits that mediate this response.

1.2 Animal Studies

1.2.1 Retinal Ganglion Cells That Detect Looming Signals

Vision is the only useful sensory modality for initiating looming-evoked fear responses. It is well established that retinal ganglion cells (RGCs) are the final output neurons of the vertebrate retina, which collect visual information

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from bipolar cells and amacrine cells. An organism as a whole cannot behaviorally respond to visual stimuli that are not also detectable by individual ganglion cells. Identifying the RGCs that can detect and transmit looming signals is a crucial step in understanding the neural basis of looming-evoked fear responses.

The light response patterns of RGCs are diverse. There are three types of signal detection in RGCs (Hartline 1938). ON-type signal detection results in a transient burst to light onset and a sustained elevated discharge rate throughout the photic stimulation. ON-OFF-type signal detection results in discharge bursts at both the onset and cessation of light stimuli. OFF-type signal detection is quiet until the stimulus light is turned off. There are two important components in a looming signal: dimming and motion; therefore, RGCs extracting this feature from the visual scene should be able to detect both stimuli. In accordance with these criteria, candidate RGC subtypes have been suggested in mice. For example, using genetic labeling, two-photon microscopy, and electrophysiology approaches, Münch et al. identified an approach-sensitive ganglion cell type in the mouse retina named PV-5 cells (Münch et al. 2009). The authors found that PV-5 cells belong to the OFF ganglion cell type, of which ~80% have dendrites that arborize in the inner plexiform layer (IPL). The spiking responses of PV-5 cells were evoked preferentially by stimuli mimicking approaching motion compared to either lateral motion or receding motion. Although the morphological and physiological features of PV-5 cells seem well positioned to detect looming signals, it remains to be determined whether PV-5 cells are necessary for looming-evoked fear responses in behaving animals. On the other hand, our recent study demonstrated that a looming stimulus can activate a previously undescribed subtype of RGC that innervates the dorsal raphe nuclei (DRNs) and superior colliculus (SC) (Huang et al. 2017). We found that dendrites of DRN/SC-projecting RGCs stratified in both the ON and OFF sublaminae of the IPL and that specific ablation of those RGCs through a saporin-based immunotoxin strategy impairs looming-evoked fear responses (freezing and escape behaviors), suggesting that those RGCs are necessary for looming-evoked fear responses. Although DRN/SC-projecting RGCs have an asymmetric dendritic field that resembles direction-selective RGCs, DRN/SC-projecting RGCs: (1) lack CART immunoreactivity and (2) show no direction preference to moving stimuli. It remains to be determined how looming stimuli activate DRN/SC-projecting RGCs that are nondirectional although directional summation in nondirection-selective RGCs has been described previously (Abbas et al. 2013).

1.2.2 Brain Circuits That Mediate Looming-Evoked Fear Responses in Mice

Looming signals detected by RGCs need to activate the brainstem fear systems to initiate fear responses. The precise circuits underlying such responses are not well understood. Accumulating evidence suggests that the SC, which is a retinal recipient structure, contributes to fear-related behaviors. For example, stimulation of SC neurons induces defensive behaviors (Sahibzada et al. 1986; Dean et al. 1988; Keay et al. 1988; Schenberg et al. 1990), and SC lesions impair defensive reactions to a sudden overhead visual stimulus (Dean et al. 1989). Therefore, if the SC receives looming-related signals transmitted from RGCs, it might be in a position to modulate looming-evoked fear responses. Consistent with this view, several circuits related to the SC have been proposed for mediating looming-induced fear behaviors. For instance, Wei et al. found that optogenetic activation of CaMKIIa neurons in the intermediate layer of the SC induced freezing-like behaviors, whereas silencing of those neurons reversibly blocked the expression of looming-evoked freezing (Wei et al. 2015). Furthermore, the authors demonstrated that looming-sensitive SC neurons can innervate the lateral posterior nucleus of the thalamus (LP), which in turn activates the basolateral amygdala (BLA) and that abrupt the signal transmission of this pathway impairs looming-evoked freezing.

Therefore, the authors provide compelling evidence that the SC-LP-BLA pathway plays a pivotal role in the regulation of looming-evoked freezing behaviors. In contrast, Shang et al. found that PV^+ excitatory neurons in the superficial layer of the SC can also detect looming signals and that specific activation of PV^+ SC neurons triggers escape-like behaviors (Shang et al. 2015). The authors also dissected the neural circuits underlying this process: PV^+ neurons in the SC can project to the parabigeminal nucleus (PBGN). Optogenetic activation of the PV^+ SC-PBGN pathway reliably induces escape behaviors. Furthermore, the authors prove that the PBGN can further innervate the central amygdala (CeA), which can also be activated by looming stimulation. Collectively, the work conducted by Shang et al. suggests that the SC-PBGN-CeA pathway underlies looming-evoked escape behaviors. Although the key neural circuits that initiate looming-evoked fear responses have been identified, another important question regarding the looming-evoked fear responses is how distinct defensive behaviors (i.e., freezing and escape) are selected by the brain. Shang et al. addressed this question by showing that SC orchestrates dimorphic fear behaviors with two divergent excitatory pathways (i.e., SC-LP and SC-PBGN) that work in a winner-take-all model (Shang et al. 2018). They proposed that general factors, including environmental context, threat stimulus features, and individual differences, determine behavioral patterns induced by looming stimuli.

Growing evidence suggests that changes in mood states can adjust looming-evoked fear responses, which is important for individual adaptations to challenges. Deciphering the neural circuits related to emotional centers that adjust looming-evoked fear responses will shed light on the mechanism of abnormal reactivity in mood disorders, such as anxiety, depression, and phobia. The monoaminergic systems derived from the midbrain DRN, locus coeruleus (LC), and ventral tegmental area (VTA) play a key role in the modulation of mood states. Changes in neural activity in the monoaminergic systems may influence the expression of fear responses through activation of related receptors distributed in fear regions, including the amygdala. In our previous study, we identified a retinoraphe projection with DRN-projecting RGCs that also send axonal collaterals to the SC (Huang et al. 2017). We demonstrated that looming signals can not only initiate fear responses by activating the retina-SC pathway but can also inhibit the serotonergic tone in the DRN, which can facilitate the induction of fear responses. Our finding suggests that the primary sensory input regulates itself via the DRN. The added synaptic delay in the circuit must clearly be outweighed by an adaptive advantage in such an important innate survival response. The role of the LC and VTA in the regulation of looming-evoked fear responses was investigated by Liping Wang's lab. Li et al. found that exposure to repeated stress caused anxiety-like behaviors accompanied by accelerated fear responses to looming stimulation (Li et al. 2018). The underlying neural mechanisms were investigated using an array of brain circuit interrogation tools, including c-Fos brain mapping, fiber photometry, chemogenetics, and optogenetics. They demonstrated that the LC-SC pathway is both necessary and sufficient for the stress-induced acceleration of looming-evoked fear responses. In addition, a very recent study conducted by Zhou et al. found that looming stimulation can also activate a subset of CaMKIIa+ neurons in the deep layer of SC, which could synapse onto CeA-projecting GABAergic neurons in the VTA (Zhou et al. 2019). Optogenetic activation of the SC-to-VTA projections induced escape behaviors, whereas inhibition of VTA GABAergic neurons impaired looming-evoked escape behaviors. These results demonstrated that visual circuits related to the VTA can also mediate looming-evoked fear responses. The precise interactions between the SC-VTA pathway identified by Zhou et al. and the SC-PBGN pathway identified by Shang et al. need to be determined (Zhou et al. 2019; Shang et al. 2015). One possible explanation of these redundant circuits for mediating looming-evoked escape behaviors is that the SC-PBGN pathway is dedicated to triggering active escape behaviors, whereas the SC-VTA pathway can also facilitate

looming-evoked escape behaviors through modulation of the neural activity in the VTA.

Recent studies also found that mood-related brain regions other than the monoaminergic systems can also regulate looming-evoked fear responses. For example, Evans et al. found that a subset of excitatory neurons in the deep layer of the medial SC (mSC) can directly synapses onto the glutamatergic neurons in the dorsal periaqueductal gray (dPAG) (Evans et al. 2018). Changes in the activity of the mSC-dPAG pathway can regulate looming-evoked escape behavior. On the other hand, Salay et al. demonstrated that midline thalamic nuclei (i.e., the nuclei of the ventral midline thalamus, the xiphoid nucleus, and nucleus reuniens) can also regulate looming-evoked fear responses, including freezing, tail rattling, and autonomic arousal (Salay et al. 2018).

1.3 Human Studies

From the evolutionary point of view, innate fear subserves "self-protection" function that promotes the initiation of fight-or-flight response in the absence of awareness. It is therefore believed that initial responses triggered by innate fear are automatic and quick. This notion is supported by electrophysiological data demonstrating that detection of fear-related stimuli is as quickly as 100 ms post-stimulus or even earlier, which is more quickly than detection of non-fear stimuli (Mogg and Bradley 2010; Vuilleumier and Pourtois 2007).

The neural mechanism underlying innate fear is most likely involve non-conscious emotion processing. A host of techniques and experimental paradigms have been used to elicit non-conscious emotion processing. For instance, a backward masking procedure briefly presented an emotional stimulus (target) that is immediately followed by a masking emotional stimulus (mask), and it is most likely that the observer cannot consciously report the presence or the content of the target. Other techniques include binocular rivalry or flash suppression, during which the stimuli are presented at a subliminally threshold. The neuroimaging studies using such techniques have shown consistently that unseen stimuli of fear elicit activity in the amygdala. For instance, Whalen and colleagues presented pictures of fearful and happy facial expressions to healthy subjects by using the backward masking procedure and in meanwhile functional magnetic resonance imaging (fMRI) data was collected (Whalen et al. 1998). Although subjects reported seeing only neutral facial expressions, fMRI results found significant more activations in the amygdala during viewing of masked fearful faces than during viewing of masked happy faces. By recording intracranial electrophysiological data, a short-latency fear-related amygdala response was found during fearful, but not neutral or happy, facial expressions (Mendez-Bertolo et al. 2016). Another line of evidence comes from investigations on blindsight patients with striate cortex lesions, who could discriminate the content of emotional stimuli presented in their blind field. The results obtained in these patients also showed that the unseen fear stimuli increased amygdala activation, which were parallel with the data from healthy subjects when masking techniques were used. Some studies further demonstrate a correlation between their proficiency and activity in the amygdala (Pegna et al. 2005; Tamietto et al. 2009). These findings suggested that fear-related information can be perceived in the absence of awareness despite lesions to the visual cortical pathway.

Converging evidence suggests a subcortical pathway is underlying innate fear processing. First, it is evidenced that 5-month-old infants look longer at spiders than at non-threatening biological stimuli (e.g., flower), and 8-month-old infants responded more rapidly to snakes than to flowers and more rapidly to angry than to happy face (Rakison and Derringer 2008; LoBue and DeLoache 2010). Given that the infants have had little experience with the threatening stimuli, these results suggested that a subcortical mechanism underlying innate fear present from birth. Second, accumulated neuroimaging evidence suggests that the visual information of threat is transmitted from retina to amygdala via a subcortical pathway comprising the superior

colliculus (SC) and pulvinar by demonstrating co-activation among these three brain regions in healthy subjects (Morris et al. 1999; Vuilleumier et al. 2003) as well as blindsight patients (Morris and Dolan 2001; Pegna et al. 2005) when they view fear-related stimuli. Dynamic causal modeling (DCM) is a powerful approach that is informed by anatomical and physiological principles to investigate effective connectivity between brain regions. Several DCM studies investigated whether the activation of these subcortical regions is causally related, and the studies have consistently showed a forward connection between the pulvinar and amygdala (McFadyen et al. 2017; Garvert et al. 2014; Rudrauf et al. 2008). Finally, lesion studies have shown that patients with unilateral pulvinar lesions impair discrimination of fearful faces in the contralateral fields (Ward et al. 2007). Furthermore, hemianopic patients without blindsight with pulvinar lesions demonstrated no facilitatory effects on detecting fearful faces, whereas hemianopic patients without pulvinar lesions showed response facilitation to fearful stimuli (Caterina et al. 2018). These findings suggest a pivotal role of pulvinar in implicit fear processing.

An important question is whether there is anatomical evidence that the SC-pulvinar-amygdala pathway exists in the human brain. Tamietto and colleagues used diffusion tensor imaging (DTI) to characterize in vivo the connectivity between the SC, pulvinar, and amygdala in ten healthy individuals and a blindsight patient with early unilateral destruction of the visual cortex (Tamietto et al. 2012). The authors found pulvinar-amygdala fiber connections and SC-pulvinar-amygdala fiber connections in the healthy individuals as well as the patient. Destruction of the visual cortex led to increased fiber connections along the subcortical pathway but only in the damaged hemisphere. This finding supports a functional role of the subcortical pathway in conveying visual emotional information critical for the blindsight patient. Similarly, Rafal et al. used probabilistic DTI tractography to reconstruct the subcortical pathway in both hemispheres for 19 of the 20 healthy human participants and 7 of the 8 macaques (Rafal et al. 2015). Importantly, it was evidenced that the microstructure of SC-amygdala pathway predicts threat bias, suggesting a functional role of the subcortical pathway in processing threat in healthy humans (Koller et al. 2018). The sample of human subjects was expanded in a multimodal neuroimaging study (McFadyen et al. 2019). The authors computationally modeled the hemodynamic activity during an emotion task and demonstrated a correlation between fiber density in this subcortical pathway and fearful face recognition as well as the strength of dynamic coupling between the SC, pulvinar, and amygdala.

In addition to the subcortical SC-pulvinar-amygdala pathway, some cortical regions may be also involved during non-conscious perception of fear. Neuroimaging studies in healthy humans suggest that fear-related stimuli selectively activate prefrontal, and orbitofrontal regions, anterior cingulate, and brain stem. The orbitofrontal cortex may extract threat value and inform threat perception via a feedback pathway to early visual regions (Barrett and Bar 2009; Kveraga et al. 2007).

In summary, an "innate alarm system" underlying perception of innate fear is a brain network comprising both subcortical and cortical regions. The amygdala seems to be a core site within this network. This network facilitates an immediate and fast response to threatening stimuli.

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