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Retinal ganglion cell maps in the brain: implications for visual processing

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Abstract

Everything the brain knows about the content of the visual world is built from the spiking activity of retinal ganglion cells (RGCs). As the output neurons of the eye, RGCs include ~20 different subtypes, each responding best to a specific feature in the visual scene. Here we discuss recent advances in identifying where different RGC subtypes route visual information in the brain, including which targets they connect to and how their organization within those targets influences visual processing. We also highlight examples where causal links have been established between specific RGC subtypes, their maps of central connections and defined aspects of light-mediated behavior and we suggest the use of techniques that stand to extend these sorts of analyses to circuits underlying visual perception.

Introduction

Over 50 years ago, Lettvin *et al.* published the seminal paper ‘What the Frog’s Eye Tells the Frog’s Brain’ [1]. Lettvin described the many elaborate features encoded by the output neurons of the eye — the retinal ganglion cells (RGCs), such as edges, looming objects, or ‘bug detectors’ that respond best to small stimuli moving against a stationary background. The broad textbook model of vision nevertheless became that RGCs have simple center-surround receptive fields that are combined within the brain to generate more complex feature representations [2]. This certainly is the case for some RGCs and visual channels [3–5]. However, Lettvin also had it right: regardless of whether you examine the eye of a fish, mouse, rat, rabbit, monkey or human, you’ll find ~20 distinct subtypes of RGCs, each responding best to a specific, often highly specialized arrangement of light and dark in the visual environment [6,7,8]. For example, some RGCs respond best to specific directions of motion [9–11] or orientations [12–14] and still others are suppressed by contrast [15] or signal the presence of looming stimuli [16]. A complete cataloging of the features encoded by different RGC subtypes is ongoing, but one thing is clear: RGCs are primed to deliver a rich set of visual information to the brain. In mammals there are also more than two-dozen brain areas that receive direct input from RGCs. Thus, the following crucial questions arise:

1. Where does each RGC subtype project to in the brain?
2. How are the visual signals encoded by different RGC subtypes integrated by local circuits within their targets?
3. How does the parallel organization of retinal maps influence visual perception and behavior?

In the following sections, we address recent progress toward answering these questions. We focus on four different eye-to-brain pathways, each serving a dedicated aspect of visual processing.

Intrinsically photosensitive RGCs: linking irradiance detectors to brain nuclei controlling specific non-image-forming behaviors

One of the great ongoing successes in the effort to link specific RGC subtypes and their maps in the brain to well defined visual behaviors comes from the study of intrinsically photosensitive RGCs (ipRGCs). All ipRGCs respond directly to light due to their expression of melanopsin photopigment [17–20]. Genetic labeling of ipRGCs from the melanopsin locus enabled selective mapping of ipRGC axonal projections within the brain and thereby revealed their two major targets: the supra-chiasmatic nucleus (SCN) — the hypothalamic circadian clock, and the olivary pretectal nucleus (OPN) — a midbrain nucleus involved in pupillary light reflexes [17,21]. Those maps of central projections in turn raised the hypotheses that: (i) ipRGCs serve to couple endogenously generated circadian rhythms to the ambient light-dark cycle (via their connections to the SCN) and (ii) ipRGCs drive pupillary constriction (via their inputs to the OPN). Indeed, ablation of ipRGCs abolishes both these behaviors [23*,24*,25*].

Until very recently it was unclear whether the same subtypes of ipRGCs send irradiance information to the SCN and OPN or whether separate, designated sets of ipRGCs control circadian versus pupillary behaviors. Hattar and co-workers discovered that the transcription factor (*Brn3b*) is expressed by the M1 ipRGCs that target the outer shell of the OPN but not by the M1 ipRGCs that target the SCN. By crossing *Melanopsin-Cre* mice to mice that conditionally express a toxin from the *Brn3b* locus, they were able to selectively ablate only the OPN-shell projecting ipRGCs, which abolished pupil reflexes while leaving circadian entrainment intact [26**] (Figure 1). This molecular/functional isolation of a ‘labeled line’ consisting of a highly specific RGC subtype and a specialized aspect of light-mediated behavior represents an important first for the field. It also underscores the extent to which molecular signatures can be used to ‘split’ RGC populations that otherwise appear homogeneous and thereby discover their specific contributions to visual processing.

The use of Cre-based strategies for labeling ipRGCs revealed there are at least five subtypes of these cells that, collectively, project to more than a dozen central targets [22*] (Figure 1). As a general group, ipRGCs have been shown to influence mood, possibly via their inputs to the amygdala or habenula [21,27], and they have also been hypothesized to drive photic-induced migraine headache via their inputs to the posterior thalamic nuclei [28]. ipRGCs also play various developmental roles, including neonatal bright light avoidance [29],

assembly of retinal vasculature [30], and patterning of early retinal activity [31,32] which in turn can influence RGC axonal refinements within the brain [32]. It is also intriguing that in both mice and primates, ipRGCs project to the dorsal lateral geniculate nucleus — the structure responsible for relaying light information to the cortex for conscious processing of visual images [22*,33,34*]. Thus, ipRGCs are poised to play diverse roles in the central processing of light information and it appears likely that each of the different M1–M5 subtypes will relate to distinct visual functions. As it stands now, however, the field lacks tools for specifically manipulating the ipRGCs that project to restricted sets of central targets other than the OPN shell. Hence, causal links between the remaining ip RGCs subtypes, their maps of central projections and discrete light-mediated behaviors, remain to be elucidated.

The superior colliculus contains functionally distinct parallel visual maps

The superior colliculus (SC) is a large multimodal structure involved in directing the head and eyes to particular locations in visual space [35]. Input from the retina is delivered to the superficial-most layers of the SC where it is topographically mapped and aligned with the auditory and somatosensory maps that reside in deeper layers [36]. Recently, there has been a surge in understanding about how different RGCs and the information they encode are mapped in the SC. In large part these advances come from the discovery of transgenic mice harboring fluorescently tagged RGC subtypes. Genetic marking of Off and On-Off direction selective RGCs (DSGCs) revealed that they selectively target the superficial half of the retinorecipient SC [37**,38**,39,40*,41] along with RGCs that respond to local object motion (similar to Lettvin's 'bug detectors') [41,42]. Alpha RGCs and ipRGCs —neither of which exhibit directional tuning, target the deeper portion of the retinorecipient SC [21,43*,44*]. Thus, the mouse superior colliculus receives visual signals from the retina in the form of at least four parallel retinotopically complete maps (Figure 2).

Are the four maps of RGC input kept separate or combined within the network of collicular neurons? Each SC neuron is known to receive input from ~6 RGCs [45] but which subtypes of RGCs converge on an individual SC neuron is unknown. Many neurons in the retinorecipient SC are sensitive to directional motion [35,46] but their position, including where their dendrites stratify along the depth of the retinorecipient layers, has not been determined and thus it is unclear if they inherit their tuning directly from DSGCs. Indeed, the dendrites of retinorecipient SC neurons can span the full depth of all four RGC input-maps, suggesting they can sample these inputs in combinatorial fashion [35,47] (Figure 2). What is needed now is a thorough characterization of retinocollicular connectivity, including which RGCs connect to each SC neuron type and where those synapses arrive along the postsynaptic dendritic arbor. Monosynaptic viral tracing techniques [48,49] would greatly aid the effort to fill these gaps in knowledge, and help resolve the broader issue of how laminar-specific mapping of axons and dendrites impacts circuit function and receptive field transformations.

Zebrafish provide a window into the integration of laminar retinal maps in the tectum

Several important steps forward were recently made in parsing how laminar maps of RGC axons relate to the response properties of their targets, using *in vivo* imaging of the larval

zebrafish tectum (homolog of the SC). First, Baier and colleagues [50^{*}] used ‘rainbow’ technology to label many different RGCs, each with different colors in the same animal, thereby revealing the highly stereotyped combinations of RGC types that converge their axons within individual tectal sublaminae. Second, Meyer and colleagues [51^{**},52^{*}] monitored calcium activity in retinotectal terminals while presenting the fish with a range of visual stimuli, such as drifting bars of different orientations and directions. This revealed that separate populations of RGCs funnel visual information to highly restricted sublaminae within the tectum, creating three parallel maps of direction and four parallel maps of orientation (Figure 3).

How does the laminar-restricted delivery of visual information to the tectum relate to the response properties of neurons in this target? In an elegant study, Bollmann and colleagues [53^{**}] compared the tuning of direction selective retinotectal axons with the tuning of genetically tagged tectal neurons. They discovered essentially two categories of direction selective tectal cells. One population was direction selective in a manner that could be directly predicted from the retinal input layer where they stratified their dendrites. The other population was also direction selective (DS) but its dendrites did not receive direct DSGC input. An additional study from Engert and co-workers [54^{*}] identified asymmetric inhibition from local interneurons as a possible substrate for generating DS tuning in the zebrafish tectum. Together, these findings indicate that DS tuning of tectal neurons can be generated from feed-forward retinal inputs or by post-synaptic circuitry. It is important to note, however, that tectal neurons also can transform RGC inputs to create entirely new feature representations. Hunter *et al.* [55^{*}] showed that some tectal neurons can exhibit directional tuning that is entirely distinct from the tuning of incoming retinal afferents. Collectively, the abovementioned studies in zebrafish illustrate that the highly restricted laminar mapping of RGC axons can instruct the tuning of target neurons, but that local circuit elements within the target can also use that information to generate receptive field properties *de novo*.

Cell-type-specific targeting of RGCs in the lateral geniculate nucleus

The recent advent of genetic tools for labeling specific RGC subtypes has greatly expanded understanding of how different visual channels are organized within the most famous mammalian retinorecipient target — the dorsal lateral geniculate nucleus (dLGN). Studies used transgenic labeling of specific RGC subtypes to demonstrate that the mouse dLGN contains at least two broad categories of functionally distinct retinal maps: a laminar map of direction selective RGC (DSGC) axons that resides adjacent to the optic tract and a laminar map comprising of axons from non-DSGCs located in the deeper ‘core’ compartment of dLGN (Figure 4) [37^{**},38^{**},39,40^{*},41,43^{*}]. Therefore, just like the SC, there exist several distinct RGC maps in the geniculate. The question then arises: how do the different input channels to the dLGN relate to the various cell types in this target? Guido and colleagues recently discovered that the mouse harbors three relay neuron types that morphologically resemble the X, Y and W cells described in earlier studies in cats and primates [56^{*}]. By comparing the location of each cell type they determined that W-like cells reside in the same region of the dLGN where DSGCs terminate (the shell). By contrast, Y-like cells reside in the region where alpha RGCs and other non-DSGCs terminate (the core). X cells were found

in both the shell and core. In mice, each dLGN neuron receives input from ~1–3 RGCs [57], but whether individual X, Y and W cells sample visual input exclusively from DSGCs versus non-DSGCs is an important issue that still awaits resolution.

Two recent studies, one using *in vivo* calcium imaging [58**] and one using electrode recordings [59**], discovered that the shell region of the dLGN is enriched for direction-tuned and orientation-tuned neurons (Figure 4). Since the shell roughly corresponds to the same region where the axons of DSGCs terminate, several key questions emerge. First, does the orientation tuning of dLGN neurons arise from the convergence of DSGCs that respond to opposing axes of motion? This seems likely given that (i) mouse dLGN neurons often receive input from multiple RGCs and (ii) orientation-selective dLGN neurons reside postsynaptic to DSGC axons (Figure 4). However, a recent study also found evidence that even some mouse RGCs are orientation selective [60*]. Thus in order to understand the basis for orientation selectivity in the mouse dLGN it is essential to resolve whether these orientation selective RGCs project to the geniculate and if so, to which laminar compartment.

The textbook model of orientation selectivity derived from work in carnivores and primates posits that few, if any, dLGN neurons exhibit direction or orientation selectivity and that visual cortex is the first place these features are observed [61]. Are direction selective retinal and dLGN neurons unique to the mouse? After all, DSGCs have not been reported in primates. There are several reports, however, of DS-tuned geniculate neurons in rabbits, cats and primates [62–67]. Additionally, Martin and colleagues recently showed that some neurons in the koniocellular layers of the marmoset dLGN are highly orientation selective [68]. In light of this, it is key to determine whether dLGN-projecting RGCs in primates include direction-tuned or orientation-tuned RGCs and if so, whether they contribute to cortical representation of these features.

Mapping direction selective retinal inputs to brain areas that control image-stabilization

As the eyes and head move, images slip on the retina; left unchecked this would blur the image of the visual scene. A specialized set of direction selective RGCs and central targets together called the accessory optic system (AOS) generate reflexive eye movements that compensate for retinal slip [70,71,72*]. Consequently, the AOS is a powerful model for probing how the mapping of DSGCs relates to visual behavior. Classic work in rabbits [70] showed that the AOS consists of On-DSGCs that project to two distinct collections of brainstem targets: (i) the nucleus of the optic tract and dorsal terminal nucleus (NOT/DTN) which help control horizontal slip compensation and (ii) the medial and lateral terminal nuclei (MTN and LTN) which encode vertical image slip. The On-DSGCs that connect to AOS targets are tailored to the behavioral demands of this system such that their directional tuning matches the major axes of visual slip experienced by the retina whenever the head moves [70,72*]. Moreover, On-DSGCs are among the rare RGC subtypes that do not provide direct input to the superior colliculus or dLGN.

Studies in mice are starting to reveal important new principles of how DSGCs signals feed the AOS. The mouse AOS appears similar to that of rabbits and primates, based on the fact that in all these species, On-DSGCs provide major drive to this system [73^{••},74^{••}]. Recent studies used genetic labeling to find, however, that the AOS also receives substantial input from On-Off DSGCs [40[•],74^{••}] (Figure 5). Moreover, the contribution of On-Off signals to the AOS appears to be target-specific. Viral labeling of the RGCs that project to the nucleus of the optic tract revealed that this target receives input from an On-Off DSGC subtype whose velocity tuning is ideally matched to the NOTs proposed role in image stabilization [74^{••}]. By contrast, other AOS targets such as the MTN do not appear to collect input from these cells. It is now crucial to understand how the two major types of DSGCs (On and On-Off) collaborate to generate slip-compensating eye movements. It is also important to resolve whether AOS nuclei harbor sub-domains encoding different directions of retinal slip [73^{••}]. Killing cholinergic starburst amacrine cells [75] or silencing On-bipolar cells [76] has been shown to completely eliminate slip-compensating eye movements. However, the field still awaits more refined manipulations that kill or silence the specific DSGC subtypes in order to elucidate their individual contributions to image stabilization. The fact that AOS-projecting RGCs are now genetically identified opens the door to find molecular signatures of these cells and to perform these sorts of analyses.

Perspectives

Here we reviewed recent advances in understanding how different RGCs map visual features to the brain. In some cases such as the ipRGCs, those maps resemble ‘labeled lines’, whereas in other cases, such as the retinal inputs to the SC, they are poised to converge in a combinatorial pattern. Understanding the relevance of this convergence to visual processing and perception represents an important unmet challenge. For example, does the combined directional tuning of dLGN neurons simply mirror the tuning of the DSGCs they receive input from? Or as Levick *et al.* proposed [77[•]], do inhibitory cells within the dLGN modify and sharpen DS responses? The answers to these sorts of questions will be important for the field of visual neuroscience and more generally, they stand to reveal important general principles of how the specificity of axonal mapping can create new, richer feature representations in the brain.

It is also worth mentioning that RGC maps display various salient features whose functional relevance for visual processing remain opaque. For instance, RGC projections are heavily collateralized to multiple subcortical targets [78–80] but the functional relevance of this collateralization has not been explored. Modern tools to control neuronal activity such as optogenetic and chemical-genetic strategies [81] should greatly help resolve this and other outstanding questions. Finally, to understand the implications of such studies for human vision will require analysis of species such as fish and mice, but also primates [82]. The question of ‘what does the eye tell the brain?’ remains an important one that is certain to deliver many new and exciting findings in years to come, especially with regard to how different retinal ganglion cell types contribute to visual perception and behavior.

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Figure 1. Intrinsically photosensitive retinal ganglion cell subtypes (ipRGCs), their connections in the brain and their influence on various aspects of light-mediated behaviors.

Figure 2.

Retinal ganglion cell maps in the superior colliculus identified from genetic labeling studies in the mouse. **(a)** Four subtypes of RGCs, each encoding a different specific feature of the visual environment. W3 RGCs encode local object motion [42]. On-Off DSGCs encode directional motion [38^{**},41]. J-RGCs are Off-DSGCs [37^{**}] and alpha RGCs respond to center-surround stimuli [43^{*}]. **(b)** Diagram of mouse head and brain showing the position of the two eyes, optic nerves and tracts and the two bilateral superior colliculi. On the right is a higher magnification view of one superior colliculus with the four RGC axonal maps stacked across its depth. **(c)** View of the four different RGC axon layers across the depth of the retinorecipient SC (comprised of upper and lower stratum griseum superficiale; uSGS, and ISGS respectively). Examples of collicular neurons that restrict their dendrites to individual or few sublaminae as well as a collicular neuron that extends its arbor across all four RGC axon layers are shown to illustrate the possible modes of convergence for the various RGC maps.

Figure 3. Calcium imaging of activity in RGC axons in the zebrafish tectum revealed direction and orientation maps. **(a)** Schematic of basic experimental design: larval zebrafish sequentially viewed bars moving in one of 12 different directions while the activity of RGCs was measured at the level of their axon terminals within the tectum. **(b)** Response maps to three different orientations and directions (see Ref. [51**] for details). **(c)** Composite maps of direction tuned RGC axons and orientation tuned RGC axons in the tectum, color-coded and combined.

Figure 4.

Laminar specific mapping and target neuron responses in the lateral geniculate of the mouse.

(a) Diagram of the mouse dLGN with its shell and core regions and the termination zones where the axons of the various genetically identified subtypes of DSGCs synapse. The terminations of axons from alpha RGCs in the core region are also shown. (b) Schematic of the RGC inputs to dLGN neurons. (c) Polar plots of direction selective, orientation selective, and center-surround neurons that were recorded from the mouse dLGN. See Ref. [59**] for details.

Figure 5.

Schematic of the accessory optic system in the mouse (adapted from [83] and [74**]). The axes of directional motion encoded by the four genetically identified subtypes of DSGCs that connect to the AOS are shown. The diagram on the right depicts the subcortical visual pathway with two optic nerves (on), optic tract and accessory optic tracts, as well as various AOS targets such as the medial terminal nucleus (MTN), nucleus of the optic tract (NOT) and dorsal terminal nucleus (DTN). The superior colliculus (SC) is also shown. The color scheme matches the different DSGC subtypes (left panel with mouse) that project along each pathway and target. Sup. fasc. of AOT = superior fasciculus of the accessory optic tract and inf. fasc. of AOT = inferior fasciculus of the AOT.