

Spotlight

Looming Danger:
Unraveling the
Circuitry for Predator
ThreatsJulieta E. Lischinsky¹
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Threat avoidance, particularly from predators, is key for survival. Through the use of optogenetics, viral tracing, and electrophysiological recordings, Zhou and colleagues identified a superior colliculus to ventral tegmental area pathway in detecting alarming visual cues and mediating defensive behaviors in mice. These findings provide novel insight into the neural circuit underlying innate predator defense.

Survival in the wild is a constant game of eating or being eaten. For prey species, the key to living for another day is to effectively detect and avoid its various predators. The mouse, a 30 g animal, stands little chance against its predators, which can come from the ground (such as a rattlesnake or a fox) or from above (such as an eagle or an owl), all of them weighing tens or hundreds of times more. Yet, mice are arguably one of the most successful species on earth: they roam in jungles, fields, as well as hustling bustling cities. A key to their success is their exceptional ability to detect and avoid potential predators in a split of a second. This ability must be supported by a neural circuit capable of quickly processing danger information, integrating it with the internal state and experience, and driving optimal motor actions. In a recent study published in *Neuron*, Zhou et al. [1] took a deep dive into the neural circuits underlying the defensive responses towards visual predatory threats.

To mimic a fast approaching aerial predator, Zhou et al. projected an expanding dark disk onto a screen above the mice. In laboratory mice, such looming stimuli reliably induces freezing, running to a nest, and hiding [2]. Previous literatures have shown that threatening looming cues take a shortcut to the brain: instead of being relayed through visual thalamus and visual cortex, looming cues are sent directly from the retina to the superior colliculus (SC), which in turn projects to motor control areas such as the periaqueductal gray (PAG) [3,4]. In this recent study, Zhou et al. found that the SC additionally channels the looming information to an unexpected area, namely the ventral tegmental area (VTA). The VTA is a well-studied region in neuroscience due to its abundant expression of dopamine and its essential role in motivation, reward and aversion, and associative learning, amongst others [5], but its function in processing innate visual threats has not been previously reported (at least to our knowledge).

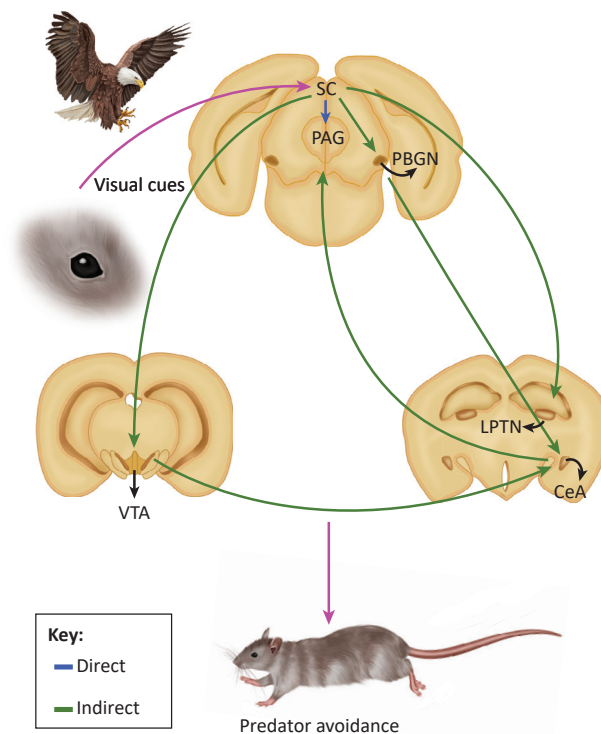
The authors first sought to understand which type of VTA cells are recruited by the looming cues. This is an important question, as VTA contains not only dopaminergic cells but also GABAergic and glutamatergic cells. These cells differ not only in their neurotransmitter type but also in their connectivity and functional relevance [5]. Using the immediate early gene *c-Fos*, a surrogate marker of neural activity, the authors discovered that nondopaminergic cells in the VTA were the major population being activated by looming stimuli. They then used fiber photometry to record the activity of VTA GABAergic neurons in freely moving animals and observed a quick rise in cell activity when the animal detected the looming signal and during flight-to-nest.

To address whether the observed neural responses of VTA GABAergic cells are behaviorally relevant, the authors optogenetically inactivated the cells and found the manipulation caused a decrease in flight and hiding during the presentation of a looming stimulus. Conversely, animals with artificially activated VTA GABAergic cells showed increased flight and hiding in the absence of a looming stimulus. Furthermore, manipulating the pathway from the SC to the VTA induced similar behavioral changes. Thus, the authors concluded that the projection from SC to VTA GABAergic cells critically mediates visually guided predator avoidance behaviors.

Where does the VTA project so that the defensive behaviors can be ultimately driven? One of the brain regions that caught the authors' attention is the central nucleus of the amygdala (CeA), which receives dense inputs from the VTA GABAergic cells. The CeA is the major output station of the amygdala for conditioned fear responses and has also been implicated in unlearned fear [6,7]. To test a potential role of the CeA in mediating visually guided predator defense, the authors pharmacologically inhibited the CeA and found that the manipulation induced an increased latency in hiding upon the presentation of looming stimulus, supporting the SC→VTA→CeA pathway in detecting and responding to aerial threat in mice.

It is worth noting that SC→VTA→CeA is not the only pathway relevant for processing visual threats. Previous studies have found that SC projections to the parabrachial nucleus (PBGN) and lateral posterior thalamic nucleus (LPTN), as well as SC projections to PAG, can all mediate aerial defensive behaviors [4,8,9]. Coincidentally, PBGN





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Figure 1. Simplified Schematic of Visual Threat Avoidance Circuitry in Mice.

Visual cues are detected in the retina and processed by the SC. The SC can then: (i) send visual input via a direct pathway to the PAG for generation of motor responses, or (ii) distribute information to secondary brain regions for further integration, which will then project to the PAG. Blue arrow: direct pathway of information processing. Green arrows: indirect pathway for information processing. Abbreviations: CeA, central amygdala nucleus; LPTN, lateral posterior thalamic nucleus; PAG, periaqueductal gray; PBGN, parabigeminal nucleus; SC, superior colliculus; VTA, ventral tegmental area.

projects to the CeA [9], whereas the CeA projects to the PAG [6]. Thus, it appears that the SC takes multiple parallel pathways to deliver threatening visual cues to the PAG for motor execution (Figure 1). Is this redundant anatomical arrangement simply a strategy to ensure the information transfer between the SC and PAG? Or perhaps the direct and indirect pathways convey important temporal and spatial information in determining an optimal defensive strategy? Indeed, while escape may appear as a simple motor action that is released upon presenta-

tion of specific stimuli, real-world successful escape behavior relies on integrating multiple external and internal variables, such as trade-offs by choosing between flight and freeze, flight trajectories towards shelter, competing physiological needs (e.g., hunger), and stored knowledge regarding the risk level [10]. Future studies that combine innovative behavioral tasks that control each behavioral variable, and various tools for simultaneous manipulating and recording multiple brain regions, will shed new light onto the basic organizing principles un-

derlying the complex architecture of the defense circuit.

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