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Keep *both* eyes on the prize: Hunting mice use binocular vision and specialized retinal neurons to capture prey

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In this issue of *Neuron*, Johnson et al. show that mice rely on binocular vision when hunting insect prey. Specific types of retinal output neurons support this behavior. They have functional properties and brain connections well-suited to their role.

Animals navigate a world of threats and opportunities. Many of these are plain to see, so evolution has sculpted sophisticated visual systems that can inform the brain of their presence. Through natural selection, each species has developed eyes, retinas, and visual brains optimized for detection and response to the visible hazards, sustenance, and mating prospects in its niche.

Evolutionary innovation in visual system design is not limitless. Physics and genetic legacy impose constraints that ensure that much about visual system architecture is conserved among related species. In vertebrate visual systems, one certainty is that there will be two eyes. But where in the head should the eyes be positioned for the greatest selective advantage?

Consider mice. We typically cast them in the role of prey, and certainly many aspects of their visual system reflect the need to sense external threats. Like many other prey species, their eyes at rest point more laterally than those of top-line predators. This affords them a nearly panoramic field of vision for continuous monitoring of the space around them for avian and terrestrial predators. Furthermore, specific retinal neurons, pathways, and effector systems have evolved to detect and respond to threatening visual stimuli, such as dimming or looming (Salay et al., 2018; Wang et al., 2021).

But in a new marvelous paper by Johnson and colleagues (Johnson et al., 2021), the mice have flipped the script by morphing into hunters. Though wild mice forage mainly for fruits, seeds, and plants, they also seek the thrill of the chase, the satisfying crunch, and the protein punch of live bugs. The paper reveals that the requirements for effective predation are as clearly imprinted on the architecture of the mouse visual system as are those for not falling prey. The paper traces the neural underpinnings of mouse hunting behavior to a strikingly small and specific collection of retinal ganglion cells (RGCs) with distinctive visual response properties and outputs well-matched to their role.

Because the mouse's two eyes point laterally, they view largely separate regions of the visual world, but, crucially, both eyes view visual space right in front of the mouse—the binocular zone. This enables *stereopsis*, the extraction of depth information from the subtly divergent views of the world seen by the two eyes (Pettigrew, 1986). In the binocular region of mouse visual cortex, some neurons are tuned for interocular disparity (depth), just as they are in primate visual cortex (Scholl et al., 2013; Poggio et al., 1988). Stereopsis provides useful depth information in immediate extrapersonal space, and humans use it to optimize their reaching and grasping (Servos et al., 1992). It has been suggested that stereopsis evolved to support predation (Pettigrew, 1986), and this new study suggests that it plays just such a role in mice as they hunt for insects.

The authors begin by providing a remarkably complete and high-resolution documentation of the kinematics of the mouse's predatory behavior when detecting, approaching, grasping, and consuming live crickets. Their analysis shows definitively that once mice detect a cricket, they orient themselves so as to keep the target within the narrow binocular zone during the final approach, grab, and bite. This in turn suggested to the authors that mice might exploit stereopsis to optimize their performance, as we do when we grab a nacho off a plate.

Supporting their hypothesis, they showed first that one-eyed mice are lousy hunters. But to get more closure on the process, they shrewdly drilled down on the indispensable subpopulation of RGCs for binocular vision—those with axons that bypass the optic chiasm and project to the same side of the brain. Like the authors, we'll call them "ipsi-RGCs."

In mice, ipsi-RGCs lie in the far temporal retina and view the frontal binocular field. As in most mammals with lateralized eyes, these comprise a small percentage of all RGCs. Not only are they limited to a small retinal sector, but most ganglion cells in that far temporal region have *crossed* projections to the brain, as they do elsewhere in the retina. This paper gives us the first thorough characterization of the ipsi-RGC population in mice. The authors exploited the unique genetic properties of these cells and retrograde axon-transport tracing to plot their distribution and numbers and to reveal their surprising willingness to locate their cell bodies in the "wrong" cellular layer of the retina. The authors' genetic access to ipsi-RGCs also enabled sophisticated and synergistic electrophysiological, anatomical, and behavioral experiments.

Mammalian ganglion cells are divisible into dozens of distinct types based on structure, function, brain projections, and genetic profile. In the mouse retina, where the picture is clearest, the consensus is that there are around 40 types (Sanes and Masland, 2015). But which of these are the source of the uncrossed pathway to the brain? Using selective genetic tagging as well as retrograde axon-transport tracing to identify ipsi-RGCs, the authors systematically characterized the morphology and visual responses of ipsi-RGCs and were able to definitively demonstrate their correspondence to only nine of the ~40 types of RGCs. Exploiting their genetic access, the authors then selectively killed off these ipsi-RGCs. Remarkably, this manipulation alone—deleting just 2% of all RGCs and only a handful of types—was enough to disrupt efficient predation.

The authors were able to pare down even further the ipsi-RGC types supporting predation. They reasoned that RGCs responsible for the localization and capture of crickets should respond well to cricket-like visual stimuli. Only five of the nine ipsi-RGC types responded to such stimuli. These were mostly plain-vanilla center-surround receptive field types, reminiscent of those known to dominate the retino-geniculo-cortical pathway in primates and carnivores. The authors were able to retrolabel these RGC types from thalamus, so their signals can be assumed to reach the visual cortex. It remains to be demonstrated that their signals are essential for stereoscopic depth tuning in cortical neurons, though that seems highly likely.

The ipsi-RGC types that responded poorly to cricket-like stimuli belonged to the class of intrinsically photosensitive RGCs. Ipsilateral projections from these RGCs were to be expected because they bilaterally innervate "non-image-forming" retinal targets such as the suprachiasmatic nucleus and olivary pretectal nucleus to drive reflexive circadian and pupillary responses. There, binocularity apparently serves mainly to assemble a representation of global environmental luminance rather than to compute stereoscopic depth.

This paper is packed with goodies: the kinematics of mouse hunting behavior, the importance of binocular vision for hunting, the functional properties of the uncrossed retinal output signals supporting stereopsis in an animal with lateralized eyes, and a dramatic demonstration of a defined functional role for several major ganglion cell types in mice. Naturally, the study sparks exciting new questions. Are there other visually mediated behaviors in mice that rely upon binocular vision, such as navigation or social interaction? What other aspects of vision are supported by the five ipsi-RGC types that support binocular predation? These neurons are present throughout the retina, not only in the far temporal retina. What is their role in the much larger monocular zone? Given their responsiveness to cricket-like visual stimuli, they might contribute to the detection of prey outside the binocular zone, but other RGC types seem likely to be involved as well, such as those known to be sensitive to local (or object) motion (Sanes and Masland, 2015).

This paper should spark a new interest in a puzzling feature of the mapping of the visual world onto the brain. In most mammals (as here in mice), many RGCs in the temporal retina send axons to the *opposite* side of the brain, counter to the textbook scheme based on human anatomy, with purely uncrossed temporal projections. Classic work in cats showed that the crossed and uncrossed temporal projections derive from different RGC types (Rowe and Stone, 1980) and that the crossed temporal projection generates representations of the ipsilateral visual field in the geniculate and superior colliculus. The Johnson study echoes the cat work in showing that these include the RGCs selective for stimulus direction or orientation, as well as high-resolution RGCs sensitive to local motion. What selective advantage is achieved by routing different sorts of temporal retinal signals to distinct brain targets on opposite sides of the midline? What became of such crossed temporal projections in the

evolution of the primate retina? If they are still present, are they so rare that they escaped notice in earlier studies? Or were they remodeled to switch their decision at the optic chiasm so that they now project ipsilaterally? Or have such RGC types been pared away entirely as our own dramatically encephalized visual system evolved? In primates, the ipsi-RGCs supporting stereopsis would comprise mainly midget and parasol cells. Are they homologous to any of the RGC types shown here to support stereopsis in mice?

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Anger management: pSI has a say in it

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In this issue of *Neuron*, Zhu et al. (2021) reveal that activities in posterior substantia innominate (pSI) neurons that project to the periaqueductal gray (PAG) are both necessary and sufficient to drive aggressive attacks in mice under various conditions.

Virtually everyone knows what rage is—a heightened state of anger where one feels the pounding heart, elevated blood pressure, rushing adrenaline, and the urge to punch someone or something. Inability to rein in rage could pose serious problems for an individual or the society. What might be the neural mechanism that underlies such an intense yet dangerous state of being? In this issue of *Neuron*, Zhu et al. (2021) shine light on this question by identifying a population of neurons in the posterior substantia innominate (pSI) that project to the midbrain to mediate pan-attack or "rage"-like response in mice (Figure 1).

pSI is a poorly studied region of the basal forebrain (Agostinelli et al., 2019), traditionally linked to arousal and attention regulation. Extending from –0.7 mm to –1.6 mm posterior of the bregma point, it is located right beneath the globus pallidus (GP), above the medial amygdala (MeA), lateral to the lateral hypothalamus (LH), and dorsa-medial to the central amygdala (CeA) (Figure 1A). Selective enrichment for choline acetyltransferase (ChAT)-positive neurons further distinguishes pSI from surrounding brain areas.

First, using c-Fos immunostaining as an indicator of neural activities, Zhu et al. (2021) found that putative pSI excitatory neurons expressing the molecular markers of Thy1 and CamKII, but not ChAT or GAD2, were selectively activated when a male resident mouse attacked a male intruder. *In vivo* single-unit recording further confirmed pSI "attack-active" neurons (~40% of all recorded units). These neurons showed ramping activities prior to the onset of attack that peaked shortly after attack initiation. Using fiber photometry recording of bulk Ca^{2+} signals, the authors further showed that activities of pSI Thy1+ (pSI^{Thy1}) neurons not only peaked during an attack but also remained elevated in between closely spaced attack bouts. In addition, the Ca^{2+} signals lasted for several seconds beyond attack termination. Such an activity pattern suggests that pSI^{Thy1} neurons may encode an aggressive state in addition to the attack action. Indeed, sniffs or tail rattles that preceded an attack were associated with higher pSI^{Thy1} Ca^{2+} signals than those that did not, indicating that pSI^{Thy1} neural activities could code for an aggressive state independent of the motor actions. Consistently, a supported vector machine (SVM) algorithm