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

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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.

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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?

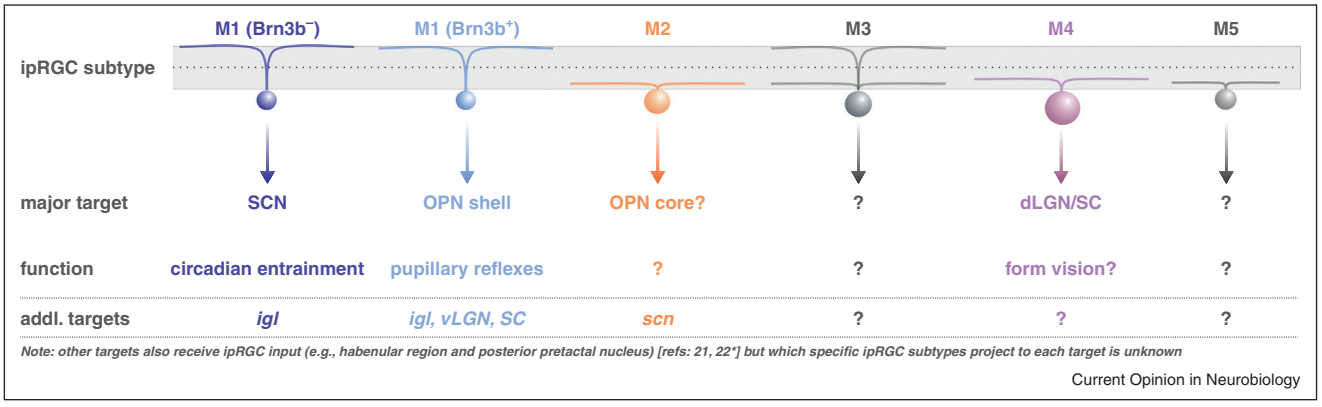
In the following sections, we address recent progress toward answering these questions. We focus on four different eye-to-brain pathways, each serving a dedicated aspect of visual processing.

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 suprachiasmatic 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 sends irradiance information to

Figure 1



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

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