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Retinal mechanisms shaping neural encoding of motion

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Abstract

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Vision is a fundamental component of the human sensory experience. In order to construct visual percepts and mediate appropriate behaviors, the brain uses myriad neural circuits to enact diverse computations and process visual information. Motion is a particularly prevalent feature of the visual world, representations for which are seen through the visual systems of many mammals. By studying neural circuits for motion processing, we gain insights into an important visual information channel utilized by the brain, and thus establish a foothold from which to further understand mechanisms of perception and behavior. The retina in particular provides the opportunity for study of relatively tractable circuits by which to understand how neural signals are integrated in space and time.

This work investigates the mechanisms of neural processing within the early visual system. Chapter 1 provides an introduction to motion processing in the retina. This chapter reviews the literature on the diversity of retinal motion detectors which have thus far been catalogued, and discusses what is presently known about their mechanisms of computation. Chapter 2 focuses on a comparative study of two retinal motion detectors in particular: the ON and ON-OFF direction selective ganglion cells. This chapter presents original research findings on the synaptic mechanisms by which these circuits jointly encode the direction and velocity of motion using electrophysiology, pharmacology, genetic knockout animals, and computational modeling. Chapter 3 concludes with a discussion of the computational role of the retina compared to central brain areas, and examines modern physiological findings alongside insights from evolutionary biology, comparative neuroanatomy and theory studies. In sum, the work within this thesis expands our understanding of the mechanisms by which retinal circuits encode motion, and in so doing contributes to our knowledge of how neural signals are integrated by the brain to mediate vision.

This work is dedicated to my mother, Julie Doll-Summers

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Acknowledgments

Completing a PhD has been one of the most challenging undertakings of my life thus far. Many aspects of graduate study are uniquely difficult – I think the frustration, isolation, and unavoidable (though mistaken) urge to link internal self-worth to external success are inevitable parts of operating at the boundaries of human knowledge. However, many of the most challenging parts of a PhD are not unique to graduate study, but rather are the struggles common to any given 6+ year span of adult life: the loss of loved ones, the dissolution of relationships, the varied modalities of global upheaval. I'm grateful for having had a deep support network of friends and mentors to guide and comfort me through these trials, both scientific and otherwise. I couldn't have done it without you.

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Chapter 1: Retinal Mechanisms for Motion Detection

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Summary

Motion is a key feature of the sensory experience of visual animals. The mammalian retina has evolved a number of diverse motion sensors to detect and parse visual motion into behaviorally relevant neural signals. Extensive work has identified retinal outputs encoding directional and nondirectional motion, and the intermediate circuitry underlying this tuning. Detailed circuit mechanism investigation has established retinal direction selectivity in particular as a model system of neural computation.

Introduction

Visual motion, whether self-generated or elicited by movement in the external world, is a pervasive aspect of an animal's sensory experience. As an animal navigates its environment, every head and eye movement produces patterns of optic flow within the visual field. Important visually guided behaviors, such as predator avoidance or prey capture, are further predicated on being able to detect externally generated object motion. Given the ethological importance of detecting motion, many visual animals have evolved to process motion information at the earliest stages of the visual system (Baden, Euler, and Berens 2020; Lettvin et al. 1959; Mauss et al. 2017).

In vertebrates, the earliest visual processing begins in the retina. Retinal ganglion cells (RGCs) form the output of the retina, and by their spiking activity, they conduct information about the visual scene to higher order brain areas. Approximately 40 to 50 different RGC types parse the world into different visual features, such as luminance, contrast, and motion (Baden et al. 2016; Sanes and Masland 2015). Motion predominates the feature tuning of many of these RGCs, with further cell-type subdivisions existing for velocity, direction, and spatial extent of motion (Wei 2018). The mechanisms by which RGCs construct these representations of motion have been the subject of extensive study (Mauss et al. 2017; David I. Vaney, Sivyer, and Taylor 2012; Wei 2018). The intermediate circuitry between the retina's photoreceptor inputs and RGC outputs form the crux of motion computations, by transforming pointwise luminance information into patterns of RGC excitation and inhibition. Some of these intermediate cells have themselves been found to be motion sensitive, thereby imparting selectivity that distinct populations of downstream RGCs can further craft into diverse, behaviorally relevant motion signals.

The retina's motion-sensitive intermediate and output cell types are summarized herein. The mechanisms by which neural representations of motion are constructed are further detailed, with particular attention to direction selectivity, where circuit mechanisms are best understood.

Motion Sensors in the Retina

In the retina, information flows via glutamatergic synapses from photoreceptors to bipolar cells, and from bipolar cells to RGCs (see Figure 2A). Horizontal cells and amacrine cells serve as interneurons respectively providing feedforward, feedback, and lateral inhibition at the photoreceptor to bipolar, and bipolar to RGC, synapses. These canonical circuit motifs are key to understanding how inhibition shapes the stationary receptive fields of RGCs.

However, many of these basic elements of retinal computation are not directly tuned for motion. Photoreceptors encode light intensity information at fixed points in the visual field and thus in isolation are insufficient to compute motion, which by definition requires correlating distinct points in space. Horizontal cells implement gain control and sharpen spatial and temporal tuning at the photoreceptor to bipolar cell synapse (Chapot et al. 2017; Drinnenberg et al. 2018; Thoreson and Mangel 2012). Bipolar cells split luminance information into parallel channels, with photoreceptor sign-inverting and sign-conserving bipolar cell types, respectively, providing the basis for the retina's ON and OFF pathways. Further subtypes of bipolar cells express glutamate receptors with different kinetics, thereby filtering different temporal frequencies of visual information into parallel streams (Awatramani and Slaughter 2000; DeVries 2000; Puthussery et al. 2014). Various combinations of these information channels are recombined to form the primary glutamatergic drive onto amacrine cells and RGCs. Motion tuning has not been explicitly observed in bipolar cells themselves, but combinations of bipolar cells with distinct kinetics have been shown to elicit postsynaptic tuning (see the section "Mechanisms of Motion Computation").

Amacrine cells are the first cells within the retina to show motion sensitivity. Amacrine cells do not project to higher brain areas, but they synapse locally within the retina to shape computations via feedback and feedforward inputs onto bipolar cells and RGCs, respectively. An estimated 30 to 50 amacrine cell types exist in the retina (Diamond 2017). The majority of amacrine cells form inhibitory GABAergic or glycinergic synapses, though some amacrine cells form excitatory glutamatergic, cholinergic, or even electrical synapses (Grimes, Schwartz, and Rieke 2014; Masland 2012; Nath and Schwartz 2017). A subset of these amacrine cell types are motion sensitive (see the section "Motion-Sensing Amacrine Cells"). Motion-tuned amacrine cells form the building blocks of RGC motion tuning.

The final outputs of retinal circuits are RGCs. Diverse RGC populations integrate distinct combinations of bipolar and amacrine cell inputs to construct neural representations of key visual features. Different RGC types encode different features of the visual world, and thus they project to distinct brain regions to mediate appropriate behaviors (Seabrook et al. 2017).

Although many motion-sensitive RGCs inherit much of their tuning from amacrine cells, convergence of multiple mechanisms often confers robustness to the varied stimuli conditions an animal may experience in the natural world (Q. Chen and Wei 2018).

Motion Sensing RGCs

Motion-processing RGCs can be split into two functional categories: those that compute directional motion, and those that compute nondirectional motion features (Figure 1). The observation of RGCs selective for particular directions of image motion was first made in the rabbit retina in the 1960s (Barlow, Hill, and Levick 1964). Since then, direction-selective ganglion cells (DSGCs) have become a classic model for studying neural computations (Cafaro and Rieke 2010; Kühn and Gollisch 2019; Zylberberg et al. 2016). Other RGC types have been found to encode nondirectional motion features, such as differential movement (Ölveczky, Baccus, and Meister 2003) between receptive field center and surround, looming motion (Münch et al. 2009), or image recurrence (Krishnamoorthy, Weick, and Gollisch 2017). Although particular stimulus features that strongly induce activity have been identified for these RGCs, many cell types are sensitive to several stimulus features and thus multiplex varied aspects of the visual scene in their spiking.

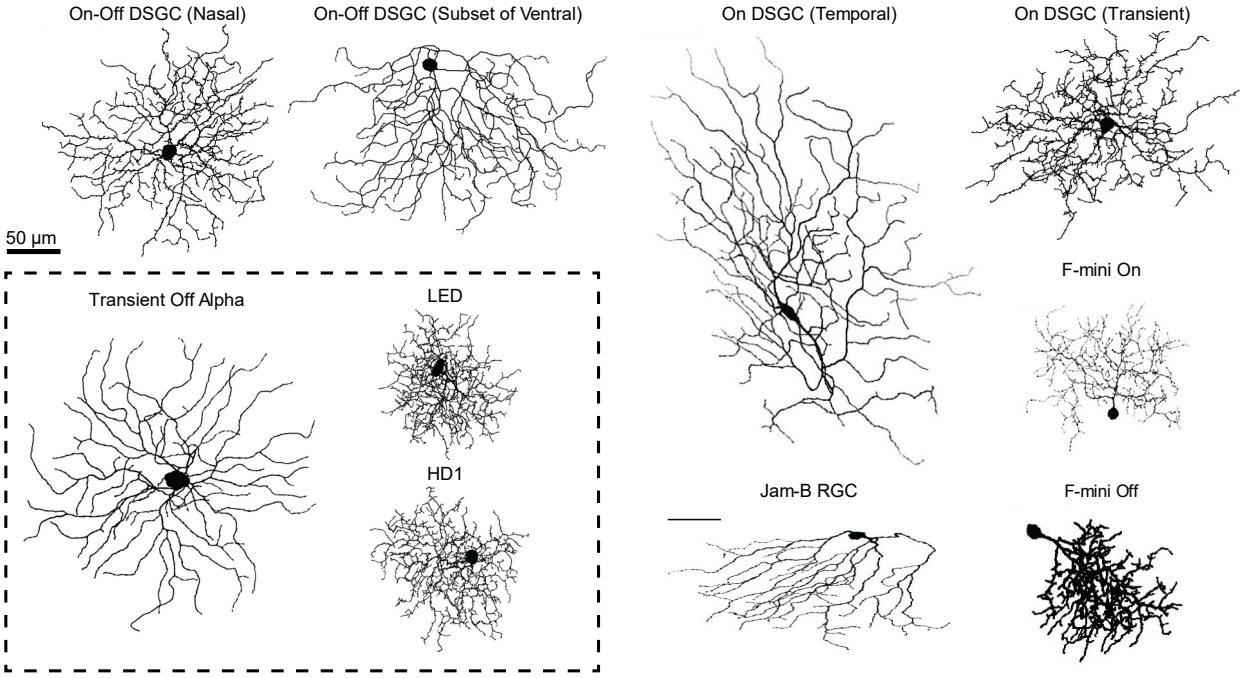


Figure 1. Example dendritic field reconstructions of motion-sensitive retinal ganglion cells (RGCs). Morphologically similar subtypes of ON and ON–OFF direction-selective ganglion cells (DSGCs) are shown by a representative example of a temporally and nasally tuned cells, respectively. The morphologically distinct ventrally tuned ON–OFF and transient ON DSGCs are shown for comparison. Inset: RGCs that are motion sensitive but not directionally tuned. Abbreviations: Jam-B RGC, junctional adhesion molecule B–positive retinal ganglion cell; LED, local edge detector; HD1, high-definition type 1 cell; F-mini = Foxp2 transcription factor, small dendrite cell. All reconstructions from EyeWire museum or rgctypes.com websites.

Direction Selective RGCs

Direction selective RGCs encode directional motion by firing strongly for motion in some preferred direction, and weakly or not at all for motion in the anti-preferred, or null,

direction. By some functional estimates, 20% to 40% of RGCs in the mouse retina are direction-selective cells (Bos, Gainer, and Feller 2016; H. Chen, Liu, and Tian 2014). Recent work identifying molecular and genetic labels has allowed for fine-grained investigation of the outputs of particular computations and enabled the discovery of new types of direction-selective RGCs (Morrie and Feller 2016; Wei 2018). ON–OFF and ON DSGCs were the first motion sensors to be described in the retina, and they are the canonical direction-selective RGCs. Transcriptionally defined RGCs have been more recently characterized and are less well understood.

ON–OFF DSGCs

The most extensively studied DSGC, the ON–OFF DSGCs, are thought to serve as detectors of local object motion, due to their moderately sized receptive fields (6.5° diameter in mouse) and strong surround suppression. ON–OFF DSGCs respond transiently to both positive and negative contrast (i.e., increments and decrements of light from background light levels), and correspondingly have bistratified dendrites that arborize in the same sublaminae as ON and OFF starburst amacrine cell processes, and ON and OFF bipolar cell terminals (David I. Vaney, Sivyer, and Taylor 2012). ON–OFF DSGCs respond to a broad range of physiological image velocities, and their direction-selective computations are velocity invariant (Grzywacz and Amthor 2007; Lipin, Rowl Taylor, and Smith 2015).

There are four main subtypes of ON–OFF DSGCs, each encoding different directions of motion. The preferred directions of each subtype have been thought to cluster along the cardinal body axes (i.e., anterior, posterior, superior, and inferior; Oyster, 1968). More recent work has shown that these preferred direction clusters are more accurately modeled as following the axes upon which the world moves in response to various types of self-motion, such as when an animal advances, retreats, rises, or falls (Sabbah et al. 2017). Some morphological and functional differences have been noted between subtypes. In mice, superior-, and some inferior-, motion-preferring DSGCs have been shown to have asymmetric dendrites biased in the direction of their tuning (Kay et al. 2011; Trenholm et al. 2011). Superior-preferring DSGCs have additionally been shown to form homologous gap junctions, which may broaden their tuning (Wei 2018; Yao et al. 2018). At least some anterior-preferring DSGCs show weaker direction-selective tuning and slower motion preference than other subtypes, though it is unclear if this is true of all anterior-preferring DSGCs (Dhande et al. 2013).

ON–OFF DSGCs send predominantly contralateral projections to the dorsal lateral geniculate nucleus (dLGN) and superior colliculus (SC), and in both structures occupy a distinct lamina from non-DSGCs (Huberman et al. 2009; Kay et al. 2011). Some differences in projection patterns exist between subtypes. A subset of posterior-preferring DSGCs also innervates the ventral LGN (vLGN) and zona incerta (Rivlin-Etzion et al. 2011). Asymmetric superior- and inferior-preferring DSGCs project to nuclei of the accessory optic system (AOS), namely the medial terminal nucleus (MTN) and nucleus of the optic tract (NOT), in addition to the SC and both the vLGN and dLGN (Kay et al. 2011). The more weakly tuned anterior DSGCs project to the NOT and SC and notably show minimal innervation of the dLGN (Dhande et al. 2013).

Investigations into the readout of DSGC tuning by higher brain areas has revealed divergent roles of DSGC outputs in generating responses in the SC versus the thalamus and primary visual cortex (V1). Directionally tuned neurons in the SC directly inherit selectivity from excitatory DSGC inputs, and loss of retinal direction-selective output consequently impairs direction-selective tuning in the SC (Shi et al. 2017). A more nuanced picture emerges in the thalamus and V1. DSGCs participate in diverse computations within the dLGN, contributing to representations of luminance, orientation, and directional motion (Liang et al. 2018; Seabrook et al. 2017). dLGN neurons integrate information from multiple RGC sources either by "relaying" the information of similarly tuned neurons or by "combining" diverse inputs to generate new feature tuning (Litvina and Chen 2017; Seabrook et al. 2017). In this way, a DSGC's encoding of an individual feature, such as motion direction or luminance changes, is demultiplexed by being pooled with the outputs of other RGCs tuned for that same image feature (Liang et al. 2018). Cortical representations of image motion further utilize directional signals in diverse ways. One study has shown that layer 4 neurons in V1 are able to compute direction selectivity de novo from untuned thalamic inputs (Lien and Scanziani 2018). However, tuning of thalamocortical boutons shows an overrepresentation for posterior directed motion, and a corresponding bias for posteriorly tuned cells has been observed within layers 4 and 5 (Sun et al. 2016). Layer 2/3 has been shown to receive direct projections from dLGN neurons postsynaptic to posterior-motion-preferring DSGCs, and another study likewise showed predominant posterior motion tuning in layer 2/3 neurons (Cruz-Martín et al. 2014; Hillier et al. 2017). After genetic disruption of DSGC tuning, cortical direction selectivity remained, but the posterior direction bias was lost (Hillier et al. 2017). Further work has developed a cortex-dependent direction-selective discrimination behavioral task, which may utilize ON–OFF DSGC signals (Marques et al. 2018).

ON DSGCs

While ON–OFF DSGCs respond to positive- and negative-contrast image motion, ON DSGCs respond only to increments in light, but they do so in a sustained manner. ON DSGCs have large receptive field centers, approximately 10° in diameter in mice, and are mostly monostratified in the ON layer, costratifying with SAC processes and ON bipolar cell terminals (David I. Vaney, Sivyer, and Taylor 2012). However, small dendritic projections into the OFF sublamina have also been reported in mice (Dhande et al. 2013). The combination of large receptive fields with relatively weak surround suppression and a preference for slower image motion than ON–OFF DSGCs supports a role for On DSGCs in detecting global image motion and gaze stabilization (Oyster 1968; Sivyer, van Wyk, et al. 2010; Sivyer, Tomlinson, and Taylor 2019; Wyatt and Daw 1975).

Original characterizations identified three subtypes of ON DSGCs with preferred directions corresponding to the vestibular axes of the semicircular canals (Oyster 1968). In rabbits, an overlapping set of three ON DSGC subtypes were discovered that encoded the same directions of positive contrast motion with transient, rather than sustained, responses (Hoshi et al. 2011; Kanjhan and Sivyer 2010). A recent study in mice suggests that ON DSGC preferred directions cluster along optic flow axes, much like for ON–OFF DSGCs, and that the requisite fourth subtype of ON DSGC has escaped previous detection due to weaker directional tuning (Sabbah et al. 2017). Large-scale functional classification and connectomic studies in mice have

identified three ON DSGC sustained subtypes, and one ON DSGC type with transient responses that might correspond to the fourth directional preference (Baden et al. 2016; Bae et al. 2018).

Central projections of ON DSGCs differ markedly from those of ON–OFF DSGCs. ON DSGCs identified in transgenic mouse lines and molecular studies project exclusively to the AOS (Lilley et al. 2019; Wei 2018). Of the ON DSGCs that project to the AOS, those encoding vertical (superior/inferior) motion project to the MTN of the AOS, with superior-motion-preferring ON DSGCs targeting the dorsal MTN and inferior-motion-preferring DSGCs targeting ventral MTN. ON DSGCs also project to the dorsal terminal nucleus (DTN) and NOT of the AOS, which are known to be involved in horizontal gaze stabilization (Wei 2018). However, specific projections of horizontal-preferring ON DSGCs to the NOT or DTN have not been confirmed. An additional population of biophysically distinct ON DSGCs that project exclusively to the SC has been identified via functional measures (Gauvain and Murphy 2015). However, the preferred directions of these DSGCs have not been documented. There has been no evidence of ON DSGC projections to LGN; AOS and SC projections are consistent with the hypothesized role of ON DSGCs' contributing to optokinetic reflexes and not perceptual vision. The central projection patterns of transient ON DSGCs are unknown.

F-Mini RGCs

More weakly tuned DSGCs have been discovered via transcriptional profiling. F-mini ON and F-mini OFF RGCs express the transcription factor Foxp2 and form a paramorphic pair of cell types with similar functional and morphological features (Rousso et al. 2016). The receptive field centers of F-mini RGCs are approximately 2.5° in diameter, and each type accounts for about 8% of all RGCs, making them some of the smallest and most numerous RGCs in the retina. F-mini RGCs exhibit transient, directionally selective responses for moderate velocities, with peak tuning at 20°/sec. Each type features asymmetric, monostratified dendrites that do not cofasciculate with SACs. While F-mini OFF dendrites always point ventrally, F-mini ON dendrites orient ventrally in the dorsal retina, and dorsally in ventral retina. The preferred direction of F-mini RGCs tracks the orientation of their dendrites, and thus F-mini OFFs are tuned for superior directed motion, while F-mini ONs can be tuned for either superior or inferior directed motion. F-mini RGCs project to both the dLGN and SC and target the same lamina as ON–OFF DSGCs (Rousso et al. 2016). It is unclear how F-mini RGCs compute direction selectivity, though models of asymmetric ON–OFF DSGCs and identification of F-mini RGCs in electron microscopy (EM) studies may lend insight into their mechanisms (Bae et al. 2018; Trenholm et al. 2011).

Jam-B RGCs

Sometimes called J-RGCs or OFF DSGCs, Jam-B RGCs were identified by their expression of junctional adhesion molecule B (Jam-B; I. J. Kim, Zhang, Yamagata, Meister, & Sanes, 2008). Jam-B RGCs exhibit monostratified and ventrally oriented asymmetric dendrites in the OFF layer of the retina, but do not cofasciculate with SACs. Tuning for multiple stimulus features has been observed in Jam-B RGCs, and some of this feature tuning depends on ambient light levels. An asymmetric surround driven by rods creates color-opponent ultraviolet-OFF/green-ON light responses and produces orientation and direction tuning for superiorly

oriented stimuli (Joesch and Meister 2016; Nath and Schwartz 2017). However, the asymmetric surround diminishes under photopic light levels, and directional tuning is lost accordingly. Under scotopic light levels, Jam-B RGCs respond maximally to spots ~8° in diameter, though in photopic conditions robust spiking is observed for spots as large as 60° in diameter due to the diminished inhibitory surround (Joesch and Meister 2016). Jam-B RGCs project to the SC and dLGN and target similarly superficial regions as ON–OFF DSGCs (I. J. Kim et al. 2008, 2010).

Nondirectional Motion Sensitive RGCs

Whereas the retina's diverse array of direction-selective RGCs appear to break down the visual scene's motion into different components based on size, speed, and direction, many other RGCs have been shown to be directly tuned for stimuli of particular ethological relevance.

Feature tuning for small-object motion, such as might be elicited by prey movement, or looming motion, such as might be elicited by an approaching predator, has been observed in RGCs in several species (Lettvin et al. 1959; Münch et al. 2009; Ölveczky, Baccus, and Meister 2003; Temizer et al. 2015). However, motion inherently produces spatiotemporal fluctuations in contrast—a visual feature many RGCs are sensitive to. The degree to which many of these RGCs represent a dedicated channel for motion features, versus encoding motion de facto, is unclear.

Object Motion Sensitive RGCs

Functional studies have identified RGCs tuned for differential motion (Baccus et al. 2008; Ölveczky, Baccus, and Meister 2003). These RGCs, dubbed object motion sensitive (OMS), are responsive to motion in any direction within their receptive field center, but only if the receptive field surround is static or has a different motion trajectory. Previously characterized RGCs featuring strong surround suppression and tuning for small edges, dubbed local edge detectors (LEDs), likely constitute some fraction of the OMS RGC population (Lettvin et al. 1959; Levick 1967; Van Wyk, Taylor, and Vaney 2006). In mice, a population of LEDs has been identified in the W3 transgenic line that feature small receptive field centers ~4° in diameter and strong tuning for differential motion of small objects (Y. Zhang et al. 2012). These W3 RGCs stratify between ON and OFF sublaminae and are responsive for both light increments and decrements. Another OMS RGC, called a high-definition type 1 (HD1) RGC, has been functionally identified and exhibits similar morphological characteristics but higher and less sustained firing rates (Jacoby and Schwartz 2017). These OMS RGCs densely populate the retina and comprise approximately 15% of all RGCs in rabbits and mice (Van Wyk, Taylor, and Vaney 2006; Y. Zhang et al. 2012). W3 RGCs project to a narrow superficial layer of the SC, but characterizing the full projection patterns of these cells has not been possible due to nonspecific labeling in the mouse line (I. J. Kim et al. 2010; Krishnaswamy et al. 2015).

Transient Off Alpha RGCs

Long thought of as a general-purpose luminance encoder, transient OFF alpha (tOFFα) RGCs have recently been identified as encoding a number of motion features (E. Y. Chen et al. 2013; Leonardo and Meister 2013). Described as classic center-surround spot detectors, tOFFα RGCs have analogs in many species, each featuring brisk responses shortly after decrements of

light (Murphy-Baum and Taylor 2018; Sanes and Masland 2015). tOFFα RGCs have distinctively large somas and sprawling arbors in the OFF sublamina that cover about 10° of the visual field in mice. While tOFFα RGCs are not tuned for directional motion, a number of recent studies have revealed surprising tOFFα RGC motion-related response properties. For example, looming stimuli, wherein a dark spot quickly expands, produce much larger responses than contracting stimuli (Münch et al. 2009). When presented with rapid image transitions, such as might be encountered during fixational eye movements, tOFFα RGCs show a strong sensitivity to image recurrence, thereby spiking much more strongly to a repeat presentation of an image than to new images (Krishnamoorthy, Weick, and Gollisch 2017). Further, tOFFα RGCs' spiking appears to weakly encode the velocity of distant moving objects. Object position is strongly encoded by spiking activity when the object is within the receptive field, and thus tOFFα RGCs multiplex several image features in the activity of one cell type (Deny et al. 2017). Motion sensitivity has also been directly demonstrated in OFF parasol RGCs, the primate retina analog to tOFFα RGCs (Appleby and Manookin 2020; Manookin, Patterson, and Linehan 2018). In mice, tOFFα RGCs project exclusively to the contralateral SC and dLGN and target specific lamina distinct from DSGCs (Huberman, Feller, and Chapman 2008).

Motion Sensing Amacrine Cells

While many studies have achieved varying degrees of success in characterizing the totality of the RGC population, progress toward cataloging the full breadth of amacrine cells has been slower (Diamond 2017; Masland 2012). Nonetheless, several prominent amacrine cell types have been identified that play key roles in retinal motion processing. Some of these amacrine cells are themselves motion sensors; thus, they allow RGCs to effectively inherit selectivity for the features to which amacrine cells are tuned. The full feature tuning of an RGC is then formed by the complement of its incident bipolar and amacrine cell inputs and the interactions between the input cells. By enacting computations prior to the RGC layer, a single amacrine cell type is able to subserve the feature tuning of diverse retinal outputs (Briggman, Helmstaedter, and Denk 2011; Lee et al. 2016; Park et al. 2015).

Starburst Amacrine Cells

Recognized in early studies for their distinct, radially symmetric morphology, starburst amacrine cells (SACs) form the basis of DSGC directional tuning. Each dendritic branch of the SAC forms a distinct computational unit with its own inputs and outputs. Branches preferentially respond to centrifugal motion outward from the soma, and in so doing form a local map of directional motion (Euler, Detwiler, and Denk 2002). SACs form GABAergic synapses with DSGCs and also release acetylcholine via a paracrine mechanism (Wei 2018). There are two types of SACs, dubbed ON and OFF SACs, which respectively are selective for light increments and decrements—though these pathways are not completely independent (Rosa et al. 2016).

ON and OFF SAC morphology is mirror symmetric, and SACs narrowly stratify on opposite sides of the inner plexiform layer. This narrow stratification, combined with the exclusive expression of choline acetyltransferase by SACs in the retina, has made SACs a frequent reference point for ON and OFF sublaminae in immunohistochemical experiments. In mice, SAC arbors span about 9° of the visual field, though the functional subunits of SAC

computation are smaller due to the compartmentalized nature of their dendrites (Müller, Shelley, and Weiler 2007; Poleg-Polsky, Ding, and Diamond 2018). SACs are among the most densely packed cells of the mammalian retina, with each point in retinal space covered by the dendrites of 30 to 70 SACs (Keeley et al. 2007; D. I. Vaney 1984). This density is critical for the successful computation of motion direction by DSGCs (Morrie and Feller 2018; Soto et al. 2019).

Although the presence of DSGCs in primate retinas remains controversial, SACs have been identified in human and nonhuman primate retinas (Rodieck 1989; Rodieck and Marshak 1992). A mutation in the *FRMD7* gene in mice, which is selectively expressed in SACs, causes loss of horizontally oriented direction selectivity and horizontal optokinetic reflexes (Yonehara et al. 2016). Mutations in the *FRMD7* gene in humans are likewise associated with congenital nystagmus and a lack of horizontal optokinetic reflexes, suggesting a functional role of SACs in primate eye movements.

VGluT3+ Amacrine Cells

One of the rare excitatory amacrine cell types, vesicular glutamate transporter type-3 expressing amacrine cells (vGluT3+ ACs) are motion sensitive and are involved in a number of motion-processing RGC circuits. vGluT3+ ACs are multistratified throughout the inner plexiform layer and feature mostly isolated dendrites that locally process ON or OFF inputs (Haverkamp and Wässle 2004; Hsiang et al. 2017; J. Johnson et al. 2004). Each point in retinal space is covered by the dendrites of about seven vGluT3+ ACs (T. Kim, Soto, and Kerschensteiner 2015). The dendritic arbors of a vGluT3+ AC span approximately 3° of the visual field, while individual neurites feature slightly smaller receptive fields (Grimes et al. 2011; Hsiang et al. 2017). vGluT3+ ACs respond robustly to differential motion in any direction, but they receive strong surround inhibition for stimuli anywhere from 3° to 30° beyond their receptive field center (Grimes et al. 2011; T. Kim, Soto, and Kerschensteiner 2015; Lee et al. 2014). ON DSGCs, ON–OFF DSGCs, W3 RGCs, and OFF alpha RGCs all receive glutamatergic innervation from vGluT3+ ACs, with W3 RGCs in particular receiving half of their excitatory drive from vGluT3+ AC inputs (T. Kim, Soto, and Kerschensteiner 2015; Krishnaswamy et al. 2015; Lee et al. 2014, 2016). vGluT3+ ACs additionally form selective glycinergic synapses with suppressed-by-contrast RGCs and a class of wide-field polyaxonal amacrine cells (Jia et al. 2020; Knop et al. 2011; Lee et al. 2016; Tien, Kim, and Kerschensteiner 2016).

TH2 Amacrine Cells

Another amacrine cell type has been implicated in differential motion tuning, the tyrosine hydroxylase promoter-driven type 2 amacrine cell (TH2 AC). TH2 ACs depolarize to both increments and decrements in light, are bistratified, and have large dendritic fields 20° to 30° in diameter (Knop et al. 2011; D. Q. Zhang et al. 2004). While the amplitudes of TH2 AC depolarizations are largely similar for global versus local motion, the spatial extent of motion induces changes in the kinetics of TH2 AC depolarizations. Local, spatially restricted motion produces slowly ramping depolarizations, while full-field global motion produces fast depolarizations (T. Kim and Kerschensteiner 2017; Knop et al. 2011). TH2 ACs form a network

of homologously gap junction–coupled cells and form GABAergic synapses onto W3 RGCs, vGluT3+ ACs, an unidentified ON–OFF RGC, and presynaptic bipolar cells (Brüggen et al. 2015). Conditional knockout of vesicular GABA transporters in TH2 ACs has minimal effect on vGluT3+ ACs but substantially reduces surround inhibition in W3 RGCs and eliminates preference for local motion over global motion (T. Kim and Kerschensteiner 2017).

Mechanisms of Motion Computation

The diverse motion sensors of the retina employ a number of mechanisms to shape signals into tuned outputs. Sequential computation wherein motion-tuned amacrine cells provide input to RGCs allows for layering of mechanisms to confer additional selectivity at the retina's output. However, as amacrine cells often compute motion signals de novo, the mechanisms by which they generate asymmetries often differ from those of RGCs. The mechanisms by which direction selectivity is generated first in the dendrites of SACs, and then subsequently in the axons of DSGCs, are discussed herein, along with a more limited discussion of the less thoroughly described mechanisms of nondirectional motion signaling.

Centrifugal Motion Preference in SACs

Direction-selective computations by the retina's canonical DSGCs are dependent upon GABA release from SACs (Figure 2A). Manipulations that remove these inhibitory inputs via SAC ablation, pharmacogenetic suppression, knockout of vesicular trafficking machinery, or disruption of SAC dendritic development, all lead to severe reductions of direction selectivity in DSGCs (Wei 2018). Tuning of canonical DSGCs is dependent on two key facets of SAC output. First, SAC processes themselves are direction selective, and exhibit larger calcium influx at release sites for centrifugal motion outward from the soma than centripetal motion inward toward the soma (Mauss et al. 2017). Recent data indicate that the compartmentalized nature of SAC dendrites means that each SAC is comprised of several distinct motion sensors, each with its own preferred direction of motion in the visual field (Morrie and Feller 2018; Poleg-Polsky, Ding, and Diamond 2018). Second, each SAC motion sensor preferentially forms inhibitory synapses with distinct subtypes of DSGCs, whereby the DSGC's null direction corresponds to the SAC dendrite's preferred direction (Briggman, Helmstaedter, and Denk 2011). Thus, each subtype of DSGC receives asymmetric inhibition such that null direction motion is suppressed relative to preferred direction motion.

Several mechanisms underlie the direction selectivity of SAC dendritic compartments. These mechanisms can be broadly categorized as falling into three groups: SAC intrinsic dendritic mechanisms, bipolar-cell-driven space–time wiring mechanisms, and lateral interactions between amacrine cells (see Figure 2B).

Dendritic Mechanisms

The idea that dendrites confer directional integration properties was first proposed by Wilfrid Rall (1964), who noted that sequential activation of excitatory inputs toward a cell's soma would lead to larger somatic depolarizations than sequential activation away from the soma. SACs apply this principle in reverse: SAC dendrites contain synaptic inputs along the

length of the process and release sites at the distal tips, and thus centrifugally directed sequential activation leads to greater release at the SAC's distal output synapses. Voltage-gated channels and a spatial gradient of chloride pumps are proposed to further contribute to this asymmetry by nonlinearly integrating synaptic inputs (Mauss et al. 2017).

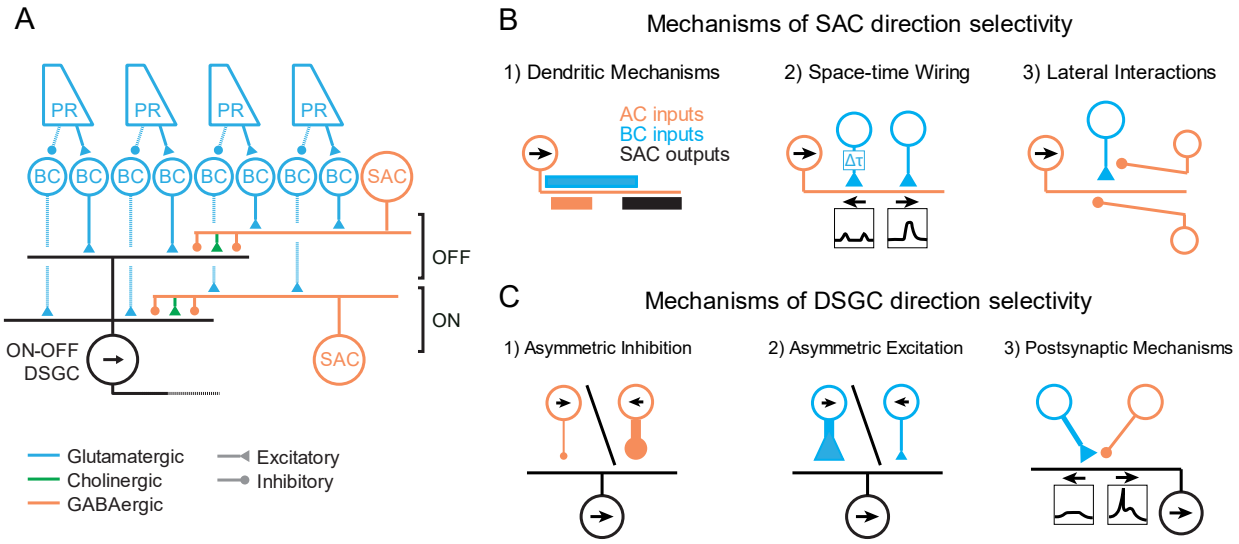


Figure 2. Visual motion detection in the mammalian retina.
(a) Schematic of the mammalian retinal circuit elements for direction selectivity. Photoreceptor (PR) signals are split into ON and OFF pathways at the level of bipolar cells (BC) via divergent glutamate receptor expression. ON and OFF BCs respectively synapse onto ON and OFF SACs, and jointly onto ON–OFF DSGCs. DSGCs receive additional asymmetric GABAergic and symmetric cholinergic input from SACs. Note that only select aspects of the connectivity are captured in this simplified schematic (modified from Mauss et al., 2017). (b) Overview of mechanisms underlying SAC centrifugal motion preference. (C) Same as B, but for DSGC direction selectivity.

The amplification of distally directed motion is further enhanced by the arrangement of glutamatergic inputs onto SAC processes. In mice, glutamate receptors are skewed toward the soma, and thus away from release sites (Ding et al. 2016; Vlasits et al. 2016). Computer simulations suggest that this input arrangement increases the electrical resistance at dendritic tips and thus contributes to larger depolarizations at the SAC's release sites for centrifugal motion (Vlasits et al. 2016). The same skewed input distribution has not been observed in rabbits, which have a uniform distribution of inputs (Wei 2018). Species differences in SAC input distributions might be due to the different angular velocities of motion experienced by animals with different eye diameters (Ding et al. 2016).

Electrical isolation of SAC processes for independent computation is another key aspect of SAC function. Global integration across the entirety of a SAC's dendritic arbors would eliminate the ability of distinct DSGC subtypes to read out null direction motion from a single population of general-purpose SACs. Cross-compartmental isolation is proposed to be achieved via perisomatic potassium channel shunting and metabotropic glutamate receptor- mediated

inhibition of voltage-gated calcium channels, which thus limit depolarizations to centripetal motion (Koren, Grove, and Wei 2017; Ozaita et al. 2004).

Space–Time Wiring

Although bipolar cells themselves are not motion tuned, careful arrangement of bipolar cells with different kinetics is capable of producing tuning postsynaptically. In the space–time wiring model of SAC computation, bipolar cells with slow-release kinetics are located proximal to the soma, while bipolar cells with faster kinetics are located more distally. In this configuration, outward motion leads to summation of slow proximal and fast distal depolarizations, whereas signals for inward motion are misaligned and lead to minimal summation due to dissipation of fast distal depolarizations before soma-proximal synapses are activated. Serial EM and physiological studies have found evidence of a space–time wiring model implemented in the dendrites of OFF SACs (Ding et al. 2016; Fransen and Borghuis 2017; Greene, Kim, and Seung 2016; J. S. Kim et al. 2014). Evidence of space–time wiring in ON SACs has been mixed, however. Spatial separation of different bipolar cell subtypes synapsing onto ON SACs has been noted in EM studies, but the subtypes appear to have only minor differences in their response kinetics (Fransen and Borghuis 2017; Ichinose, Fyk-Kolodziej, and Cohn 2014; Stincic, Smith, and Taylor 2016; Vlasits et al. 2016).

Lateral Interactions

Inhibition onto SACs also plays a modest role in generating dendritic direction selectivity. In mice, pharmacological blockade of GABA-A receptors reduces SAC dendrite direction selectivity for high-contrast stimuli but has a limited effect on tuning for low-contrast motion (Ding et al. 2016; Poleg-Polsky, Ding, and Diamond 2018; Vlasits et al. 2016). Blockade of GABA-A receptors has produced mixed results in rabbits, ranging from having no effect, to complete abolition of SAC direction selectivity (Wei 2018). These differences may reflect differing roles of GABA inhibition in different stimulus regimes, or off-target effects of pharmacological manipulations on presynaptic bipolar cells.

Targeted genetic manipulations have also been used to isolate the direct impact of inhibition on SAC processes. Conditional knockout of the α2 subunit of GABA-A receptors in SACs leads to a reduction of tuning in OFF, but not ON, SACs, though ON SAC tuning in this mouse is impaired when noise is introduced via a background stimulus undergoing a stationary flicker (Q. Chen et al. 2016). Interestingly, SAC-specific knockout of vesicular GABA transporters has minimal effect on either ON or OFF SACs, despite EM studies finding that SACs account for over 90% of the amacrine cell inputs onto other SACs (Q. Chen et al. 2016; Ding et al. 2016). Thus, reciprocal inhibition between SACs is not likely to be a major driver of tuning, and inhibitory inputs influencing tuning of OFF SACs likely come from other amacrine cell sources.

RGC Mechanisms of Direction Selectivity

The dendrites of SACs form a high-density map of motion direction throughout the retina, which is read out by selectively wired subtypes of canonical DSGCs. The SAC network

contributes to the spatiotemporal patterns of excitation and inhibition DSGCs receive, asymmetries in which confer tuning. Additional circuit mechanisms reinforce the directional tuning, and perhaps generate tuning de novo in noncanonical DSGCs. The mechanisms can be coarsely split into three categories: those providing asymmetric inhibition, those providing asymmetric excitation, and postsynaptic mechanisms (see Figure 2C).

Asymmetric Inhibition

Due to SACs' centrifugal motion preference and selective wiring to DSGCs, motion in the null direction provides greater inhibition to canonical DSGCs than motion in the preferred direction. Inhibitory synapse formation on a DSGC's null side—the side of a DSGC from which null directed motion will originate—ensures that DSGC null motion will align with SAC centrifugal motion preference, and thus elicit strong inhibition. Conversely, preferred direction motion activates SAC dendrites centripetally and provokes weak inhibition. Manipulations that block DSGC GABA receptors or that silence SAC outputs substantially diminish tuning, making most DSGCs equally responsive to motion in all directions (Hillier et al. 2017; David I. Vaney, Sivyer, and Taylor 2012; Vlasits et al. 2014). Other non-SAC amacrine cells additionally provide DSGCs with isotropic inhibition, which shapes the structure of receptive fields in ways that are not yet fully understood (Morrie and Feller 2018; Park et al. 2015; Pei et al. 2015).

Asymmetric Excitation

Voltage-clamp recordings have also shown asymmetric excitation in canonical DSGCs, wherein larger excitatory conductances are observed for preferred direction motion than for null directed motion (Pei et al. 2015; David I. Vaney, Sivyer, and Taylor 2012). Canonical DSGCs integrate both glutamatergic and cholinergic excitatory inputs, the former arriving from a combination of bipolar cells and vGluT3+ ACs, the latter provided by SACs (Wei, 2018). The relative roles of these neurotransmitters appear to vary across stimulus conditions, and perhaps across species. Bipolar cell inputs to SACs show higher contrast sensitivity than corresponding DSGC inputs, and thus cholinergic inputs from SACs are the dominant source of DSGC excitation under low-contrast visual conditions (Poleg-Polsky and Diamond 2016b; Sethuramanujam et al. 2016, 2017). In high-contrast conditions, the magnitudes of glutamatergic and cholinergic excitation are roughly equal.

Tuning has been observed in voltage-clamp experiments where glutamatergic inputs onto canonical DSGCs have been pharmacologically isolated, but tuning is not seen in bipolar cell terminal calcium imaging or glutamate imaging experiments (Fried, Münch, and Werblin 2005; Lee, Kim, and Zhou 2010; Park et al. 2014; Yonehara et al. 2013). This discrepancy has led some to suggest that excitatory tuning is a voltage clamp artifact of poor space clamp, wherein large null direction inhibition causes an underestimate of null direction excitation (Park et al. 2014; Poleg-Polsky and Diamond 2011). However, such a hypothesis predicts that larger, or more asymmetric, inhibitory conductances should produce greater tuning of excitatory inputs, and no such correlations have been observed (Pei et al. 2015; Percival et al. 2019). Tuning is abolished upon application of GABA receptor antagonists but remains in SAC-specific vesicular GABA transporter knockout mice, implying that non-SAC amacrine cells may generate excitatory tuning via presynaptic inhibition (Fried, Münch, and Werblin 2005; Lee, Kim, and

Zhou 2010; Park et al. 2014; Pei et al. 2015). In ON DSGCs, glutamatergic inputs have also been implicated in generating asymmetric excitation via a mechanism analogous to space–time wiring in SACs. One study presents physiological evidence and partial EM reconstructions of ON DSGC dendrites hinting that fast bipolar cells synapse on the null side of ON DSGCs, while slower bipolar and glutamatergic amacrine cells populate the preferred side, thus leading to summation for preferred, but not null directed, motion (Matsumoto, Briggman, and Yonehara 2019).

Cholinergic excitation tuning has been reported in rabbit, but not mouse, retinas (Fried, Münch, and Werblin 2005; Lee, Kim, and Zhou 2010; Park et al. 2014; Sethuramanujam et al. 2016). Interestingly, despite preferential wiring of SAC inhibitory synapses onto the null side of DSGCs, SAC–DSGC paired recordings show similar cholinergic excitation with stimulation of either preferred or null side pairs, implying acetylcholine release via a paracrine mechanism (Briggman, Helmstaedter, and Denk 2011; Lee, Kim, and Zhou 2010; Pei et al. 2015). This introduces a spatial offset of excitation and inhibition, wherein preferred motion yields cholinergic excitation via paracrine release before inhibitory synapses are activated, whereas null motion shunts excitation via simultaneous inhibitory input (Hanson et al. 2019; Sethuramanujam et al. 2016). Thus, asymmetries in the timing of cholinergic excitation contribute to DSGC tuning, even when the amplitude of excitation is untuned.

Postsynaptic Mechanisms

Weakly tuned presynaptic inputs can generate robust DSGC tuning after amplification via a number of postsynaptic mechanisms. Nonlinear conductances due to voltage-gated ion channels sharpen tuning by generating dendritic spikes, and thus slightly larger depolarizations for preferred relative to null direction motion can produce substantially different spiking outputs (Wei 2018). DSGC selectivity is maintained across input conditions by multiplicative scaling of synaptic inputs, meaning that preferred direction depolarizations remain larger than null depolarizations by the same proportion. This is achieved by a combination of tuned inhibition shunting null direction excitation and voltage-dependent NMDA receptor conductances (Poleg-Polsky and Diamond 2016a; Sethuramanujam et al. 2017). Recent work suggests that local dendritic processing and tight alignment of cholinergic and GABAergic inputs ensure shunting of null direction excitation (Jain et al. 2020). These mechanisms ensure consistent DSGC output across diverse visual conditions.

Dendritic asymmetries also contribute to tuning in a subset of DSGCs and are present in all noncanonical DSGCs (I. J. Kim et al. 2008; Rousso et al. 2016; Trenholm et al. 2011). Asymmetric ventrally oriented ON–OFF DSGCs maintain direction selectivity in the presence of GABA-A receptor antagonists, whereas most DSGCs show substantially reduced selectivity (El-Quessny, Maanum, and Feller 2020; Trenholm et al. 2011). Modeling has suggested that outward Rall integration coupled with voltage superlinearities at distal tips could confer inhibition-independent tuning (Trenholm et al. 2011). Noncanonical DSGCs do not cofasciculate with SACs and might similarly implement directional dendritic integration (I. J. Kim et al. 2008; Rousso et al. 2016). Ventrally oriented ON–OFF DSGCs are also the only known direction-selective RGCs to form a network of homologously gap-junction-coupled cells, which may

additionally promote dendritic spiking and accurate encoding of the position of moving objects (Trenholm, Schwab, et al. 2013; Trenholm, McLaughlin, et al. 2013; Yao et al. 2018).

Nondirectional Motion Mechanisms

While mechanisms of nondirectional motion tuning have not received the same degree of concerted research focus as direction selectivity, recent work has lent insight into circuit mechanisms of these computations. In the OMS W3 circuit in particular, a circuit model has emerged wherein presynaptic vGluT3+ and TH2 ACs provide excitatory and inhibitory drive and are themselves respectively tuned for local and global motion. Selectivity for spatially restricted motion in vGluT3+ ACs is mediated by pre- and postsynaptic surround suppression and is abolished by tetrodotoxin application, implicating spiking amacrine cells (T. Kim, Soto, and Kerschensteiner 2015). The source of global motion tuning in the depolarization kinetics of TH2 ACs is unclear, but faster responses appear to more effectively drive neurotransmitter release, leading to greater postsynaptic inhibition in W3 cells (T. Kim and Kerschensteiner 2017). TH2 AC kinetics further enables W3 RGC tuning by introducing a temporal offset, whereby TH2 AC–mediated inhibition of W3 RGCs lags excitation during local motion stimulation but shunts excitation during global motion (Baccus et al. 2008; T. Kim and Kerschensteiner 2017; Y. Zhang et al. 2012). Additional roles of presynaptic inhibition or adaptation of bipolar cell inputs have also been implicated in sharpening tuning for local motion in OMS circuits more generally (Baccus et al. 2008; Ölveczky, Baccus, and Meister 2007; Venkataramani et al. 2014).

Conclusions

Visual motion signals are a critical component of an animal's sensory experience. Diverse motion sensors both at the retina's output and within its intermediate circuitry employ an array of mechanisms to parse the external world into parallel motion channels. Active research into motion-tuning mechanisms within the retina continues to elucidate the principles by which the early visual system sculpts low-level sensory information into behaviorally relevant signals about the natural world.

Chapter 2: Distinct Inhibitory Pathways Control Velocity and Directional Tuning in the Retina

A version of this work has been submitted for publication, and will appear on bioRxiv.

Summers, M. T., Feller, M.B. Distinct Inhibitory Pathways Control Velocity and Directional Tuning in the Retina.

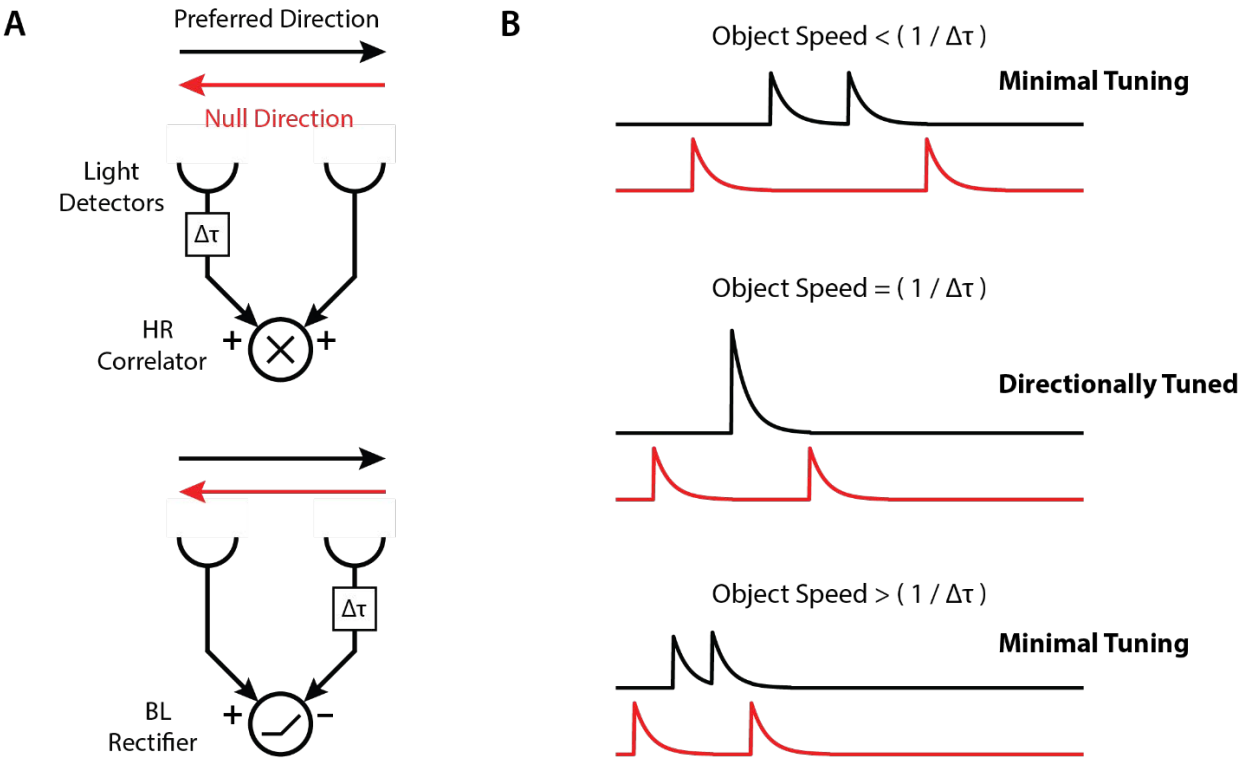
Summary

The sensory periphery is responsible for detecting ethologically relevant features of the external world, using compact, predominantly feedforward circuits. Visual motion is a particularly prevalent sensory feature, the presence of which can be a signal to enact diverse behaviors ranging from gaze stabilization reflexes, to predator avoidance or prey capture (Summers, El Quessny, and Feller 2021; Seabrook et al. 2017; Yilmaz and Meister 2015). To understand how the retina constructs the distinct neural representations required for these diverse behaviors, we investigated two circuits responsible for encoding different aspects of image motion: ON and ON-OFF direction selective ganglion cells (DSGCs). Using a combination of 2-photon targeted whole cell electrophysiology, pharmacology, and conditional knockout mice, we show that distinct inhibitory pathways independently control tuning for motion velocity and motion direction in these two cell types. We further employ dynamic clamp and numerical modeling techniques to show that asymmetric inhibition provides a velocity-invariant mechanism of directional tuning, despite the strong velocity dependence of classical models of direction selectivity (Tukker, Taylor, and Smith 2004; Borst and Euler 2011; Frye 2015). We therefore demonstrate that invariant representations of motion features by inhibitory interneurons act as computational building blocks to construct distinct, behaviorally relevant signals at the earliest stages of the visual system.

Introduction

Rather than acting as a simple camera forming a pixel-by-pixel map of image luminance, the mammalian retina is comprised of diverse arrays of feature detectors, each encoding distinct components of the visual scene such as color, oriented edges, or motion (Baden et al. 2016; Summers, El Quessny, and Feller 2021). These output channels convey visual information to differing brain regions to mediate appropriate behaviors, such as pupillary light reflexes, looming responses, or optokinetic reflexes (Seabrook et al. 2017). Directional image motion is a particularly ubiquitous feature which is encoded for by an estimated 35% of the mouse retina's output neurons (Bos, Gainer, and Feller 2016). However, different DSGC types meet different behavioral demands, and thus encode different types of motion. ON DSGCs project to the accessory optic system, and are thought to mediate gaze stabilizing reflexes by encoding low velocity, global motion (Wyatt and Daw 1975; Yonehara et al. 2008; Dhande and Huberman 2014). ON-OFF DSGCs on the other hand target the image-forming brain regions of the superior colliculus and lateral geniculate nucleus, and are thought to encode local object motion across a broad range of velocities (Barlow, Hill, and Levick 1964; Grzywacz and Amthor 2007; Huberman et al. 2009). How the retina constructs distinct representations of sensory features

using a limited pool of largely feedforward interneurons remains an active area of research (Sivyer, Van Wyk, et al. 2010; Lipin, Rowl Taylor, and Smith 2015).



Extended Figure 1. Canonical models of direction selectivity are critically dependent on motion speed. (a) Mechanistic models of direction selectivity, (*top*) Hassenstein-Reichardt Correlator and (*bottom*) Barlow-Levick Rectifier. Both models depend upon comparing signals from spatially offset subunits with a differential time delay Δt. (b) Example activity traces instantiating a Hassenstein-Reichardt Correlator model in response to preferred and null directed object motion. Directional tuning is the ability to generate substantially different responses for preferred versus null direction motion.

Biophysical constraints render the generation of directionally selective responses particularly mysterious (Extended Fig. 1). Theoretical models of direction selectivity depend upon comparing spatially offset luminance signals with some time delay; this time delay should impose strong velocity tuning on the effective generation of directionally tuned responses (J. S. Kim et al. 2014; Fransen and Borghuis 2017). However, different DSGC types show a range of different velocity tunings, perhaps implying the use of multiple mechanisms for computing directional motion, each implemented at different speeds (Grzywacz and Amthor 2007; Borst and Euler 2011; Matsumoto, Briggman, and Yonehara 2019; Trenholm et al. 2011). We sought to leverage the respective tuning of ON and ON-OFF DSGCs for low and high velocity directional motion to understand how biophysical mechanisms might contribute differentially to tuning across a range of speeds that spanned the lower bound of optokinetic reflex tuning to the upper end of saccade-like velocities (Kretschmer et al. 2017; Sakatani and Isa 2007). Surprisingly, we found that a single mechanism mediated by starburst amacrine cells (SACs)

provides velocity invariant directional tuning, while a glycinergic amacrine cell source independently controls velocity tuning.

Materials and Methods

Animals

All animal procedures were approved by the UC Berkeley Institutional Animal Care and Use Committee and conformed to the NIH Guide for the Care and Use of Laboratory Animals, the Public Health Service Policy, and the SFN Policy on the Use of Animals in Neuroscience Research. Retinas from adult mice (P28-P80) of either sex were prepared as previously described(Wei et al. 2011), but in brief were dissected under infrared illumination, mounted over a 1-2 mm^2 hole in filter paper, and stored in oxygenated Ames' media in the dark at room temperature. ON DSGCs were targeted for current clamp, voltage clamp, and dynamic clamp experiments in Hoxd10-GFP (Tg(Hoxd10-EGFP)LT174Gsat/Mmucd) animals (Dhande et al. 2013), which were sometimes crossed with *Vgat*$^{flox/flox}$ (*Slc32a1<tm1Lowl>/J*) or *ChAT-IRES-Cre* (129S6-*Chat*$^{tm2(cre)Lowl}$/J) mice. ON-OFF DSGCs were targeted in these mice, and additionally in Trhr-GFP (B6;FVB-Tg(Trhr-EGFP)HU193Gsat/Mmucd) and Drd4-GFP (Tg(Drd4-EGFP)W18Gsat/Mmnc) mice (Rivlin-Etzion et al. 2011; Huberman et al. 2009). Similar responses were observed for cells recorded from each of these different transgenic lines. Knockout experiments were performed on Hoxd10 / *Vgat*$^{flox/flox}$ / *ChAT-IRES-Cre* mice, which were generated by crossing each line. ON and ON-OFF DSGCs were distinguished in Hoxd10 lines on the basis of response polarity to a brief light step and morphological stratification.

Two-photon targeted whole-cell recordings

Retinas were placed under the microscope in oxygenated Ames' medium at 32– 34°C. GFP+ cells were identified using a two-photon microscope tuned to 920 nm to minimize bleaching of photoreceptors. The inner limiting membrane above the targeted cell was dissected using a glass electrode. Current clamp and dynamic clamp recordings were conducted with internal solution composed, in mM, of: 115 K+ gluconate, 9.7 KCl, 1 MgCl2, 0.5 CaCl2, 1.5 EGTA, 10 HEPES, 4 ATP-Mg2, 0.5 GTP-Na3, 0.025 TexasRed (pH = 7.2 with KOH, osmolarity = 290). Voltage clamp recordings were performed with internal solution containing the following, in mM: 110 CsMeSO4, 2.8 NaCl, 20 HEPES, 4 EGTA, 5 TEA-Cl, 4 Mg-ATP, 0.3 Na3GTP, 10 Na2Phosphocreatine, 5 QX-Br, 0.025 Texas Red (pH = 7.2 with CsOH, osmolarity = 290). Holding voltages for measuring excitation and inhibition after correction for the liquid junction potential (-10 mV) were −60 mV and 0 mV, respectively. Signals were acquired using pCLAMP 9 recording software and a Multiclamp 700A amplifier (Molecular Devices), sampled at 10 kHz, and low-pass filtered at 6 kHz. Strychnine experiments were performed in Ames' media with 2 μM strychnine hydrochloride (Sigma-Aldrich).

Visual stimuli

Visual stimuli were generated via custom MATLAB functions written with Psychophysics Toolbox on a computer running a 60 Hz DMD projector (EKB Technologies) with a 485 nm LED light source. The DMD image was projected through a condenser lens, and aligned on each

experimental day to the photoreceptor layer of the sample. All stimulus protocols were centered on the soma of the recorded cell, and were presented after at least 10 seconds of adaptation on a dark background (9.4 x 10^3 R*/rod/s). Bars, gratings, and dots were all of positive contrast, and equal intensity (2.6 x 10^5 R*/rod/s).

Baseline direction selectivity was first assessed with 100 μm (3.2 °) wide by 650 μm (21 °) long bars moving at either 200 μm/s or 500 μm/s (6.5 °/s and 16.1 °/s respectively). Responses were recorded for at least 3 repetitions of bars moving in 8 block shuffled directions, each separated by 45 degrees. Online analysis was then used to determine a DSGC's preferred direction for velocity stimuli: for current clamp, this was the vector sum angle of spike counts, for voltage clamp, this was 180 degrees offset from the vector sum angle of IPSC magnitudes. For voltage clamp experiments on knockout mice lacking directional inhibition, two orthogonal "preferred" and "null" axes were used for velocity experiments to ensure at least four total directions were probed for residual tuning.

Elongated moving bars and drifting gratings were presented for at least 3 repetitions in preferred and null directions at block shuffled velocities. Moving bars were 100 μm (3.2°) wide and ranged from 150 - 1800 μm/s (4.8 - 58.1 °/s). Drifting gratings were presented for 6 seconds each within a 300 μm radius mask, and had a 250 μm spatial period. Temporal frequencies were varied from 0.2 to 7.2 cycles/sec (1.6 - 58.1 °/s).

Random dot kinetogram (RDK) stimuli matched previously described parameters(Marques et al. 2018). Direction selectivity in response to RDK motion was assessed similarly to baseline measurements, with at least 3 repetitions of RDKs moving in 8 block shuffled directions. RDK stimuli were presented for 5 seconds each at 20% density and were 100% coherent. Individual dots were 62 μm (2 °) in diameter and moved at 775 μm/s (25 °/s).

Dynamic clamp

We constructed a microcontroller based dynamic clamp device following published specifications (Desai, Gray, and Johnston 2017), also found on dynamicclamp.com. The current (I) delivered to a cell was calculated as:

$$I(t) = G_{Exc}(t) * (V(t - \Delta t) - E_{Exc}) + G_{Inh}(t) * (V(t - \Delta t) - E_{Inh})$$

Where G_{Exc} and G_{Inh} are the respective time varying conductance traces for excitation and inhibition recorded from elongated bar visual stimuli, V is the cell membrane potential, and E_{Exc} and E_{Inh} are 0 mV and −60 mV reversal potentials respectively. Conductances used as dynamic clamp inputs were taken from individual cells and were averaged over 3 trials for each velocity of visual stimulus. At least 3 repetitions of preferred and null direction conductances were presented for dynamic clamp experiments, at block shuffled velocities.

Conductance modeling

The contributions of synaptic conductances to tuned depolarizations were simulated via a parallel conductance model implemented in MATLAB (Wehr and Zador 2003). Conductances G_{Exc} and

G_{Inh} used as model inputs were taken from individual cell voltage clamp recordings in response to elongated drifting bars, and were rectified and trial averaged for each velocity of visual stimulus. For each velocity, a simulated cell's voltage time series trace was numerically integrated via the forward Euler method:

$$V(t + \Delta t) = V(t) + dV/dt * \Delta t$$

Where dV / dt was derived from the current flow across an RC circuit with empirically determined values for capacitance C_m (80 pF), resting conductance G_{Leak} (4.2 nS) and resting membrane potential E_{Leak} (−55 mV):

$$dV/dt = [\, G_{Exc}(t) * (V(t) - E_{Exc}) + G_{Inh}(t) * (V(t) - E_{Inh}) + G_{leak} * (V(t) - E_{leak}) \,] / C_m$$

The amplitude of simulated depolarizations was compared between preferred and null directions, and direction selectivity indices were calculated at each speed.

Manipulations of specific tuning mechanisms were made by swapping or shifting in time the conductances used to integrate voltage. In each case, fractional loss of directional selectivity was assessed for a simulated cell at a given velocity via:

$$DS\ Loss = (DS_{Original} - DS_{Manipulation}) / DS_{Orignal}$$

Where $DS_{Original}$ and $DS_{Manipulation}$ are the direction selectivity indices (see below) of a simulated cell at a given velocity.

The impact of three model manipulations was assessed. (1) Removal of asymmetric excitation was simulated by integrating null direction depolarizations as normal, but substituting in null for preferred direction excitation when integrating preferred direction depolarizations. This null swapped excitation was appropriately shifted in time so as to preserve the same preferred direction timing offset between peak excitation and inhibition. (2) Removal of differential timing offsets was simulated by integrating null direction depolarizations as normal, but shifting preferred direction inhibition (almost exclusively forward) in time to match the excitation and inhibition timing offsets measured in the null direction. (3) Removal of asymmetric inhibition was simulated by integrating preferred direction depolarizations as normal, but substituting in preferred for null direction inhibition when integrating null direction depolarizations. This preferred swapped inhibition was appropriately shifted in time so as to preserve the same null direction timing offset between peak excitation and inhibition.

Analysis

Analysis was performed using custom MATLAB scripts. All analyses of drifting bar stimuli were restricted to the ON window immediately subsequent to a bar entering the DSGC's receptive field. Grating and RDK analyses utilized the full period for which a stimulus was present.

Instantaneous firing rates were determined from current clamp and dynamic clamp data via kernel density estimation with a 200 ms Gaussian kernel. Peak firing rate was then taken to be the maximal instantaneous firing rate achieved within the analysis window. Voltage clamp data was baseline subtracted and lowpass filtered at 30 Hz. Peak current amplitudes and total charge transfer were calculated within the aforementioned analysis window. Depolarizations were measured from current clamp data by removing spiking activity via lowpass filtering at 20 Hz, and then measuring amplitude by baseline subtraction.

Directional selectivity indices were calculated from responses to preferred (R_{Pref}) and null (R_{Null}) direction motion as:

$$DS\ Index = (R_{Pref} - R_{Null}) / (R_{Pref} + R_{Null})$$

For current clamp and dynamic clamp recordings, responses were measured from peak firing rate. Peak EPSC and IPSC magnitudes were used for voltage clamp recordings. The signs of DSIs calculated from IPSCs were flipped to better reflect their contributions toward tuning. For conductance model simulated and lowpass filtered current clamp depolarizations, responses were measured as the depolarization amplitude from baseline. Negative values (rare cases where $R_{Null} > R_{Pref}$) where rectified to zero.

Speed indices were calculated from preferred direction responses to high (R_{High}) and low (R_{Low}) velocity motion as:

$$Speed\ Index = (R_{High} - R_{Low}) / (R_{High} + R_{Low})$$

Values thus tended toward −1 for responses tuned to low velocities and toward +1 for responses tuned to high velocities, while zero indicated equal responses to high and low speeds. Due to the lengthy recordings required to isolate ON responses for low velocity object motion, R_{Low} was determined from responses to 4.8 °/s moving bars, while 1.6 °/s was used for analysis of drifting grating responses. Responses to 58.1 °/s motion were used for R_{High} in both gratings and bars.

Statistics

Details of statistical tests, number of replicates, and p values are indicated in the figures and figure captions. Statistical methods were not used to predetermine sample size.

Code and data availability

Modeling data and code can be found at https://github.com/FellerLabCodeShare/DSGC-Velocity-Project. Additional datasets and analysis code are available upon request.

Results

To compare the tuning of ON and ON-OFF DSGCs, we designed a set of stimuli to isolate the directionally tuned ON responses of each cell type (Extended Fig. 2a). We performed 2-photon targeted current clamp recordings from GFP-labelled DSGCs in response to elongated drifting bars, where bar length scaled with velocity (Fig. 1a). We were thus able to separate the dual directional tuning computations in ON-OFF DSGCs for increments and decrements of light, and accordingly restricted our analysis to the ON response. Consistent with previous reports, we found ON DSGCs responded strongly at low velocities (~5-10 °/sec) but weakly if at all at higher velocities, while ON-OFF DSGCs were broadly responsive over a range of physiological speeds, with slight preference for moderate to high velocities (~20-60 °/sec) (Fig. 1b, g, Extended Fig. 3.

Cell Type	Measure	Condition	Mean	Std Dev	P Value	Cells	Mice
ON-OFF	Spikes	Bars	0.21	0.23	3.8×10^{-3}	16	11
ON-OFF	Spikes	Gratings	0.54	0.32	0.01	8	5
ON	Spikes	Bars	-0.63	0.28	8.4×10^{-5}	21	17
ON	Spikes	Gratings	-0.91	0.25	0.02	7	6
ON-OFF	Sym. Inh.	Bars	0.07	0.15	0.04	29	19
ON-OFF	Asym. Inh.	Bars	0.06	0.21	0.05	29	19
ON-OFF	Sym. Exc.	Bars	0.09	0.22	0.09	16	10
ON-OFF	Asym. Exc.	Bars	0.18	0.53	0.18	16	10
ON	Sym. Inh.	Bars	0.36	0.16	1.2×10^{-6}	31	22
ON	Asym. Inh.	Bars	-0.13	0.21	3.1×10^{-3}	31	22
ON	Sym. Exc.	Bars	-0.09	0.11	0.01	15	10
ON	Asym. Exc.	Bars	-0.17	0.68	0.39	15	10
ON	Sym. Inh.	Bars, Strychnine	0.10	0.29	0.52	11	8
ON-OFF	Sym. Inh.	Bars, VGAT KO	0.02	0.10	0.62	12	5
ON	Sym. Inh.	Bars, VGAT KO	0.34	0.07	9.7×10^{-4}	11	6
ON-OFF	Spikes	Dynamic Clamp	0.35	0.13	0.03	6	4
ON	Spikes	Dynamic Clamp	0.67	0.31	2.0×10^{-3}	10	6

Extended Data Table 1. Speed tuning indices
Speed tuning indices of DSGC inputs and outputs. Index values range from −1, which indicates preference for low velocities, to +1, which indicates preference for high velocities. Values tending toward zero indicate equal responses to high and low velocities. All P values are comparisons made to a zero median distribution via Wilcoxon signed-rank test.

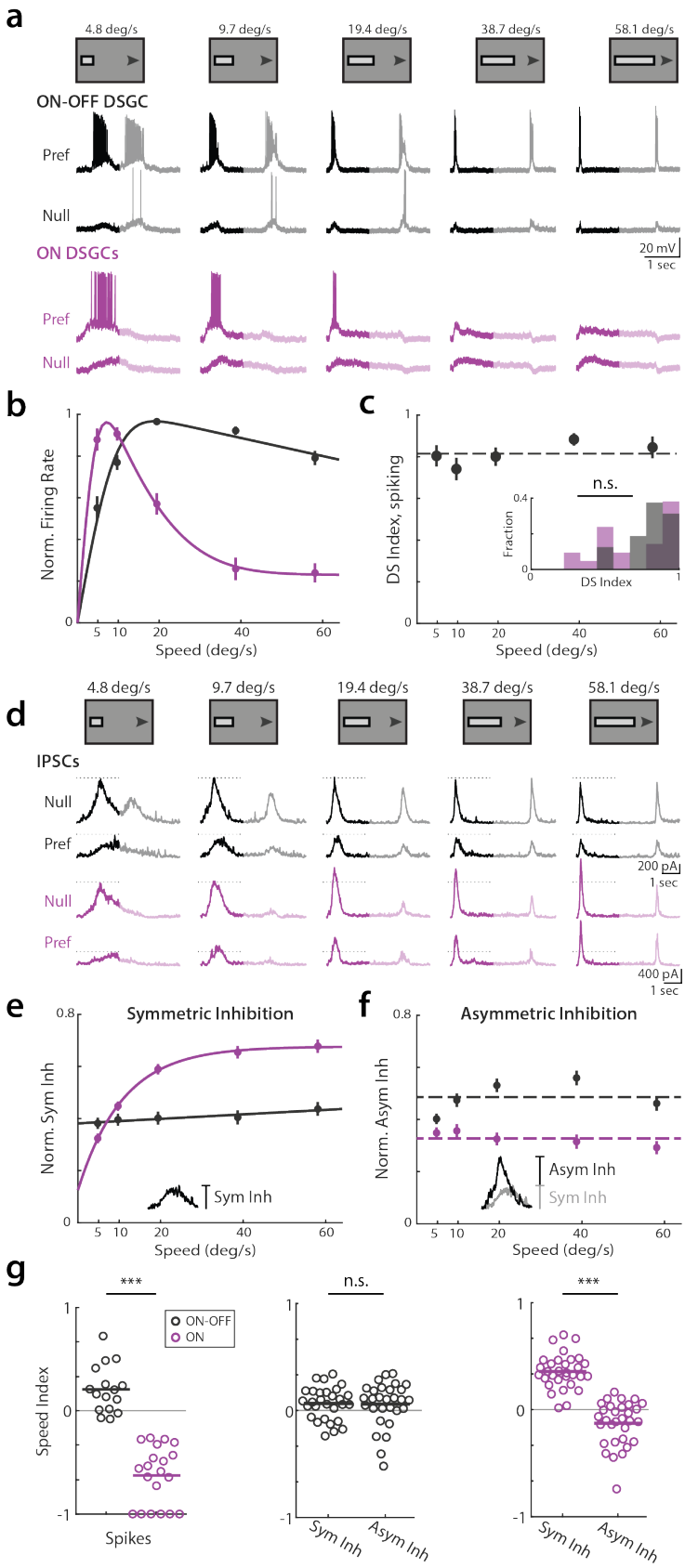
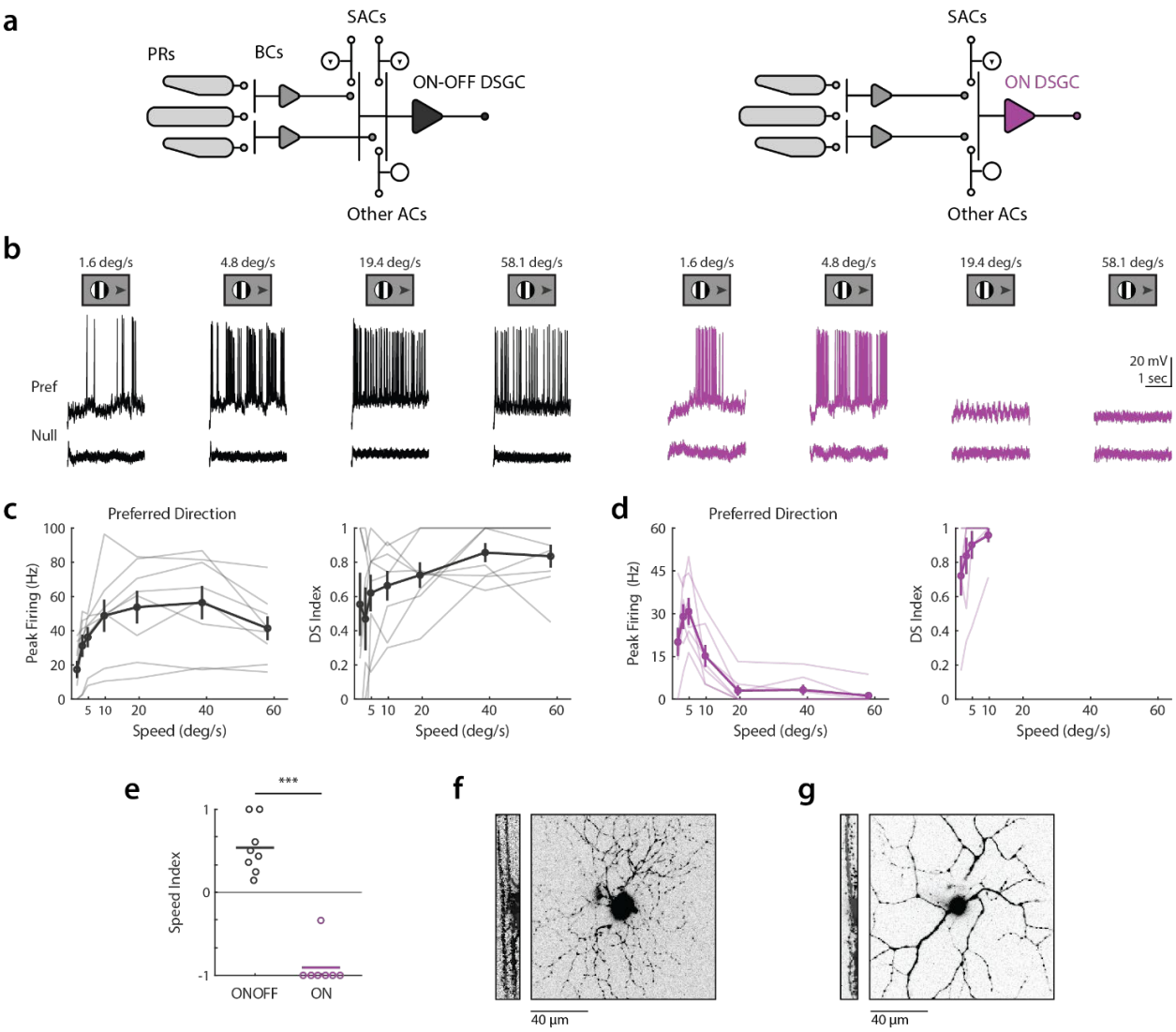
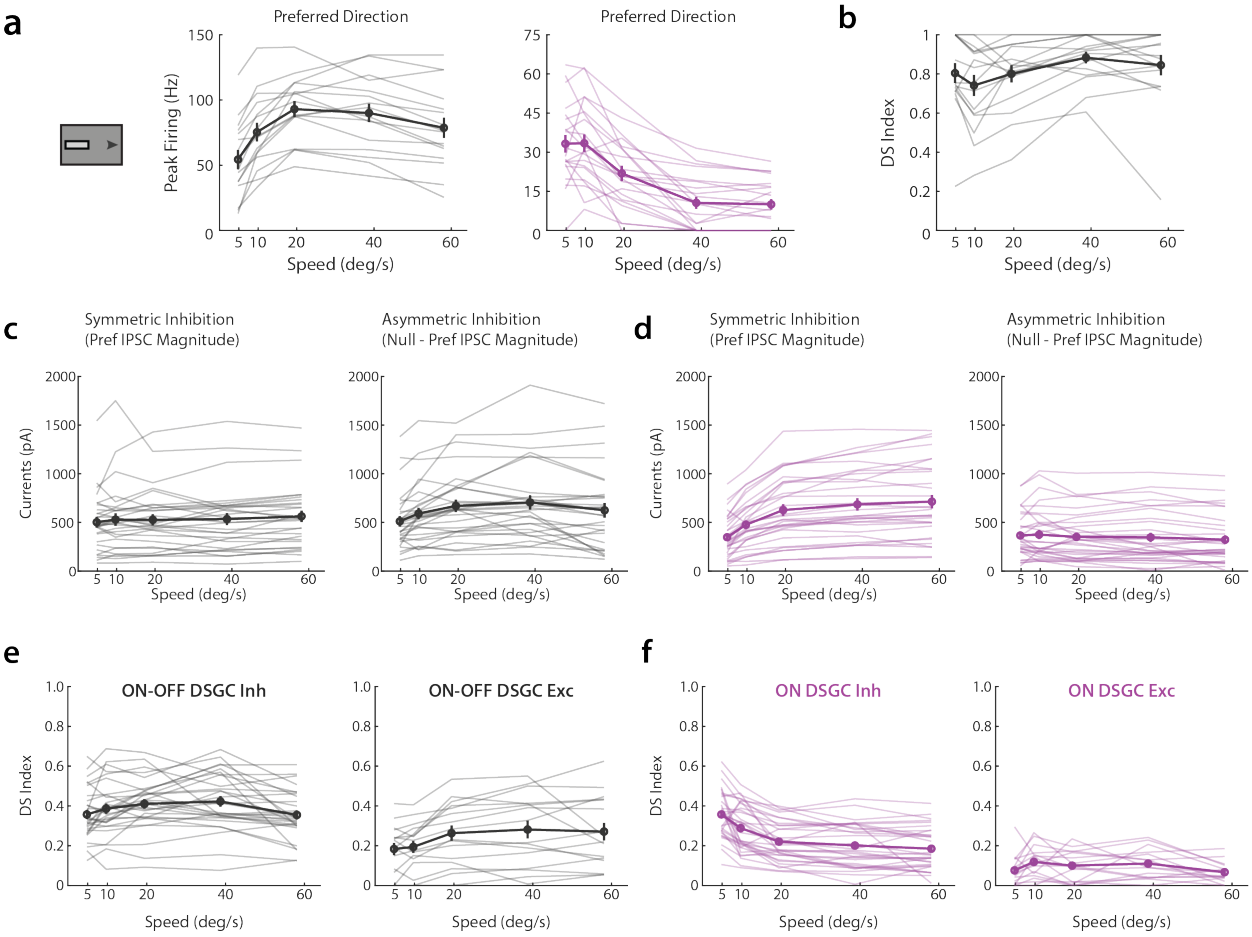


Figure 1. Velocity invariant asymmetric inhibition confers broad directional tuning.
(a) Example ON-OFF (*black*) and ON (*purple*) DSGC current clamp recordings for elongated bar stimuli where bar length scales with speed. Opaque lines shows analysis window restricted to On responses. (b) Population-averaged velocity tuning curves of normalized peak firing rate. Error bars show standard error of the mean, solid lines show fits to an integral over difference of Gaussians. (c) Population-averaged velocity tuning curve of DSI in ON-OFF DSGCs. Dashed line shows velocity-averaged DSI. Inset shows DSI histogram comparing velocity-averaged ON-OFF DSGC DSIs with ON DSGC DSIs at the velocities for which their firing rate is highest. Comparison was made via two-sided Wilcoxon rank-sum test, NS, P = 0.60, 16 ON-OFF DSGCs in 11 mice, 21 ON DSGCs in 17 mice. (d) Example ON-OFF (*black*) and ON (*purple*) DSGC IPSC recordings for drifting bar stimuli. Opaque traces shows analysis window restricted to ON responses. Dashed lines indicate IPSC amplitude at the lowest tested velocity. (e) Population-averaged velocity tuning curves of symmetric inhibition normalized to each cell's maximal null direction IPSC. Error bars show standard error of the mean, solid lines show exponential fits. Inset shows measurement of symmetric inhibition as amplitude of preferred direction IPSC. (f) Population-averaged velocity tuning curves of asymmetric inhibition normalized to each cell's maximal null direction IPSC. Dashed lines show velocity-averaged asymmetric inhibition. Inset shows measurement of asymmetric inhibition as amplitude difference of null minus preferred direction IPSC. (g) Speed indices of current clamp spike data (*left*), and symmetric and asymmetric inhibition (*middle, right*). Spiking speed indices between cell types was compared via two-sided Wilcoxon rank-sum test; ***P = 3.6 x 10^{-7}, 16 ON-OFF DSGCs in 11 mice, 21 ON DSGCs in 17 mice. IPSC speed indices were compared via two-sided Wilcoxon signed-rank test; ON-OFF IPSCs, NS, P = 0.92, 29 cells in 19 mice; ON IPSCs, ***P = 1.6 x 10^{-6}, 31 cells in 21 mice.



Extended Figure 2. DSGCs are feature detectors for directional motion.
(a) Circuit schematics of ON-OFF (*left*) and ON (*right*) direction selective ganglion cells (DSGCs). PRs; photoreceptors. BCs; bipolar cells. ACs; amacrine cells. SACs; starburst amacrine cells. (b) Example current clamp recordings *(ON-OFF black, ON purple*) in response to gratings drifting at several temporal frequencies in the cell's preferred or null direction. (c) ON-OFF DSGC dependence of preferred direction spiking (*left*) and directional selectivity (*right*) on grating velocity. (d) Same as in c, but for ON DSGCs. Directional selectivity is difficult to assess at high velocities due to low overall spiking. (e) Speed tuning indices of preferred direction spiking. Comparison made via two-sided Wilcoxon rank-sum test; ***$P = 3.1 \times 10^{-4}$, 8 ON-OFF DSGCs in 5 mice, 7 ON DSGCs in 6 mice. (f) Example ON-OFF DSGC TexasRed cell fill, showing xy projection (*right*) and xz ON and OFF layer bistratification (*left*). (g) Same as f, but for a monostratified example ON DSGC.

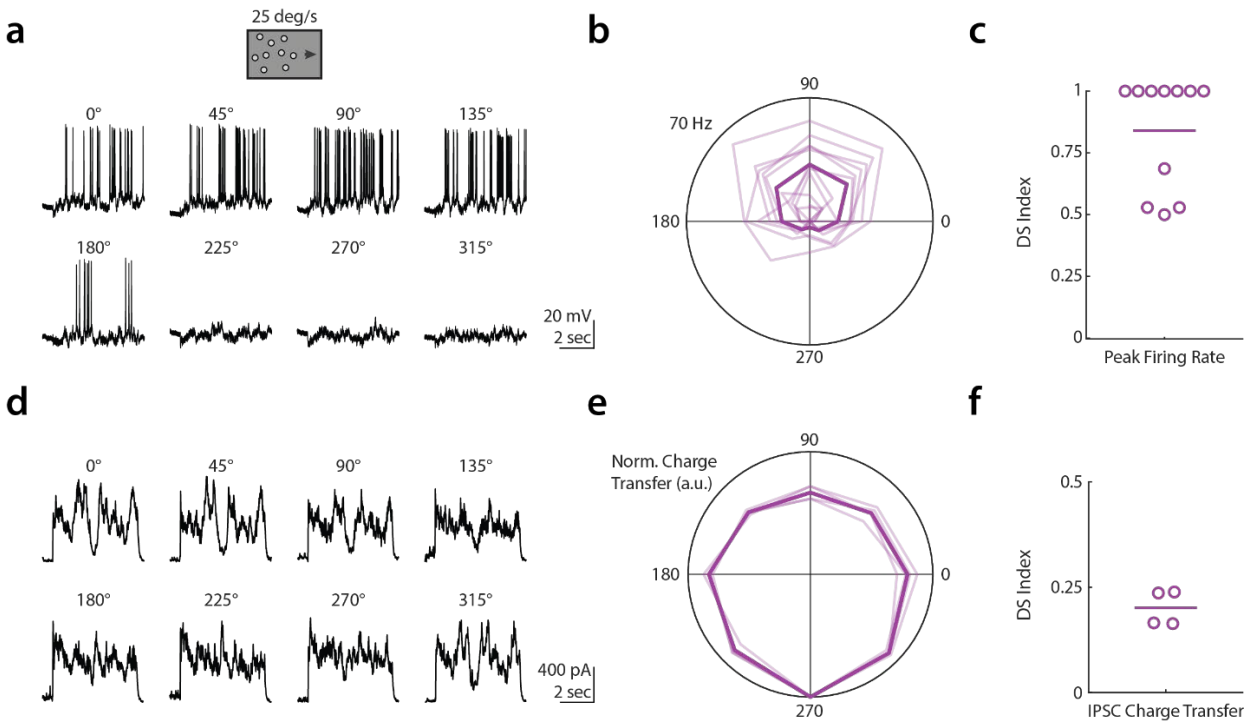
We quantified directional tuning with a directional selectivity index (DSI; ranging from +1 to 0, these values respectively indicating complete or no preference for preferred vs null direction motion). While ON DSGC DSI was difficult to assess at high velocities due to minimal spiking activity, ON-OFF DSGC directional selectivity was largely speed invariant. We found no significant difference when comparing DSIs of ON DSGCs at velocities eliciting peak firing



Extended Figure 3. Velocity tuning of DSGCs and their synaptic inputs.
(a) Summary plot of unnormalized velocity tuning curves based on current clamp recordings of ON-OFF (*black*) and ON DSGCs (*purple*) in response to drifting bar stimuli. In this and all other panels, transparent lines show individual cells while bold lines are the population average. Error bars show standard error of the mean. (b) ON-OFF DSGC direction selectivity indices versus velocity. ON DSGC directional selectivity is difficult to assess at high velocities due to low overall spiking and so is not included. (c) Summary plot of unnormalized velocity tuning curves of ON-OFF DSGC symmetric (*left*) and asymmetric (*right*) inhibition based on voltage clamp recordings. Symmetric inhibition was defined as the amplitude of preferred direction IPSCs, while asymmetric inhibition was measured as the amplitude of null direction IPSCs minus the magnitude of symmetric inhibition. (d) Same as in c, but for ON DSGCs. (e) ON-OFF DSGC direction selectivity indices of synaptic inputs versus velocity. Direction selectivity indices calculated directly from preferred versus null IPSC (*left*) and EPSC (*right*) amplitudes. (f) Same as e, but for ON DSGCs.

with the DSIs of ON-OFF DSGCs averaged across the range of speeds tested (Fig. 1c), indicating both cell types are comparably tuned when active.

Other visual stimuli complemented this result. Spatially restricted drifting gratings presented at several temporal frequencies recapitulated the velocity and directional tuning of our elongated bar stimuli, ruling out potential artifacts due to greater surround suppression for our high speed bars (Extended Fig. 2). Motivated by a previous observation that optokinetic reflexes,



Extended Figure 4. ON DSGCs encode high velocity motion of random dot kinetograms.
(a) Example ON DSGC current clamp recordings for random dot kinetogram (RDK) stimuli moving coherently in one of eight directions. (b) Polar plot directional tuning curves of ON DSGCs spiking for RDK stimuli. Preferred directions are aligned to 90 degrees. Transparent lines are tuning of individual cells, bold line is population average. (c) Direction selective indices computed from peak firing rate. (d) Same as a, but ON DSGC inhibitory postsynaptic currents (IPSCs) recorded in voltage clamp. (e) Same as b, but for normalized inhibitory charge transfer. Directions of maximal inhibition are aligned to 270 degrees. (f) Same as c, but for inhibitory charge transfer.

normally strongly tuned for low velocity stimuli, are engaged by random dot kinetogram (RDK) motion at a range of speeds (Marques et al. 2018), we further recorded from ON DSGCs in response to coherent RDKs moving at 25 °/sec. We were surprised to find that ON DSGCs were responsive and showed robust directional tuning, implying that ON DSGCs retain a tuning mechanism even at this relatively high velocity (Extended Fig. 4).

To investigate the synaptic origins of velocity and directional tuning, we performed voltage clamp recordings in each DSGC type. We assessed inhibitory inputs onto DSGCs by interpreting inhibitory postsynaptic currents (IPSCs) to be composed of symmetric and asymmetric components. Symmetric inhibition was taken to be the magnitude of IPSCs for preferred direction stimuli, while asymmetric inhibition was determined as the difference between null and preferred direction IPSC magnitudes. With this analysis, it became clear that ON and ON-OFF DSGCs received distinct patterns of symmetric inhibition, but very similar asymmetric inhibition (Fig. 1d). Symmetric inhibitory inputs onto ON DSGCs were strongly velocity tuned and increased rapidly for stimuli above 5 °/sec, while symmetric ON-OFF DSGC inhibition was only weakly tuned (Fig. 1e, g, Extended Fig. 3). However, both cell types received asymmetric inhibition that was largely untuned with respect to velocity, in contradiction

to traditional models of direction selectivity. We quantified these tuning differences with a speed index (ranging from -1 to +1 to denote tuning for low vs high speeds respectively, with 0 indicating no preference between speeds) (Fig. 1g, Extended Data Table 1). Directionally tuned inhibition was also measured for ON DSGCs in response to high velocity RDKs, further suggesting that asymmetric inhibition is not a velocity-restricted source of directional tuning (Extended Fig. 4).

We hypothesized that distinct interneuron pathways control tuning for velocity versus direction, the former unique to ON DSGCs, and the latter providing common inputs to both DSGC types. We set out to test this hypothesis by attempting to manipulate velocity tuning independently of directional tuning. Inspired by previous work in rabbit retinas showing glycinergic suppression for saccade-like stimuli (Sivyer, Tomlinson, and Taylor 2019), we performed voltage clamp recordings in response to elongated drifting bars before and after bath application of glycine receptor antagonist strychnine (Fig. 2a). Strychnine application selectively abolished the velocity tuning of ON DSGC symmetric inhibition, leaving IPSC magnitudes at the lowest velocities largely unchanged while substantially reducing inhibition for high velocity stimuli (Fig. 2b, d). Asymmetric inhibition however was unaffected by strychnine, indicating selective disruption of velocity tuning pathways (Fig. 2c). The magnitude of ON-OFF DSGC IPSCs were similarly unchanged by strychnine application (data not shown). Current clamp recordings in ON DSGCs in the presence of strychnine were consistent with increased firing for high velocity stimuli (Extended Fig. 5).

To test whether a single amacrine cell source provided velocity invariant asymmetric inhibition, we generated *Hoxd10-GFP / Vgat*$^{flox/flox}$*/ Chat-IRES-Cre* mice to fluorescently target DSGCs for voltage clamp recordings in animals for which vesicular GABA transporters had been conditionally knocked out of SACs (Pei et al. 2015). Nearly all asymmetric inhibition was abolished in these mice for both ON and ON-OFF DSGCs (Fig. 2e, g). The remaining symmetric inhibition showed no differences in velocity tuning between control and knockout animals (Fig. 2f, h). Hence SACs are responsible for directional tuning independent of velocity tuning in ON and ON-OFF DSGCs.

Differences in the intrinsic biophysical properties of ON and ON-OFF DSGCs could also contribute to velocity tuning via differential integration of similar synaptic inputs (Emanuel, Kapur, and Do 2017). To test whether intrinsic biophysical properties generate velocity tuning in ON DSGCs, we used a microcontroller based dynamic clamp device to deliver artificial conductances previously recorded from ON-OFF DSGCs (Fig. 3a, b). We found that ON-OFF DSGC conductances were sufficient to recapitulate ON-OFF DSGC velocity and directional tuning in ON DSGCs (Fig. 3c-e), indicating that synaptic inputs are sufficient to explain the directional tuning of ON-OFF DSGCs across velocities.

Previous work has assumed that multiple mechanisms would be required to generate direction selectivity for the full range of velocities to which ON-OFF DSGCs are responsive (Grzywacz and Amthor 2007; Borst and Euler 2011). We observed well-tuned inhibition across velocities, but alternative mechanisms might play an outsized role at some speeds, e.g. due to a large driving force for excitatory conductances. Additional mechanisms implicated in direction selectivity include tuning of excitatory inputs, and the relative timing of excitation and inhibition

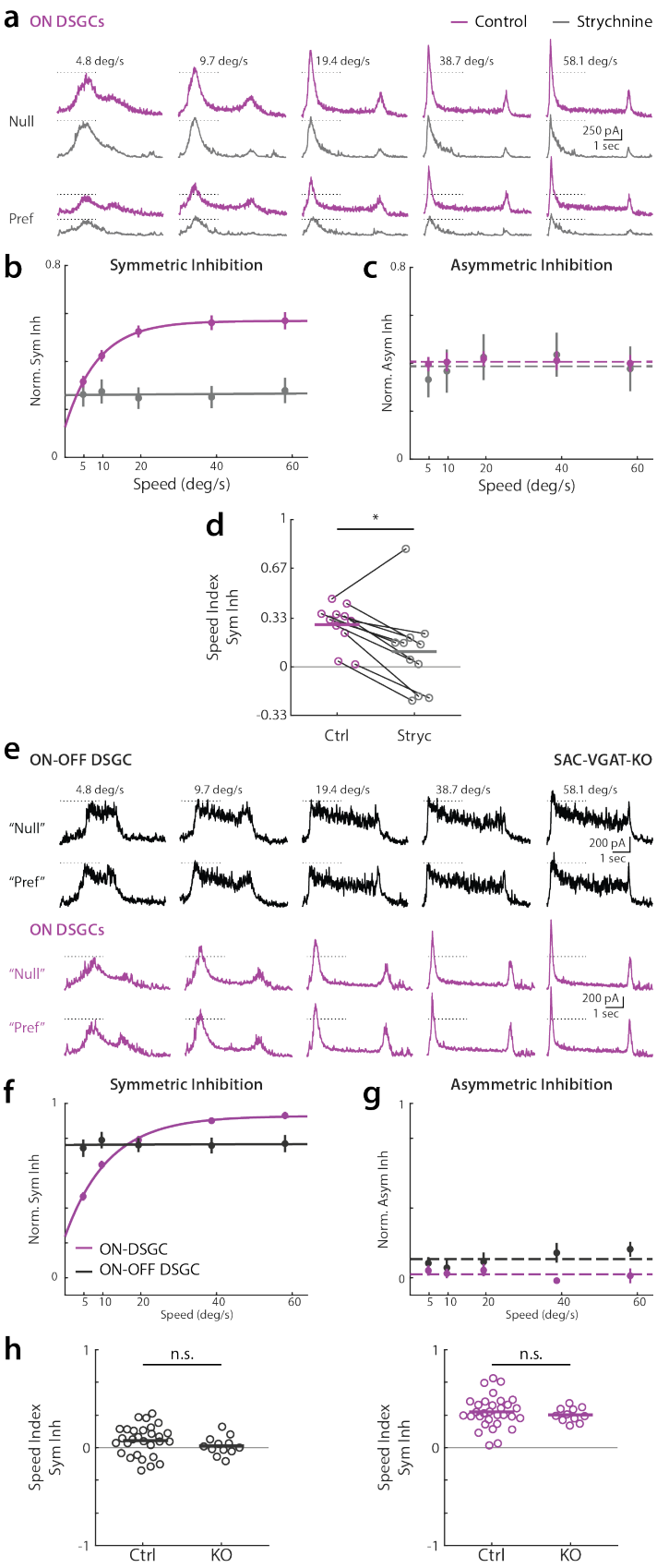
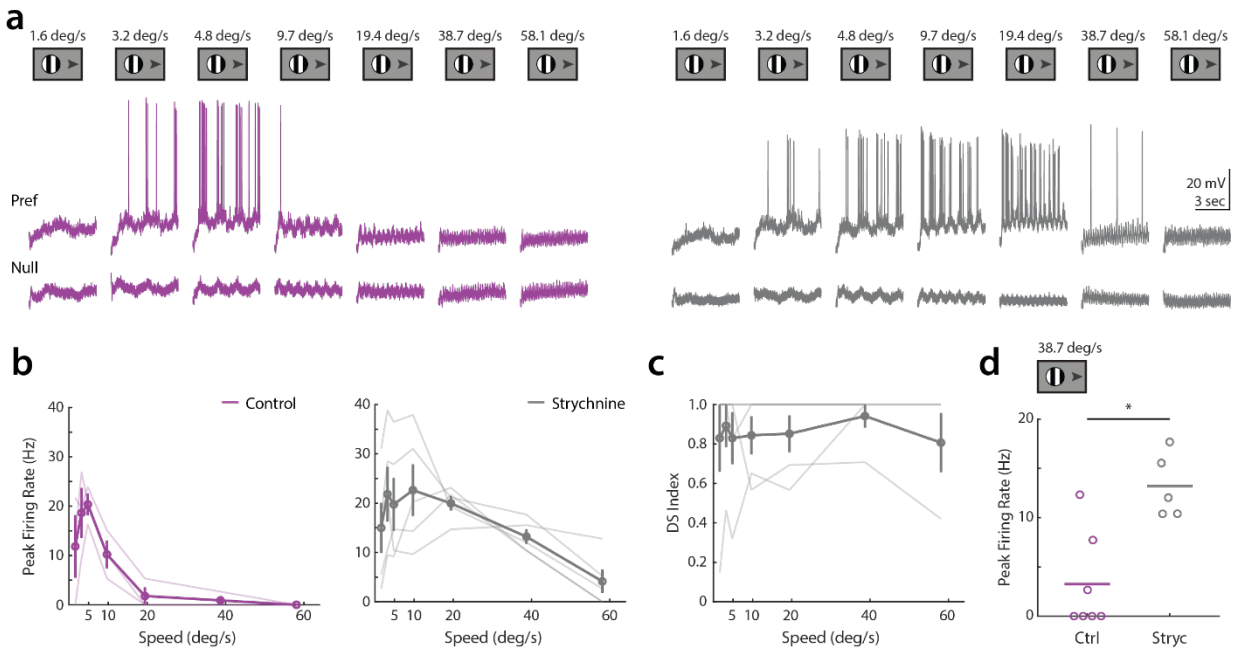


Figure 2. Independent inhibitory pathways control velocity and directional tuning. (a) Example ON DSGC IPSC recordings for elongated bar stimuli before (*purple*) and after (*gray*) strychnine wash. Dashed lines indicate IPSC amplitude at the lowest tested velocity. (b) Population-averaged velocity tuning curves of symmetric inhibition for control and strychnine conditions normalized to cell's maximal null direction IPSC before wash. Error bars show standard error of the mean, solid lines show exponential fits. (c) Population-averaged velocity tuning curves of asymmetric inhibition for control and strychnine conditions normalized to cell's maximal null direction IPSC before wash. Dashed line shows velocity-averaged asymmetric inhibition. (d) Symmetric inhibition speed indices before and after strychnine wash. Comparison made via two-sided Wilcoxon signed-rank test; **P* = 0.04, 11 cells in 8 mice. (e) Example ON-OFF (*black*) and ON (*purple*) DSGC IPSCs for elongated bar stimuli in *Hoxd10-GFP / Vgat$^{flox/flox}$ / Chat-IRES-Cre* mice. Dashed lines indicate IPSC amplitude at the lowest tested velocity. (f) Population-averaged velocity tuning curves of symmetric inhibition in KO mice normalized to cell's maximal IPSC. Error bars show standard error of the mean, solid lines show exponential fits. (g) Population-averaged velocity tuning curves of asymmetric inhibition normalized to cell's maximal IPSC. Dashed lines show velocity-averaged asymmetric inhibition. (h) Symmetric inhibition speed indices in control and knockout animals. Comparison made via two-sided Wilcoxon rank-sum test; ON-OFF IPSCs, NS, *P* = 0.19, 29 cells in 19 control mice and 12 cells in 5 knockout animals. ON IPSCs, NS, *P* = 0.61, 31 cells in 21 control mice and 11 cells in 6 knockout animals.



Extended Figure 5. Glycine receptor antagonist strychnine increases ON DSGC spiking at high velocities. (a) Example ON DSGC current clamp recordings for gratings drifting at several temporal frequencies in the cell's preferred or null direction, both before (*purple, left*) and after (*gray, right*) strychnine wash. (b) Dependence of preferred direction peak firing rate on drifting grating velocity, before (*left*) and after (*right*) strychnine wash. Transparent lines show individual cells, bold line is population average. Error bars show standard error of the mean. (c) Dependence of direction selectivity index on drifting grating velocity after strychnine wash. Transparent lines show individual cells, bold line is population average. Error bars show standard error of the mean. (d) Comparison of peak preferred direction firing rate at the second highest tested velocity (38.7 deg/sec) in control and strychnine conditions. Lines indicate cells for which recordings both before and after wash were collected. Comparison made via two-sided Wilcoxon rank-sum test; **P* = 0.02, control 7 cells in 6 mice, strychnine 5 cells in 3 mice.

(Matsumoto, Briggman, and Yonehara 2019; Wei 2018). Though we found minimal evidence for tuned excitatory inputs to ON DSGCs, there was modest tuning for ON-OFF DSGCs (Extended Fig. 6). Furthermore, the total charge transfer of synaptic inputs had similar directional preference to EPSC and IPSC amplitudes, providing evidence against intrinsically velocity-dependent space-time wiring mechanisms (Extended Fig. 7). We also found that ON-OFF DSGC inhibition arrived earlier relative to excitation for null rather than preferred direction motion, consistent with a ~50 um spatial offset (Extended Fig. 8) (Pei et al. 2015; Hanson et al. 2019).

To assess the relative contributions of potential mechanisms for directional tuning, we used numerical modeling to simulate depolarizations in a passive membrane model using the time-varying excitatory and inhibitory conductances we had recorded (Wehr and Zador 2003). By integrating our voltage clamp measured ON-OFF DSGC conductances in time, we were able to recapitulate depolarizations measured in current clamp (Extended Fig. 9). We then tested the contributions of potential mechanisms of directional tuning in generating tuned depolarizations

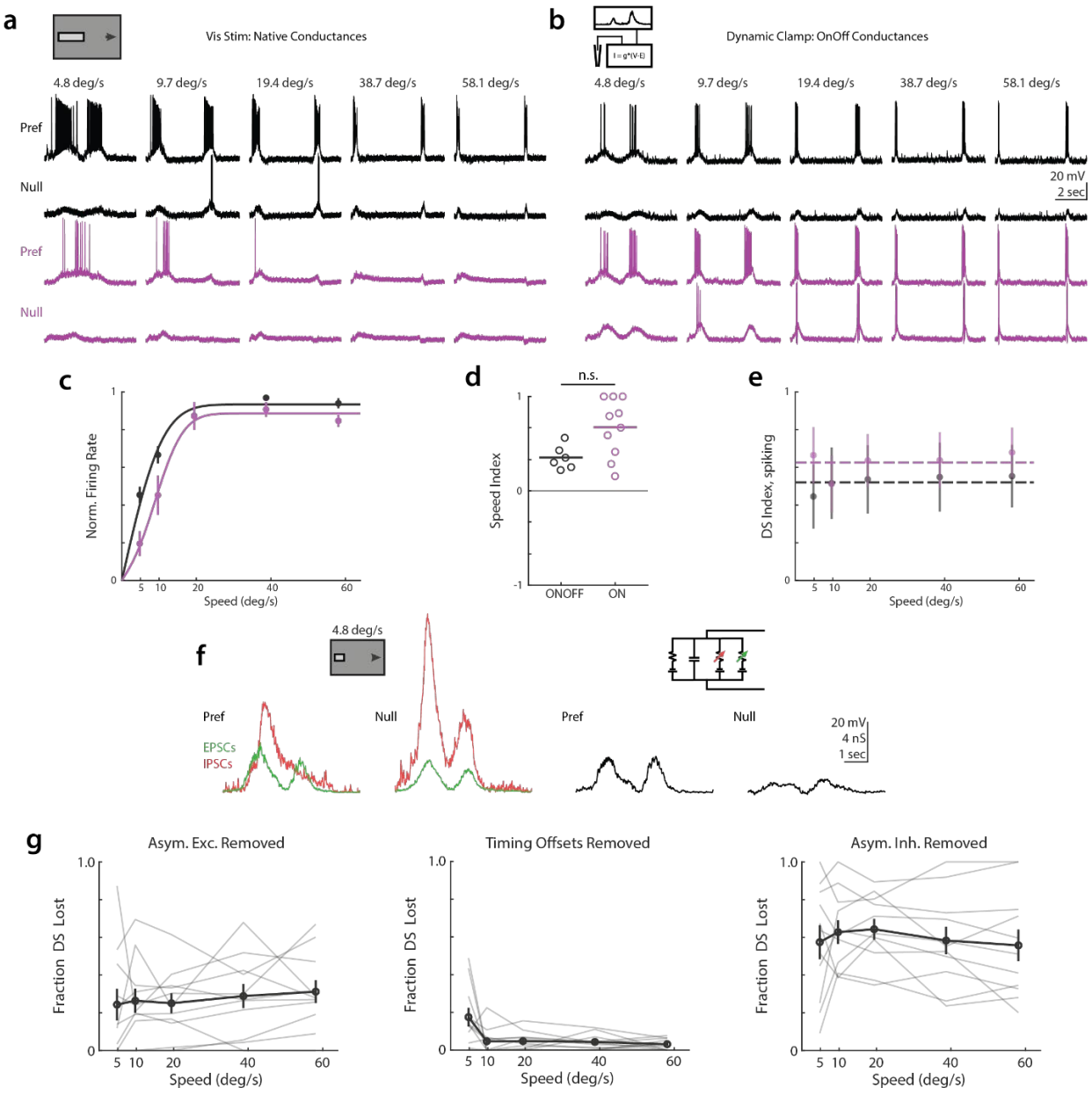
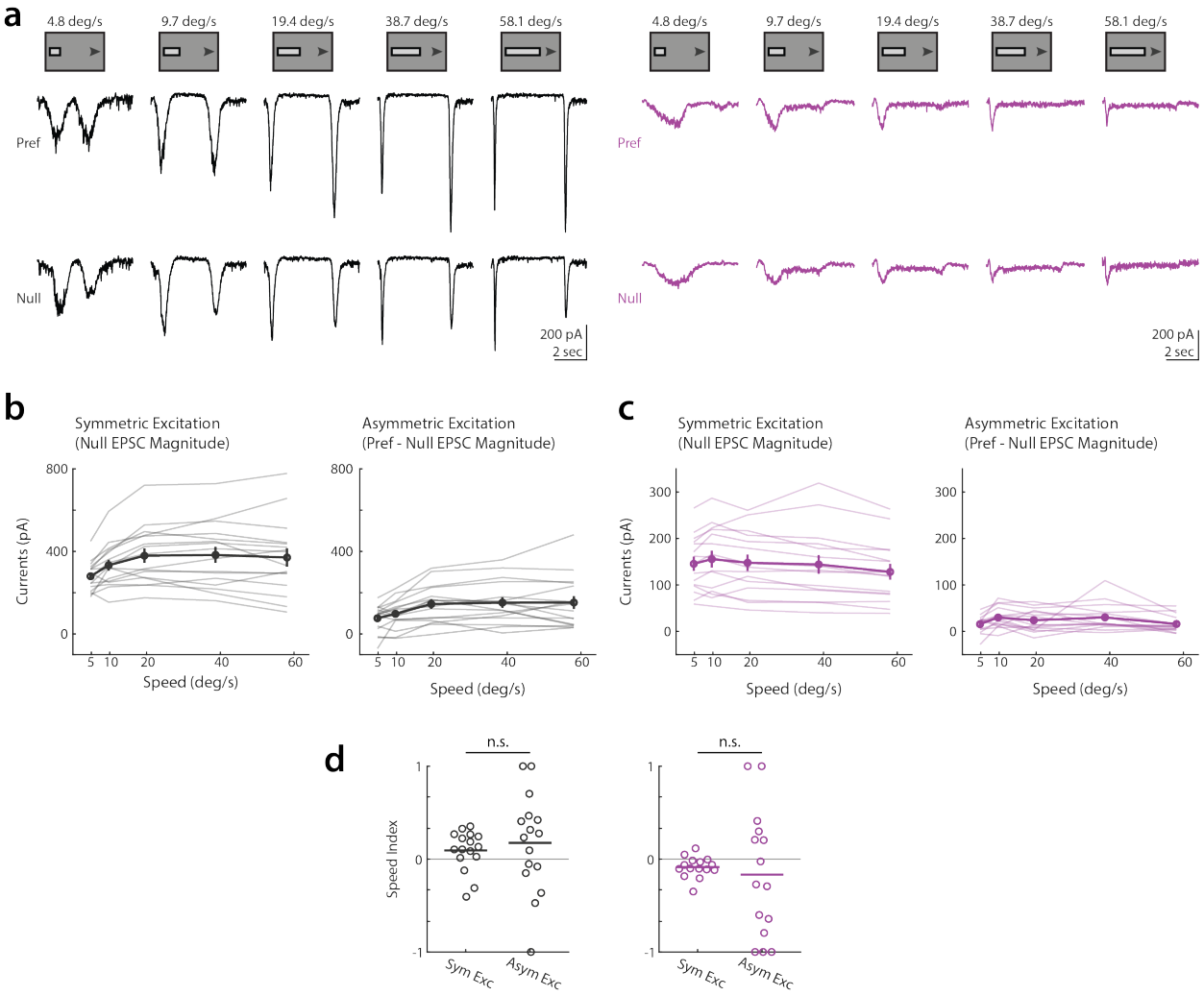


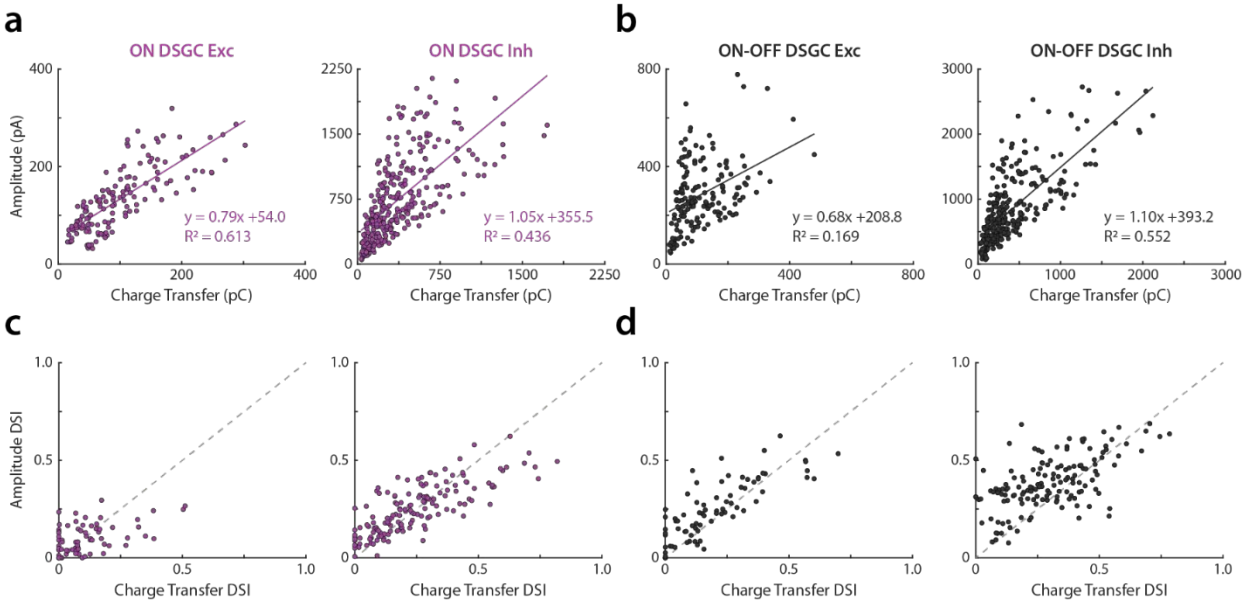
Figure 3. Velocity invariant inhibition is sufficient and necessary for broad directional tuning.
(a) Example ON-OFF (*black*) and ON (*purple*) DSGC current clamp recordings for elongated bar stimuli where bar length scales with speed. (b) Same as (a), but for stimulation with dynamic clamp inputs using ON-OFF DSGC conductances. (c) Population-averaged velocity tuning curves of dynamic clamp recordings normalized to peak firing rate. Error bars show standard error of the mean, solid lines show fits to an integral over difference of

at each of our recorded velocities. We found that loss of asymmetric excitation and removal of differential timing offsets minimally hindered the generation of directionally selective signals. Loss of asymmetric inhibition however significantly impacted the ability of simulated cells to produce directionally tuned depolarizations at every velocity (Fig. 3g).

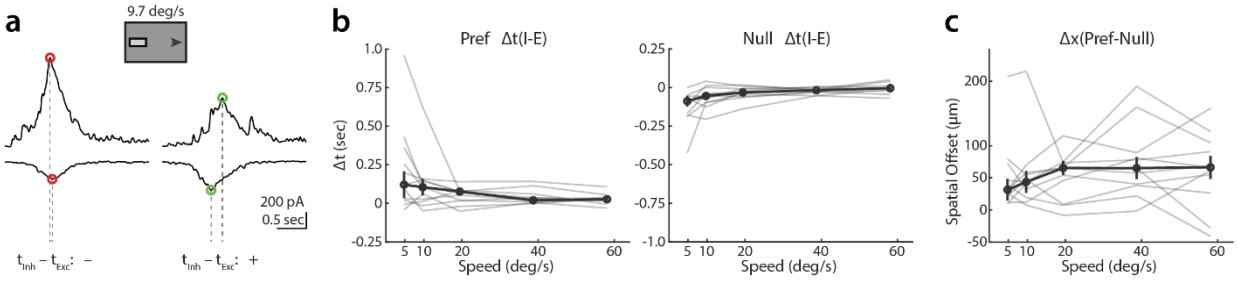
(Figure 3 Caption, continued): Gaussians. (d) Speed indices for ON-OFF and ON DSGCs stimulated via dynamic clamp. Comparison made via two-sided Wilcoxon rank-sum test; NS, $P = 0.06$, 6 ON-OFF DSGCs in 4 mice, 10 ON DSGCs in 6 mice. (e) Population-averaged velocity tuning curve of DSI in response to dynamic clamp stimulation. Dashed line shows velocity-averaged DSI. (f) Example voltage integration for conductance clamp model. ON-OFF DSGC excitatory (*green, smaller*) and inhibitory (*red, larger*) conductances recorded from voltage clamp data were used to simulate preferred and null direction depolarizations, from which direction selectivity was assessed. (g) Velocity tuning of fractional direction selectivity loss for conductance model manipulations removing asymmetric excitation (*left*), differential timing offsets (*middle*), and asymmetric inhibition (*right*). Bold lines show population averaged responses and standard error of the mean, thin transparent lines show individual simulated cells.



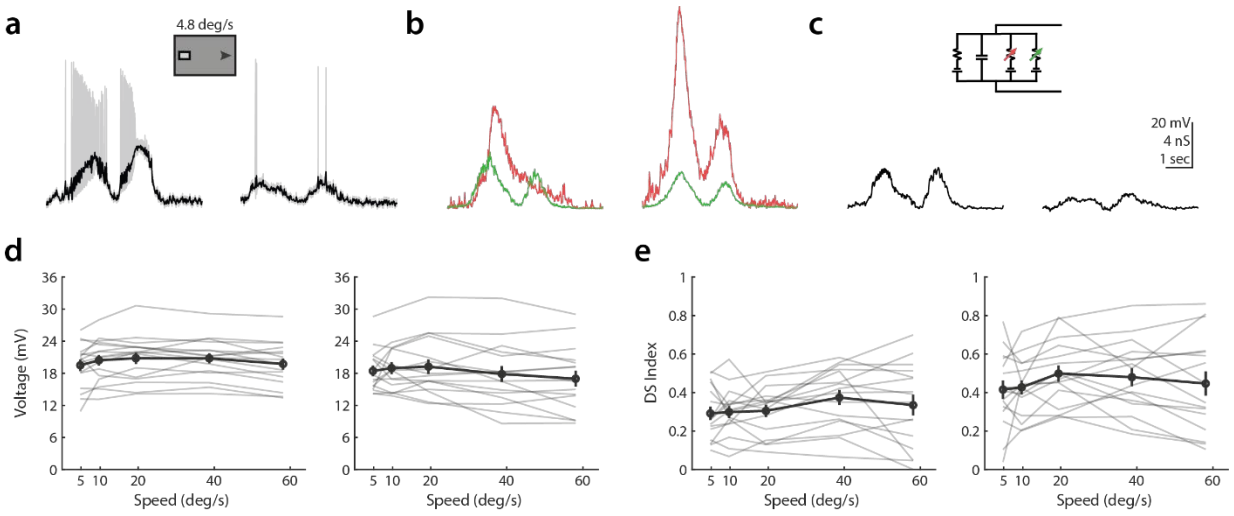
Extended Figure 6. Excitatory synaptic inputs to DSGCs.
(a) Example ON-OFF (*black*) and ON DSGC (*purple*) excitatory postsynaptic currents (EPSC) recordings for elongated bar stimuli. (b) Summary plot of relationship between the magnitude of ON-OFF DSGC excitation (*symmetric on left, asymmetric on right*) and stimulus velocity. Transparent lines show individual cells, bold line is population average. Error bars show standard error of the mean. Symmetric excitation was defined as the amplitude of null direction EPSCs, while asymmetric excitation was measured as the amplitude of preferred direction EPSCs minus the magnitude of symmetric excitation. (c) Same as in b, but for ON DSGCs. (d) Speed tuning indices of symmetric and asymmetric excitation for ON-OFF (*black*) and ON DSGCs (*purple*). Comparisons made via two-sided Wilcoxon signed-rank test; ON-OFF EPSCs, NS, $P = 0.12$, 16 cells in 10 mice; ON EPSCs, NS, $P = 0.60$, 15 cells in 10 mice.



Extended Figure 7. Total synaptic input is well approximated by EPSC and IPSC amplitudes.
(a) Relationship between ON DSGC EPSC (*left*) / IPSC (*right*) amplitude and charge transfer. Individual points are the mean values for a given cell at a set velocity. Solid lines are linear fits, with slope, intercept, and coefficient of determination inset. (b) Same as a, but for ON-OFF DSGCs. (c) Relationship between ON DSGC direction selectivity of EPSC (*left*) / IPSC (*right*) amplitude and charge transfer. Individual points are the value for a given cell at a set velocity. Dashed gray line is unity. (d) Same as c, but for ON-OFF DSGCs.



Extended Figure 8. Relative timing differences between excitation and inhibition.
(a) Example ON-OFF DSGC IPSCs (*top*) and EPSCs (*bottom*) illustrating relative timing differences for preferred (*right*) and null (*left*) directed stimuli. IPSC peaks preceding EPSC peaks are treated as negative timing differences, while EPSCs preceding IPSCs are treated as positive timing differences. (b) Dependence of ON-OFF DSGC I-E timing differences on velocity for preferred (*left*) and null (*right*) directed stimuli. Transparent lines show individual cells, bold line is population average. Error bars show standard error of the mean. (c) Directionally tuned component of timing differences represented as a spatial offset. Transparent lines show individual cells, bold line is population average. Error bars show standard error of the mean.



Extended Figure 9. Conductance modeling recapitulates subthreshold depolarizations.
(a) Example preferred (*left*) and null (*right*) direction ON-OFF DSGC depolarizations, after removal of spikes via lowpass filtering. (b) Example EPSCs (*green, smaller*) and IPSCs (*red, larger*) recorded from an ON-OFF DSGC in response to preferred (*left*) and null (*right*) bars as in (a). (c) Example depolarizations from numerical integration of preferred (*left*) and null (*right*) conductances from (b) in a simple parallel conductance model, using forward Euler method. (d) Comparison of depolarizations measured in current clamp (*left*) and via conductance modeling (*right*). (e) Same as (d), but for direction selectivity.

Conclusions

The sensory periphery constructs distinct neural representations to subserve the goals of both reflexive and volitional motor outputs (Seabrook et al. 2017). Feature detectors in the periphery must efficiently compute representations of the external world, without the neuronal resources of central sensory brain regions. Here we demonstrate that distinct inhibitory pathways independently control tuning for the velocity and direction of motion on the retina (Fig. 2), and correspondingly expose directional tuning in ON DSGCs at velocities beyond those for which they are typically responsive (Extended Fig. 4, 5). Intriguingly, these results show the unexpected role of SAC-mediated asymmetric inhibition as the predominant source of directional tuning at a broad range of velocities (Fig. 3), defying the narrow speed tuning of classical models of direction selectivity (Tukker, Taylor, and Smith 2004; J. S. Kim et al. 2014; Fransen and Borghuis 2017). We thus illustrate the unexpected computational breadth of early visual circuits, and how compact sensory systems can blend shared inputs to develop diverse, behaviorally relevant feature tuning.

Chapter 3: Neural Coding in the Early Visual System

Many cyanobacteria and even unicellular eukaryotes possess photosensitive proteins that are capable of instigating simple light-driven behaviors (Brunet et al. 2019). However, the sophisticated circuitry of vertebrate visual systems allows access to a rich repertoire of visually guided behaviors. This chapter will discuss and speculate upon the relative roles of visual processing within the retina and central brain areas.

What functions does the retina perform? Photoreceptors transduce energy from the external world into neural signals; neural circuits then enact computations upon these signals to transform them into physiologically relevant outputs. Within the retina, a number of excitatory and inhibitory interneuron cell types interact to construct distinct tuning among diverse retinal ganglion cell (RGC) types. The tuned spiking activity of RGCs conveys information from the sensory periphery to central brain areas, which is used either to initiate simple motor outputs or as the basis for further sensory computations.

What does further computation within central visual areas accomplish? One tempting hypothesis might be that the greater computational "depth" of cortical neural networks is required for complex feature selectivity. The processing that occurs within the retina is relatively compact in comparison to the successive layers of computation performed within the mammalian visual cortex. Successive layers of computation within the visual hierarchy are thought to generate increasingly complex representations of the structures within the visual world. Relative to early cortical areas, neurons in higher visual regions show tuning for increasingly specific visual features (e.g. simple center-surround receptive fields give rise to oriented edge tuning, receptive fields for which are then assembled to give rise to contour and face tuning), and encode these features in an increasingly invariant manner (e.g. irrespective of location within the visual field). Cortical circuits might therefore enact computations that are beyond the computational capabilities of the retina.

There are several examples of complex feature selectivity within the retina, however, which undermines the hypothesis that these complex computations are reserved for cortex. Color opponent retinal circuits wherein a spatially diffuse spectral signal is subtracted have been proposed to implement figure-background segmentation in certain visuoecological situations (Baden 2021). Although tuning for oriented edges was first described in visual cortex (Hubel and Wiesel 1962), orientation selective tuning has also been found in RGCs and even amacrine cells within the retina (Bloomfield 1994; Murphy-Baum and Rowland Taylor 2015; Nath and Schwartz 2016). Neurons showing tuning for directional image motion have also been found in the retina, along with primary and higher order visual cortex. Interestingly, in many respects direction selectivity (DS) within the retina more closely resembles the tuning of primate area MT than primary visual cortex in that DS RGC responses are largely invariant to the speed and spatial frequency of motion (Grzywacz and Amthor 2007). Thus, the retina is capable of constructing relatively complex representations of visual features, even within its comparatively succinct processing pipeline.

Theory work further weakens the idea that the computational architecture of the cortex is intrinsically more powerful than that of the retina. Though higher order visual functions such as

object recognition and face discrimination are clearly beyond the skein of the mammalian retina, in principle these functions are within the computational capacity of a hypothetical retina. Work on artificial neural networks has established that feedforward networks with a single hidden layer (a similar architecture to the retina) are capable of representing arbitrary functions, a result called the universal approximation theorem (Cybenko 1989; Hornik 1991). The universal approximation theorem provides a theoretical framework by which to understand the fundamental differences, or lack thereof, between computations within central brain regions and the sensory periphery. Although the number of neurons required to compute higher order visual functions using only a single intermediate hidden layer may prove unfeasibly large given biological constraints, the hierarchical computations of visual cortex are not a rigorous prerequisite for complex feature selectivity.

Experimental evidence from comparative neuroanatomy further confirms that post-retinal processing is not strictly necessary for vision. Indeed, some animals employ complex "camera-type" eyes (a designation denoting possession of a cornea, lens, and retina) while largely lacking a central nervous system. Box jellyfish perform visually guided behaviors such as obstacle avoidance and directed phototaxis despite lacking a central brain, suggesting that the visual processing necessary for these behaviors is largely carried out by the jellyfish retina (Skogh et al. 2006; Nilsson et al. 2005). While it remains unclear whether animal eyes have truly monophyletic origins, the remarkable conservation of genetic programs for eye specification further suggest that eyes evolved prior to brains (Gehring 2005). Homologs of the transcription factor gene *Pax6* specify eye development in a range of species spanning primates, mice, insects, and mollusks, and expression of mouse or squid *Pax6* variants induces ectopic development of eyes in *Drosophila* (Halder, Callaerts, and Gehring 1995; Tomarev et al. 1997). Certain motifs within retinal visual processing are also highly conserved. The division of luminance onset and offset information into ON and OFF pathways via parallel interneurons with and without sign inverting metabotropic glutamate receptors is seen in mammals as well as sea lamprey, implying an evolutionary origin of at least five-hundred million years, dating back to the Cambrian explosion (Ellis et al. 2020). Thus the biological tools for performing visual behaviors long precede modern brain structures.

The role of retinal computations and their contributions to downstream circuits have shifted throughout evolutionary history. Within the mouse, the mechanisms by which primary visual cortex and the evolutionarily older superior colliculus construct representations of directional motion appear to differ. Despite the aforementioned overrepresentation of DS RGCs in the mouse retina, one study suggests that primary visual cortex constructs DS tuning de novo from spatiotemporally offset thalamic inputs (Lien and Scanziani 2018). In contrast, DS neurons within the superior colliculus appear to directly inherit tuning from the excitatory input of DS RGCs, and genetic manipulations to eliminate retinal DS correspondingly abolish tuning within the colliculus (Shi et al. 2017). The disparity in tuning mechanisms between these image forming areas might reflect the distinct visuoecological circumstances of ancestral mammals when each of these regions began to emerge. The nocturnal bottleneck theory proposes that early mammals were displaced from diurnal ecological niches during the age of the dinosaur, a period when the colliculus was likely the dominant visual brain region, rather than the nascent neocortex (Gerkema et al. 2013; Husband and Shimizu 2001). The ecological demands of navigating

nocturnal niches might have placed different evolutionary pressures on collicular versus cortical vision and the relative role of retinal circuits in that processing.

Given the theoretical and observed computational capacity of retinal circuits, what added value do organisms receive from post-retinal visual processing? One clear advantage of downstream processing is access to stereoscopic information. Interestingly, some comparative neuroanatomical studies have suggested that the amount of complex processing occurring within retinal circuits is inversely proportional to the binocular proportion of an animal's visual field (Husband and Shimizu 2001). Owls and primates, which both have frontal eyes and large binocular visual fields, show enrichment for RGCs with simple ON and OFF receptive fields (Pettigrew 1978). Rabbits and mice on the other hand, both of which have lateral eyes, appear to frontload many visual computations and have a preponderance of specialized RGC circuits to compute visual features within the retina. This is exemplified by DS RGCs, the presence of which remains controversial in primate retinas (Dhande et al. 2019; Patterson et al. 2021), but which dominate the mouse retina with an estimated 40% of RGCs encoding DS information (Bos, Gainer, and Feller 2016). A tendency for simpler RGC tuning supporting binocular vision is seen even within the topography of the mouse retina, where the density of sustained ON and OFF alpha type RGCs is much greater in the region of temporal retina corresponding to the binocular visual field – cell types that have been shown to be particularly important for predation of crickets in mice (Bleckert et al. 2014; K. P. Johnson et al. 2021; Heukamp, Warwick, and Rivlin-Etzion 2020).These reports suggest that highly binocular visual animals, or even regions of the retina, perform general-purpose computations and offload more complex feature processing to downstream brain regions that can integrate visual information from both eyes.

Other trade-offs likely exist between frontloading or backloading visual computations. Firstly, processing within the sensory periphery necessarily use fewer synapses, which is likely advantageous for faster neural signaling to mediate reflexive actions. One such example is gaze stabilization reflexes, which are mediated by signals originating from ON DS cells within the retina – though physiological evidence of DS RGCs in primates remains sparse, disruption of the *Frmd7* gene is known to reduce horizontal DS in the mouse retina and produces similar optokinetic reflex deficits in mice and humans, implying a retinal locus for these behaviors (Yonehara et al. 2016; Thomas et al. 2011). A second consideration is the relatively implastic nature of retinal computations, which might prove disadvantageous for non-reflexive behaviors (Tiriac, Bistrong, and Feller 2021), whereas the mammalian visual cortex's successive stages of intermediate feature selectivity may provide a substrate for correlation and learning. Thirdly, recurrent connections may be of greater importance for some kinds of computations. Although avian retinas receive substantial feedback projections from the optic tectum by way of the isthmo-optic nucleus (Wilson and Lindstrom 2011), feedback onto the mammalian retinas is much sparser and appears to be largely non-visual in nature (Gastinger et al. 2006). Meanwhile, the recurrent connections and state-dependent modulation accessible to mammalian circuits in central brain regions likely allows for more dynamic visual computations (Polack, Friedman, and Golshani 2013; Keller, Roth, and Scanziani 2020). The relative importances of speed and modularity of processing might have influenced the evolutionary pressures on performing particular computations within the retina or in central brain areas.

Clearly, the investigation of neural processing in the early visual system is a rich area of study inviting examination with the tools of molecular, synaptic, evolutionary, computational, and many more domains of biology. Several broad outstanding questions are poised to advance our understanding of the retina in particular, and vision at large. What biophysical mechanisms shape the extensive functional diversity of RGC types, and how does the tremendous yet largely underexplored diversity of amacrine cell interneurons contribute to these computations? What are the present day or ancestral ecological specializations that constrain or enhance early visual processing? Given the diversity of RGC type functional properties and projection patterns, how are each of these distinct visual information channels integrated into downstream brain areas, and how do these projections shape behaviors? While unraveling the links between particular neural computations and visual behaviors will require prolonged and careful inquiry, time spent with these mysteries promises to offer worthwhile insights into fundamental components of the human sensory experience.

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