ANNUAL REVIEWS

Annual Review of Vision Science

Neural Mechanisms of Motion Processing in the Mammalian Retina

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Annu. Rev. Vis. Sci. 2018. 4:165–92

First published as a Review in Advance on August 10, 2018

The *Annual Review of Vision Science* is online at vision.annualreviews.org

https://doi.org/10.1146/annurev-vision-091517-034048

Keywords

motion detection, synaptic circuit, synapses, retina, direction selectivity, starburst amacrine cell

Abstract

Visual motion on the retina activates a cohort of retinal ganglion cells (RGCs). This population activity encodes multiple streams of information extracted by parallel retinal circuits. Motion processing in the retina is best studied in the direction-selective circuit. The main focus of this review is the neural basis of direction selectivity, which has been investigated in unprecedented detail using state-of-the-art functional, connectomic, and modeling methods. Mechanisms underlying the encoding of other motion features by broader RGC populations are also discussed. Recent discoveries at both single-cell and population levels highlight the dynamic and stimulus-dependent engagement of multiple mechanisms that collectively implement robust motion detection under diverse visual conditions.

1. INTRODUCTION

When visual animals navigate through the natural environment, images projected on their retinas are constantly moving owing to a combination of self-motion from head and eye movements and object motion in the visual field. Detecting and distinguishing motion information are fundamental tasks of the visual system for appropriate visual reflexes, perception, and visually guided behavior. In vertebrate animals, motion processing begins in the retina, where dedicated neural mechanisms and circuits implement the encoding of motion features. The extracted motion information is conveyed to downstream brain areas via the spiking activity of retinal ganglion cells (RGCs).

The neural mechanisms of motion processing in the retina are inherent to the functional circuitry formed by five classes of retinal neurons (**Figure 1**). According to the current estimates, incoming visual signals undergo parallel processing by around 30 retinal neural circuits (Baden et al. 2016, Sanes & Masland 2015). Distinct retinal circuits with unique input-output relationships are assembled from the selective wiring between subsets of the cell types in each class. The diversity of retinal circuits is highlighted in the second synaptic layer, where 12–14 types of bipolar cells, 30–50 types of amacrine cells, and about 30 types of ganglion cells stratify their neurites at specific sublaminae of the inner plexiform layer (IPL) (Baden et al. 2016, Franke et al. 2017, Helmstaedter et al. 2013, Sanes & Masland 2015).

The main body of work on retinal motion processing investigates a circuit that computes motion direction. The output neurons of this direction-selective circuit, direction-selective ganglion cells (DSGCs), were discovered in the rabbit retina by Barlow, Hill, and Levick in the 1960s (Barlow & Hill 1963, Barlow et al. 1964). DSGCs are maximally activated by motion in their preferred direction and strongly suppressed by motion in the opposite, null direction. As an experimentally accessible circuit with a well-defined computation, the direction-selective circuit has since inspired scientists to develop theoretical frameworks, generate computational models, and pinpoint its neural substrate at the cellular and synaptic levels. This review is primarily on the neural basis of retinal direction selectivity, particularly the recent work in the mouse retina because of the technical advantages for using this species. An emerging thesis from recent work is that reliable motion detection is achieved by multilayered neural mechanisms that are differentially engaged

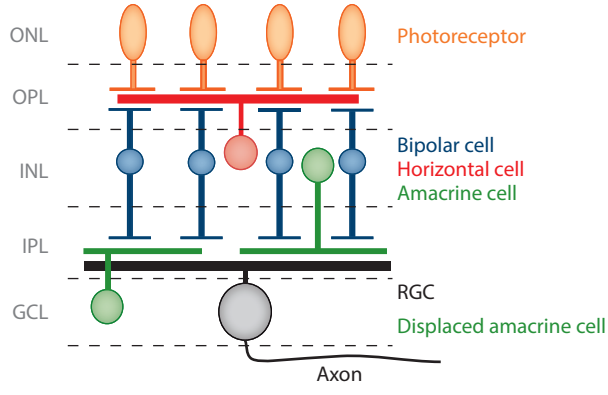

Figure 1

The canonical organization of a retinal circuit. Glutamatergic signaling occurs from photoreceptors to bipolar cells and from bipolar cells to retinal ganglion cells (RGCs). At each step of this glutamatergic pathway, horizontal and amacrine cells, which are also driven by the glutamatergic inputs from photoreceptors and bipolar cells, respectively, profoundly modify network activity through lateral interactions. Abbreviations: GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; ONL, outer nuclear layer; OPL, outer plexiform layer.

Table 1 A brief comparison of direction-selective ganglion cells identified in rabbit and mouse[a]

RGC types	Rabbit	Mouse
On DSGC, sustained	No gap junction coupling is found	
	Project to AOS	
	Do not show a bias of dendritic arbor distribution on the preferred-null axis	
	Three preferred directions are detected	Four preferred directions are detected; posterior subtype shows weaker directional tuning
On DSGC, transient	Three preferred directions are detected; gap junction coupled to amacrine cells	Not reported
On-Off DSGC	Four preferred directions	
	Mainly project to dLGN and SC	
	Superior subtype cells show gap junction coupling among themselves	
	Do not show a bias of dendritic arbor distribution on the preferred-null axis	Superior and some inferior cells show dendritic arbors displaced from the soma in the preferred direction; the others do not show this bias
On-Off DSGC, anterior	Not reported	A distinct anterior subtype with slower speed tuning and weaker directional tuning than other On-Off DSGCs; project to SC and NOT
J-RGC (JAM-B)	Not reported	Also show color opponency and orientation selectivity
F-mini (On/Off)	Not reported	Small receptive field; prefer vertical directions, project to SC and dLGN

[a]Please refer to the text for references.
Abbreviations: AOS, accessory optic system; dLGN, dorsal lateral geniculate nucleus; DSGC, direction-selective ganglion cell; JAM-B, junctional adhesion molecule B; NOT, nucleus of the optic tract; RGC, retinal ganglion cell; SC, superior colliculus.

under different visual conditions. The last part of the review discusses motion processing beyond direction selectivity in broader populations of RGCs.

For related topics, the reader is referred to recent excellent reviews by Clark & Demb (2016) and Mauss et al. (2017), which compare direction selectivity in the mammalian retina and the insect visual system from theoretical and circuit perspectives, and by Morrie & Feller (2016) for the development of retinal direction selectivity.

2. TYPES OF DSGCs AND THEIR CENTRAL PROJECTIONS

A brief summary of the rabbit and mouse DSGC types discussed in this section is shown in **Table 1**.

2.1. On and On-Off DSGCs Identified in the Rabbit Retina

The first two types of DSGCs reported in the rabbit retina are On-Off DSGCs and On DSGCs based on their responses to bright and dark contrasts (Barlow et al. 1964). On-Off DSGCs have medium-size, bistratified dendritic arbors that costratify with the dendrites of On and Off starburst amacrine cells (SACs) in the On and Off sublaminae of the IPL (Amthor et al. 1984, Famiglietti 1992). When probed with flashing spots, the receptive fields (RFs) of On-Off DSGCs closely match with their dendritic fields (Yang & Masland 1992, 1994). In contrast, On DSGCs have

larger, monostratified dendritic arbors that costratify with On SACs in the On sublamina, with occasional small dendritic branches in the Off sublamina (Amthor et al. 1989, Buhl & Peichl 1986, Famiglietti 1992, He & Masland 1998). Compared to On-Off DSGCs, On DSGCs are tuned to motion at slower speeds and exhibit more sustained light response (Barlow et al. 1964, Oyster 1968, Sivyer et al. 2010, Wyatt & Daw 1975). They also differ in their central projection patterns. On-Off DSGCs mainly project to the superior colliculus (SC) and lateral geniculate nucleus (LGN), indicating that they participate in eye movement and pattern vision. In contrast, On DSGCs do not project to these major targets but innervate the nuclei in the accessory optic system (AOS) (Berson 2008, Simpson 1984). The preference for slower motion speed and the exclusive projection to the AOS support a critical role of On DSGCs in the optokinetic response.

The On-Off DSGCs in the rabbit retina consist of four subtypes based on their preferred directions in the posterior, anterior, superior, and inferior directions in the visual field (or nasal, temporal, ventral and dorsal directions in the retina) (Oyster 1968). Consistent with this functional classification, On-Off DSGCs that prefer the same direction tile the retina with regular spacing (Amthor & Oyster 1995, Devries & Baylor 1997), indicating that each subtype independently samples the visual space. Among the four subtypes, only the superior DSGCs are gap junction coupled with one another in the mature retina (Kanjhan & Vaney 2008).

Three subtypes of On DSGCs with sustained light responses were originally reported in the rabbit retina (Oyster 1968), all of which lack gap junction coupling. An additional type of rabbit On DSGCs was later discovered (Hoshi et al. 2011, Kanjhan & Sivyer 2010), which shows transient responses to light and gap junction coupling to amacrine cells (Ackert et al. 2006, 2009). They prefer the same motion directions as the sustained On DSGCs but have different dendritic morphology. Their central projection pattern is unknown.

2.2. DSGCs Identified in the Mouse Retina

As in the rabbit, subtypes of On-Off DSGCs and sustained On DSGCs were later discovered in the mouse retina (Sun et al. 2006, Weng et al. 2005, Elstrott et al. 2008). As discussed in detail below, the functional subtypes also have unique molecular signatures, since they are selectively labeled in transgenic mouse lines and express distinct sets of endogenous genes. Molecular and genetic labeling has greatly accelerated the characterization of DSGC types in the mouse retina, revealing additional complexities within the known types and leading to the discovery of new types (Sanes & Masland 2015).

2.2.1. On-Off DSGCs. The four subtypes of On-Off DSGCs in the mouse exhibit functional properties that are similar to those in the rabbit. One morphological difference between the two species is that the dendritic arbors of all four subtypes in the rabbit do not show any spatial asymmetry along the preferred-null axis, but the superior subtype and some inferior subtype DSGCs in the mouse show asymmetric dendritic arbors biased toward the preferred direction (Kay et al. 2011, Trenholm et al. 2011). In a study on the superior subtype DSGCs, dendritic asymmetry does not contribute to the direction selectivity at the optimal motion speed for these cells and partially contributes to their direction selectivity at slow speed (Trenholm et al. 2011). The implication of this dendritic asymmetry for visual processing in the mouse is not yet clear.

Multiple transgenic lines and endogenous molecules have been identified to label On-Off DSGC subtypes (Huberman et al. 2009, Kay et al. 2011, Rivlin-Etzion et al. 2011, Trenholm et al. 2011). These molecular and transgenic markers corroborate and complement functional and morphological classifications of DSGC subtypes. Technically, they have propelled the transition from the rabbit to the mouse as the preferred model organism for studying retinal

direction selectivity. The ability to efficiently target DSGCs with a known preferred direction, even during early development before the maturation of light response, has enabled experiments on the assembly of the direction-selectivity circuit that were previously not feasible in the rabbit (Morrie & Feller 2016, Wei et al. 2011, Yonehara et al. 2011).

Specific labeling of On-Off DSGC subtypes also allows for a more complete and detailed survey of their central projections. In the main targets, the dorsal lateral geniculate nucleus (dLGN) and SC, On-Off DSGC axons occupy the most lateral or superficial layers of the retinorecipient zones (Huberman et al. 2009, Kay et al. 2011). In addition, subtypes of On-Off DSGCs provide moderate inputs to several other central nuclei. The posterior subtype On-Off DSGCs labeled in Trhr-GFP mice also innervate zona inserta and ventral LGN in the thalamus (Rivlin-Etzion et al. 2011). The superior and inferior subtypes labeled in the transgenic FSTL4-CreER line (also termed BD-RGCs) show additional axonal projection to the AOS nuclei, including medial terminal nucleus (MTN) and nucleus of the optic tract (NOT) (Kay et al. 2011).

A distinct subtype of On-Off DSGCs with anterior-direction preference has been found in the Hoxd10-GFP transgenic mouse line that also labels On DSGCs (Dhande et al. 2013). The On-Off DSGCs labeled in these mice show weaker direction tuning and slower speed tuning than the other On-Off DSGC subtypes and lack Cart expression seen in the other genetically labeled subtypes preferring posterior, superior, and inferior directions (Kay et al. 2011). Hoxd10-GFP-positive On-Off DSGCs project to the NOT in addition to SC (Dhande et al. 2013), indicating that they are involved in the horizontal slip–compensating eye movement during optokinetic nystagmus together with On DSGCs. It is unclear whether this anterior subtype consists of all On-Off DSGCs preferring this direction or whether another anteriorly tuned population is present in the mouse retina that is more comparable to the other three subtypes.

2.2.2. On DSGCs. Three subtypes of sustained On DSGCs equivalent to those in the rabbit have been found in the mouse (Sun et al. 2006) and are labeled in Hoxd10-GFP and Spig1-GFP transgenic lines (Dhande et al. 2013; Yonehara et al. 2008, 2009). A fourth subtype of On DSGCs preferring posterior-direction motion has recently been revealed in the mouse retina in a study that examines the relationship between the preferred directions of DSGCs and the geometry of the optic flow (Sabbah et al. 2017). These cells show significantly weaker directional tuning than the other three subtypes and therefore likely had fallen below the more stringent threshold of direction-selectivity metrics used in previous studies.

2.2.3. Additional types of mouse RGCs that show direction selectivity. Three molecularly defined mouse RGC types—J-RGCs, F-mini On, and F-mini Off RGCs—also exhibit direction-selective responses under specific stimulus conditions. All of them have highly asymmetric dendritic arbors oriented in the preferred direction. Their dendrites do not stratify in the same sublaminae as SACs. Given the critical role of SACs in generating direction selectivity of On-Off DSGCs and On DSGCs (Amthor et al. 2002, Vlasits et al. 2014, Yoshida et al. 2001), the lack of extensive dendritic overlap between SACs and these RGCs indicates that these ganglion cells rely on distinct mechanisms for generating direction selectivity.

J-RGCs were discovered in a transgenic mouse line that labels RGCs driven by the promoter for junctional adhesion molecule B (JAM-B) (Kim et al. 2008). Their monostratified dendrites in the Off sublamina of the IPL show a striking asymmetry toward the superior direction in the visual field. J-RGCs exhibit weak direction selectivity under scotopic conditions, which likely arises from an asymmetric RF surround (Joesch & Meister 2016, Kim et al. 2008). At high ambient light levels, the strength of the inhibitory surround is diminished. This is accompanied by a loss of direction selectivity (Joesch & Meister 2016). Besides this relatively fragile direction selectivity, J-RGCs

show color opponency and robust orientation selectivity under a broad range of light conditions (Joesch & Meister 2016, Nath & Schwartz 2017).

The other two types, F-mini On and F-mini Off RGCs, are defined by intersectional patterns of transcription factor expression. Both types express the transcription factor Foxp2 and together account for ~16% of all mouse RGCs (Rousso et al. 2016). Their properties are similar in many aspects and therefore constitute a paramorphic pair of cell types to represent similar features in the On and Off channels. The F-mini RGCs are among the smallest RGCs in the mouse retina with an RF center size of ~2° (Rousso et al. 2016). Their direction-selective responses are tuned to intermediate motion speeds between those of On DSGCs and On-Off DSGCs. F-mini RGCs prefer motion in the vertical directions that match their soma-to-dendrite directions (Rousso et al. 2016).

Both J-RGCs and F-mini RGCs project to SC and the lateral shell of dLGN but not to the AOS, indicating that they participate in image-forming visual pathways.

3. NEURAL MECHANISMS UNDERLYING DIRECTION SELECTIVITY OF INDIVIDUAL DSGCs

Direction selectivity has been primarily studied in On-Off DSGCs owing to their relative abundance in the retina and the availability of multiple genetic markers. Here, findings from the rich literature are organized into two main sections. Section 3.1 summarizes a set of mechanisms that *implement* the directional selectivity of DSGC spiking activity. These mechanisms include directionally tuned synaptic inputs onto DSGCs, followed by postsynaptic signal processing at DSGC dendrites. Section 3.2 focuses on mechanisms that *preserve* direction selectivity under diverse visual conditions. Multilayered mechanisms confer robustness of motion detection and are important to the animal during navigation in the versatile natural environment.

3.1. Mechanisms that Implement Direction Selectivity

The direction selectivity of DSGC spiking activity is implemented by the concerted action of pre- and postsynaptic mechanisms. Inhibitory and excitatory inputs onto DSGCs exhibit directionally tuned amplitude and temporal dynamics. Distinct spatiotemporal patterns of synaptic inputs in the preferred and null directions are further processed postsynaptically by DSGC dendrites to ensure optimal direction selectivity of the spiking activity. In this section, I first discuss the neural mechanisms underlying the directional tuning of DSGC inhibition (Section 3.1.1) and excitation (Section 3.1.2), then discuss the postsynaptic mechanisms of synaptic integration at DSGC dendrites (Section 3.1.3).

3.1.1. Directionally tuned inhibitory inputs onto DSGCs. Shortly after the discovery of On-Off DSGCs in the rabbit retina, Barlow & Levick (1965) proposed the null-direction inhibition model in which DSGC spiking is selectively suppressed during motion in the null direction. Subsequent whole-cell patch clamp recordings from rabbit DSGCs demonstrated stronger and faster inhibitory inputs onto DSGCs in the null direction and weaker and delayed inhibition in the preferred direction (Fried et al. 2002, Taylor & Vaney 2002). It is now well established that this directional inhibition comes from SACs. Indeed, SAC-mediated null-direction inhibition is well accepted as a universal and essential mechanism of direction selectivity for DSGCs. When gamma-aminobutyric acid (GABA) release from SACs is genetically disrupted, the direction selectivity of DSGCs is significantly reduced (Pei et al. 2015).

SACs are the only cholinergic neurons in the retina and also release GABA (Brecha et al. 1988, Vaney & Young 1988). As an axonless neuron, the SAC releases neurotransmitters from varicosities

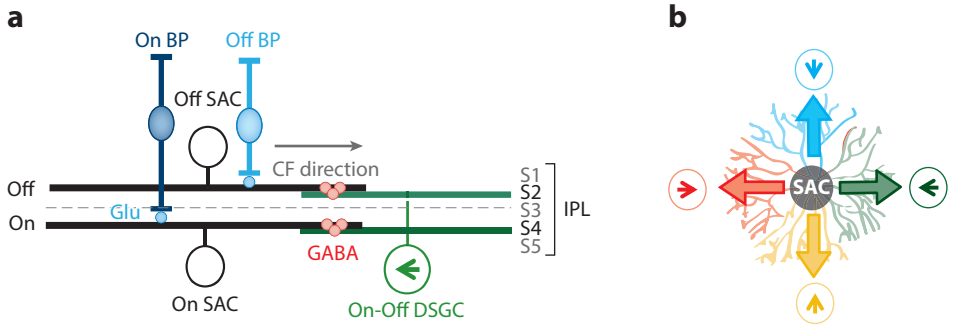

Figure 2

Inhibitory synaptic organization between starburst amacrine cells (SACs) and direction-selective ganglion cells (DSGCs) underlying null-direction inhibition of DSGCs. (*a*) Side-view schematic of the inhibitory connection between SACs and an On-Off DSGC in the inner plexiform layer (IPL). The dendrites of On and Off SACs receive glutamatergic inputs from On and Off bipolar cells (BPs) at sublaminae S2 and S4, respectively. The DSGC receives GABAergic inputs mainly from SAC distal dendrites oriented in the null direction (*rightward*) of the DSGC. Motion in the null direction strongly activates the presynaptic SAC dendrites in the centrifugal (CF) direction (*gray arrow*), leading to strong null-direction inhibition to the DSGC. Green arrow indicates DSGC preferred direction. (*b*) Top view shows the asymmetric inhibition from a SAC (*center*) to four On-Off DSGC subtypes. Each SAC dendritic quadrant preferentially forms GABAergic synapses with the DSGC with the same color. Preferred directions of DSGCs are represented by arrows in the circles. Adapted from Chen & Wei (2018).

in the distal regions of its radially symmetrical dendrites. On and Off SACs send monostratified dendrites to two narrow sublaminae in the On and Off layers of the IPL, which are often used to divide the IPL depth into five sublaminae (S1–S5), with Off and On SAC dendrites occupying S2 and S4 (Famiglietti 1983) (**Figure 2*a***). At each sublamina, SAC dendrites receive glutamatergic excitation from bipolar cells and release GABA and acetylcholine to the On or Off dendritic layers of On-Off DSGCs (Famiglietti 1983, 1991). Owing to their relatively high soma density and large dendritic field (~900 cells/mm^2; ~220-μm dendritic diameter in the mouse), dendrites of more than 100 SACs oriented in all directions overlap with the dendritic field of a single On-Off DSGC (~200-μm dendritic diameter) at each sublamina in the mouse retina (Keeley et al. 2007).

The directionally tuned inhibition between SACs and DSGCs relies on two properties of SACs. First, the activation of SAC dendrites is directionally tuned to the centrifugal direction (away from the soma). Second, GABAergic inputs onto a DSGC primarily come from SAC dendritic branches that are oriented in the null direction of the DSGC (**Figure 2*a*,*b***). During motion in the DSGC's preferred direction, its presynaptic SAC dendrites are activated in the centripetal direction, resulting in minimal SAC dendritic activation and little GABA release onto the DSGC. In contrast, during motion in the null direction, these SAC dendrites are centrifugally activated and provide strong GABAergic inhibition to DSGCs (**Figure 2**).

3.1.1.1. Mechanisms underlying centrifugal direction selectivity of SAC dendrites. As one of the central components in the null-direction inhibition model, centrifugal direction selectivity of SAC dendrites was first experimentally demonstrated in the rabbit retina by Euler et al. (2002) using a combination of multiphoton calcium imaging and patch clamp recording. The underlying mechanisms have since then been actively pursued in rabbit and mouse retinas (summarized in **Figure 3**).

Cell-intrinsic mechanisms, including dendritic morphology and passive and active membrane properties, play an important role in generating centrifugal direction selectivity of SAC dendrites.

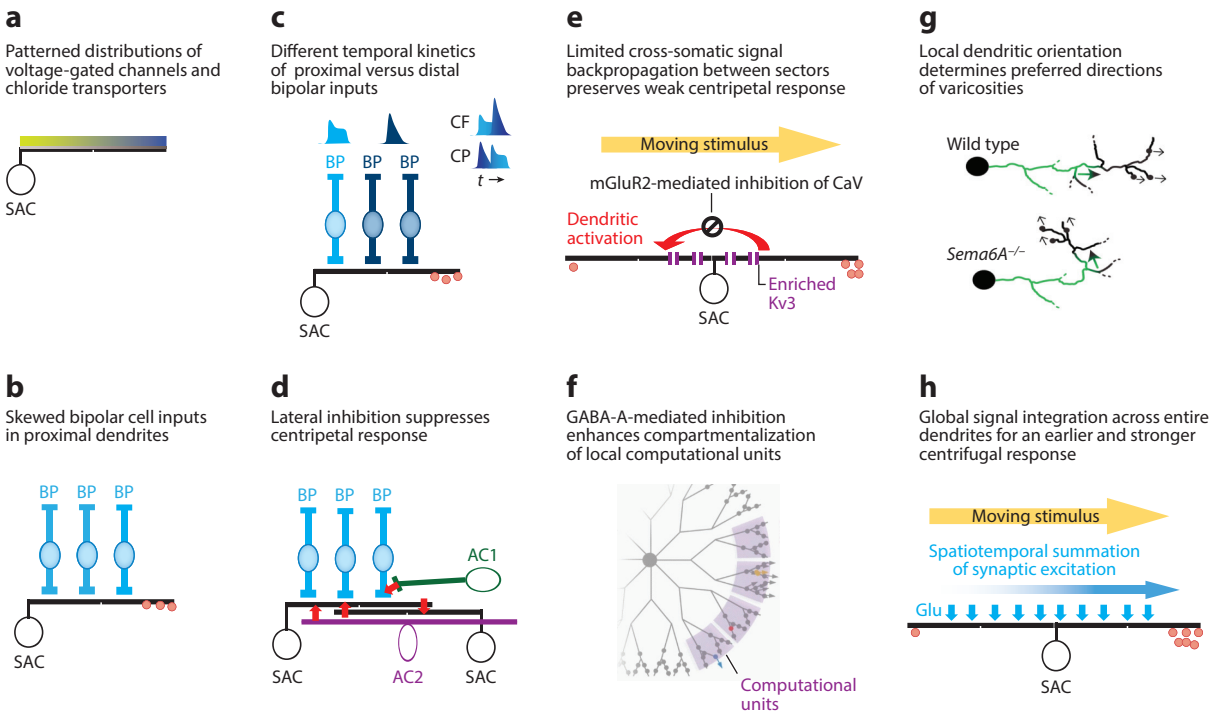

Figure 3

Models of centrifugal direction selectivity of starburst amacrine cells (SACs). (*a*) Distributions of active dendritic conductances and chloride transporters along SAC dendrites contributes to their centrifugal direction selectivity. (*b*) Segregated glutamatergic inputs onto two proximal thirds of SAC dendrites and neurotransmitter release (*red dots*) from the distal third contribute to the direction selectivity of SAC distal dendrites in the mouse. (*c*) Space-time wiring specificity model. Proximal and distal bipolar cell (BP) inputs have different response kinetics that give rise to strongest summation in the centrifugal direction (*top waveforms*). (*d*) Multiple sources of GABAergic inhibition shape SAC response. These include reciprocal inhibition (SAC-SAC), feedforward inhibition (AC2-SAC), and presynaptic inhibition (AC1-BP). Inhibitory transmission is represented as red arrows. (*e*) Electrotonic isolation between dendritic sectors is controlled by metabotropic glutamate receptor 2 (mGluR2)-mediated inhibition of Cav channels and enriched distribution of Kv3 channels in proximal dendrites. (*f*) GABAergic inhibition shapes the local computational units beyond secondary branching points. Panel adapted from Poleg-Polsky et al. (2018). (*g*) *Sema6A* mutant highlights the role of distal dendritic segments in determining preferred directions of distal varicosities. Arrows indicate preferred directions of dendritic segments and varicosities. Panel adapted from Morrie & Feller (2018). (*h*) Global signal integration across SAC dendritic arbors along the motion trajectory improves the strength and timing of SAC centrifugal response. Additional abbreviations: AC, amacrine cell; CF, centrifugal; CP, centripetal; Glu, glutamate; *t*, time.

Direction-dependent, nonlinear signal integration by SAC dendrites has been attributed to voltage-gated calcium and potassium channels, tetrodotoxin-insensitive sodium channels, and differential expression of chloride cotransporters in proximal and distal dendrites (Euler et al. 2002, Gavrikov et al. 2006, Hausselt et al. 2007, Oesch & Taylor 2010, Ozaita et al. 2004) (**Figure 3*a***). Together, SAC dendrites are capable of transforming the untuned glutamatergic excitatory inputs into directional outputs at distal dendrites even when inhibitory circuitry is pharmacologically blocked (Euler et al. 2002, Hausselt et al. 2007, Oesch & Taylor 2010), highlighting intrinsic mechanisms as an integral part of motion processing by SAC dendrites.

Synaptic excitation has been implicated in generating SAC direction selectivity in two models in the mouse retina. In the first model, glutamatergic inputs onto SACs are skewed toward the

proximal two-thirds of the dendrites (Ding et al. 2016, Vlasits et al. 2016). Computational modeling indicates that the spatial segregation of excitatory inputs and synaptic release contributes to direction selectivity in distal varicosities (**Figure 3*b***) (Vlasits et al. 2016). In the second model of space-time wiring specificity based on differential targeting of bipolar cell types along SAC dendrites, centrifugal direction selectivity can arise from different temporal kinetics of bipolar cell–evoked responses in the proximal and distal SAC dendrites (**Figure 3*c***) (Greene et al. 2016, Kim et al. 2014). This model is supported in Off SACs by connectomic analysis (Ding et al. 2016, Kim et al. 2014) and recordings of Off SACs (Fransen & Borghuis 2017). However, whether the space-time model applies to On SACs is still under investigation. On bipolar cell type BC7 targets more proximal regions of On SACs than the three BC5 types do in connectomic analysis (Ding et al. 2016), but the kinetics of these bipolar types are not consistent with the space-time model when their responses are probed with sinusoidal or step light restricted to the RF center (Ichinose et al. 2014). Furthermore, On SAC excitatory postsynaptic currents (EPSCs) evoked in proximal and distal dendrites show a less pronounced difference in temporal kinetics when stimulated by circular white noise (Fransen & Borghuis 2017) and show no difference when stimulated with bright annuli (Stincic et al. 2016, Vlasits et al. 2016) or light bars (Stincic et al. 2016) using the filtered back projection method (Johnston et al. 2014). Future studies on the response kinetics of bipolar cell types during motion stimuli will yield more insights into their contributions to the direction selectivity of SAC dendrites, since RF properties of distinct bipolar cell types are profoundly influenced and diversified by lateral inhibition through center-surround interactions (Franke et al. 2017).

The role of synaptic inhibition in SAC directional tuning has also been intensively studied. Reciprocal inhibition of neighboring SACs was the first discovered type of inhibitory inputs onto SACs in the rabbit by electron microscopy (Famiglietti 1991) and paired whole-cell voltage clamp recording (Lee & Zhou 2006). SAC-SAC inhibition was also detected in the mouse retina by paired recording (Chen et al. 2016, Kostadinov & Sanes 2015) and accounts for over 90% of the total number of amacrine cell inputs to SACs based on connectomic analysis (Ding et al. 2016). This microcircuit motif has been proposed to participate in centrifugal direction selectivity of SAC dendrites by providing lateral inhibition in the centripetal direction when a visual stimulus moves from the surround to the soma (**Figure 3*d***) (Ding et al. 2016, Lee & Zhou 2006, Münch & Werblin 2006). The support for this hypothesis comes from pharmacological blockade of GABA-A receptors, which results in reduced direction selectivity of SAC dendrites (Chen et al. 2016, Ding et al. 2016, Lee & Zhou 2006, Poleg-Polsky et al. 2018, Vlasits et al. 2016). However, GABA-A receptor antagonists also block inhibitory synapses other than SAC-SAC inhibition, including feedforward inhibition from non-SAC amacrine cells to SACs and presynaptic inhibition at the bipolar axonal terminals (**Figure 3*d***) (Ding et al. 2016, Lee & Zhou 2006). When SAC-SAC inhibition is selectively disrupted by conditionally knocking out vesicular GABA transporters (Vgat) in SACs, the direction selectivity of On and Off SACs during a moving bar stimulus is not impaired (Chen et al. 2016), indicating that mechanisms other than SAC-SAC inhibition are sufficient to implement direction selectivity under this condition. The physiological function of SAC-SAC inhibition remains an important outstanding question.

GABAergic inhibition of SACs is completely eliminated in a conditional knockout (cKO) mouse line with SAC-specific deletion of the GABA receptor alpha 2 (Gabra2) subunit (Chen et al. 2016). This manipulation leads to reduced direction selectivity of Off, but not On, SACs during the moving bar stimulus, revealing divergent inhibitory control in the On and Off pathways. Since Off SACs show reduced direction selectivity in Gabra2 but not Vgat cKO mice, feedforward inhibition from non-SAC amacrine cells to Off SACs is likely involved in suppressing centripetal dendritic activation of Off SACs. In contrast, On SACs show no reduction of direction selectivity

in either Gabra2 or Vgat cKO mice during the same moving bar stimulus, indicating that direct GABAergic inputs onto On SACs are not required for direction selectivity under this condition (Chen et al. 2016). Interestingly, addition of a flickering checkboard to the moving bar stimulus as a source of background noise reveals the functional significance of inhibitory inputs onto On SACs, since the On component of On-Off DSGC response became less directionally tuned in Gabra2 cKO under this stimulus condition. It is likely that noise in the background is more efficient in activating inhibitory inputs onto On SACs and thereby uncovers the differences of motion responses between wild type and Gabra2 cKO groups. It also indicates that lateral inhibition of On SACs is required for optimal noise resilience of direction selectivity. However, whether SAC-SAC inhibition and/or feedforward inhibition onto SACs is involved in this function has not been determined. The mechanisms underlying this noise resilience are also unknown.

It is noteworthy that the distribution of synaptic inputs along SAC dendrites is different between mice and rabbits. Early anatomical studies using electron microscopy indicate that synaptic inputs onto SAC dendrites in the rabbit are distributed along the entire dendritic length (Famiglietti 1991). In contrast, amacrine cell inputs onto mouse SACs are concentrated in the proximal dendrites (Ding et al. 2016, Kostadinov & Sanes 2015). Computational modeling suggests that this difference between species may confer different linear speed tuning of SACs on the retina to conserve angular velocity tuning in the two species with different eye diameters (Ding et al. 2016).

3.1.1.2. Local versus global dendritic processing by SAC dendrites during linear motion. A remarkable feature of SACs is their highly compartmentalized dendrites. On the basis of four preferred directions of postsynaptic On-Off DSGCs, the dendritic field of a presynaptic SAC can be divided into four quadrants. Each quadrant has a distinct preferred direction and inhibits a distinct subtype of On-Off DSGCs (Briggman et al. 2011, Euler et al. 2002, Fried et al. 2002, Lee et al. 2010, Wei et al. 2011) (**Figure 2*b***). Sufficient isolation between dendritic quadrants during linear motion stimuli is important for maintaining a weak centripetal response by limiting the backpropagation of the strong centrifugal response from the opposite quadrant. The perisomatic and proximal dendritic region is indeed well equipped for dampening dendritic activation and preventing cross-somatic propagation of membrane depolarization mediated by active conductances (**Figure 3*e***). SAC soma and proximal dendrites are enriched in Kv3 voltage-gated potassium channels, which provide a voltage-dependent shunt near the soma (Ozaita et al. 2004). Furthermore, the backpropagation of dendritic signals across the soma is controlled by metabotropic glutamate receptor 2 (mGluR2) signaling in SACs through inhibition of dendritic voltage-gated calcium channels (Koren et al. 2017). Endogenous mGluR2 signaling may ensure sufficient electrotonic isolation of SAC dendrites even in the presence of strong ionotropic glutamate receptor activation. Together, Kv3 channels and mGluR2-mediated inhibition of calcium channels likely work in concert to prevent regenerative electrical events from initiating and propagating to sectors that are not activated in the centrifugal direction.

Functional compartmentalization of SAC dendrites not only is evident between the radial dendritic sectors but also occurs at a finer spatial scale within the sector. Cable properties of the thin distal dendrites favor their electrical isolation (Miller & Bloomfield 1983). Indeed, calcium imaging experiments with Oregon Green BAPTA-1 show that visually evoked calcium signals of varicosities within a dendritic sector can be further clustered into multiple functional groups beyond the secondary branching points (Morrie & Feller 2018, Poleg-Polsky et al. 2018). GABA-A receptor-mediated inhibition contributes to the functional clustering of SAC varicosities by improving the strength of their directional tuning and reducing the variability in their preferred directions within a cluster (Poleg-Polsky et al. 2018) (**Figure 3*f***). The impact of local dendritic orientation is highlighted in a study on *Sema6A* mutant mice. SAC dendrites in these mutants

show increased tortuosity instead of extending radially from the soma (Morrie & Feller 2018, Sun et al. 2013). Intriguingly, although SAC varicosities in *Sema6A* mutants remain direction selective, their preferred directions are altered and align best to the orientation of the dendritic segments after the fourth branch point near the end of the excitatory input distribution (Morrie & Feller 2018). Therefore, local dendritic computation within a small segment of distal dendrites plays an important role in determining the preferred directions of SAC output synapses (**Figure 3*g***).

Since direction selectivity can be generated within a SAC dendritic sector during spatially restricted moving stimuli (Hausselt et al. 2007, Koren et al. 2017, Lee & Zhou 2006), most investigations of SAC direction selectivity consider each sector as an independent computational unit, where synaptic inputs onto a dendritic branch are processed locally in a direction-dependent manner. Although electrotonic isolation is prominently featured in SAC function, as discussed above, the radial sectors nonetheless are connected by the soma. Linear motion across the retina activates multiple dendritic sectors of a SAC along the motion trajectory. Does the directionally tuned dendritic response arise solely from local computation within each sector? Or do other sectors also contribute to motion-evoked responses in a given sector?

A role of global dendritic integration in generating the centrifugal response has been supported by computational modeling (Tukker et al. 2004) and experimentally demonstrated in two-photon calcium imaging experiments that compare the SAC centrifugal response evoked by a full-field moving bar with those evoked by moving bars restricted to subregions of a SAC dendritic field (Koren et al. 2017) (**Figure 3*b***). Compared to activating only a local sector, global dendritic activation maximizes the amplitude of the centrifugal response and triggers the response when the moving stimulus reaches a spatial location earlier in the motion trajectory (Koren et al. 2017). Therefore, SAC sectors are not completely independent during visual processing. Spatiotemporal summation of dendritic excitation over the entire dendritic field along the motion trajectory is necessary for a strong and early-onset centrifugal response in distal dendrites during full-field linear motion (**Figure 3*b***).

3.1.1.3. Asymmetric wiring of GABAergic synapses between SACs and DSGCs. The conversion of directionally tuned activation of SAC dendrites to directionally tuned inhibition of DSGCs requires highly asymmetric wiring between SAC dendrites and DSGCs along the preferred-null axis (**Figure 2*a***). This asymmetry has been demonstrated functionally by paired recordings between SACs and On-Off DSGCs in the rabbit (Fried et al. 2002, Lee et al. 2010) and the mouse (Wei et al. 2011). Similar asymmetric inhibition also exists between SACs and On DSGCs (Brombas et al. 2017, Yonehara et al. 2011). In the mouse retina, this asymmetry arises in an activity-independent manner during the second postnatal week before the onset of light response (Wei et al. 2011, Yonehara et al. 2011), owing to an asymmetric increase of synapse number (Morrie & Feller 2015; also see review by Morrie & Feller 2016).

Consistent with the functional asymmetry, the structural asymmetry of SAC-DSGC connection is reported in a remarkable study that combines functional calcium imaging and serial block-face electron microscopy to reconstruct the synaptic connectivity between SACs and On-Off DSGCs (Briggman et al. 2011). Owing to the antiparallel relationship between the orientation of the presynaptic SAC dendrites and the preferred directions of the postsynaptic On-Off DSGCs, each quadrant of the radial SAC dendritic field selectively forms synaptic contacts with one of the four On-Off DSGC subtypes (**Figure 2*b***). It is noteworthy that the anatomical asymmetry, which agrees well with the functional asymmetry for GABAergic connections between SACs and On-Off DSGCs, is not consistent with the symmetric cholinergic excitation between the same cell pairs measured in dual patch clamp recordings (Lee et al. 2010, Pei et al. 2015). The cholinergic connectivity pattern between SACs and DSGCs is discussed in more detail in the next section.

3.1.2. Directionally tuned synaptic excitation of DSGCs. Excitation of DSGCs consists of glutamatergic and cholinergic components. EPSCs of On-Off DSGCs measured in whole-cell voltage clamp recordings are stronger in the preferred direction than the null direction in both rabbit and mouse retinas during full-field moving bar stimuli (Fried et al. 2005, Lee et al. 2010, Pei et al. 2015, Taylor & Vaney 2002). Pharmacologically isolated glutamatergic EPSCs are tuned to the preferred direction (Fried et al. 2005, Lee et al. 2010, Park et al. 2014). But this directional tuning has not been detected using alternative methods such as calcium imaging in bipolar cells and glutamate imaging using an extracellular glutamate sensor iGluSnFR expressed in DSGCs (Chen et al. 2014, Park et al. 2014, Yonehara et al. 2013). Cholinergic EPSCs measured in voltage clamp experiments show directional tuning in some studies (Fried et al. 2005, Lee et al. 2010) but not in others (Park et al. 2014, Sethuramanujam et al. 2016).

Unlike the strikingly asymmetric wiring pattern of SAC-DSGC inhibition, the neural basis of directional DSGC excitation is not clear. GABAergic mechanisms have been implicated in shaping DSGC excitatory inputs because DSGC excitation becomes nondirectional in the presence of GABA receptor antagonists (Fried et al. 2005, Lee et al. 2010). This directional excitation does not depend on asymmetric cholinergic connectivity between SACs and DSGCs. Indeed, cholinergic inputs onto a DSGC are evenly distributed from SACs located at both the null and preferred sides of the DSGC in paired recording experiments (Lee et al. 2010, Pei et al. 2015) (**Figure 4**). This functional symmetry contradicts the anatomical asymmetry of SAC-DSGC synaptic contacts in the connectomic analysis (Briggman et al. 2011), an interesting discrepancy that implies differential distributions of acetylcholine and GABA release sites of a SAC to its postsynaptic DSGCs. An explanation for directional DSGC excitation has been suggested from a technical perspective: Because of the imperfect space clamp, the null-direction EPSCs in whole-cell voltage clamp

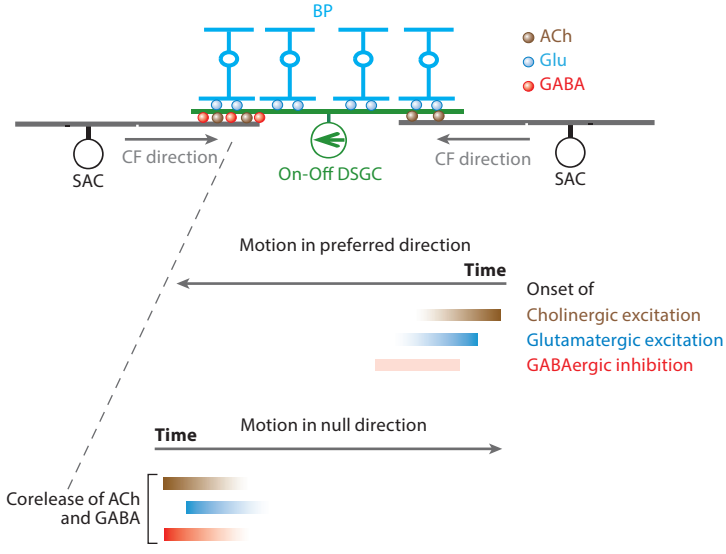

Figure 4

Excitatory and inhibitory synaptic organization onto direction-selective ganglion cells (DSGCs). GABAergic, cholinergic, and glutamatergic inputs onto a DSGC are organized in spatially distinct patterns along the preferred-null axis. Asymmetric wiring occurs between the starburst amacrine cell (SAC) and DSGC for GABAergic, but not cholinergic, synapses. Spatial wiring patterns of glutamatergic, cholinergic, and GABAergic connections result in a direction-dependent temporal relationship among them. Onset timings of synaptic inputs are color coded. Only one dendritic layer is illustrated for clarity. Additional abbreviations: ACh, acetylcholine; BP, bipolar cell; CF, centrifugal; GABA, gamma-aminobutyric acid.

recordings may be more severely distorted and underestimated than preferred-direction EPSCs because of the concomitant strong null-direction inhibitory inputs (Poleg-Polsky & Diamond 2011, Vaney et al. 2012). However, the space clamp issue cannot fully account for the measured EPSC patterns, because the direction selectivity of EPSCs is not correlated with the direction selectivity or the absolute amplitude of inhibitory postsynaptic currents (IPSCs) in both mouse and rabbit DSGCs (Pei et al. 2015, Percival et al. 2018).

To remove the influence of directional inhibitory inputs on EPSC measurements in voltage clamp recordings, GABA release from SACs is genetically disrupted by conditionally knocking out Vgat from SACs (Pei et al. 2015). In these Vgat cKO mice, motion-evoked IPSCs of DSGCs are significantly reduced and become nondirectional. In the absence of directional inhibition, direction selectivity of On-Off DSGC spiking activity is significantly reduced but not completely abolished. A subset of DSGCs still show directional tuning of their excitatory inputs and spiking activity, though this residual direction selectivity is significantly weaker than that in the wild type mice (Pei et al. 2015). As in the wild type mice, directional excitation in Vgat cKO mice is abolished by GABA receptor antagonists. The neural mechanisms underlying this directional tuning remain to be elucidated, since directional excitation cannot be explained by the dendritic morphology of DSGCs, asymmetric wiring of SAC-DSGC cholinergic synapses, or the space clamp issue. It is notable that the contribution of cholinergic excitation to DSGC response varies with contrast levels (Sethuramanujam et al. 2016) and the spatiotemporal patterns of the motion stimuli (Grzywacz et al. 1998a,b). Whether directional cholinergic excitation of DSGCs is more prominent during certain visual stimuli than others deserves future investigation.

Together, multiple lines of evidence support that directional excitation of DSGCs is not merely a technical artifact, albeit many outstanding questions remain. DSGC excitation appears to be weakly tuned and exhibits greater variability across cells compared to the prominent and robust directional inhibition. Nevertheless, a small directional bias of excitation may act cooperatively with directional inhibition and contribute to optimal direction selectivity of DSGCs. A better understanding of the structure-function relationship of SAC-DSGC cholinergic synapses as well as synaptic and circuit mechanisms that selectively control SAC acetylcholine release will be important next steps for resolving this puzzle.

3.1.3. Postsynaptic mechanisms of direction selectivity at DSGC dendrites. Although the postsynapses on DSGC dendrites are uniformly distributed without a bias on the preferred-null axis (Briggman et al. 2011, Jakobs et al. 2008, Jeon et al. 2002), postsynaptic mechanisms at DSGC dendrites play an important role in amplifying and preserving the direction selectivity of DSGC spiking response. These mechanisms, including nonlinear spatiotemporal integration of synaptic inputs, temporal interactions of excitation and inhibition, and local dendritic computation, are discussed in this section.

Synaptic activation of *N*-methyl-D-aspartate receptor (NMDA) receptors together with shunting GABAergic inhibition leads to a multiplicative scaling of postsynaptic response that enhances the fidelity of direction selectivity (Poleg-Polsky & Diamond 2016a). Local direction-selective dendritic response is further amplified by dendritic spikes that propagate to the soma with high probability to enhance the direction selectivity of the spiking output (Brombas et al. 2017, Oesch et al. 2005, Schachter et al. 2010, Sivyer & Williams 2013).

The direction-dependent temporal relationship between excitation and inhibition, which arises from the synaptic organization of the bipolar cell-SAC-DSGC circuitry, is important for signal integration at DSGC dendrites. During moving bar stimuli, the average IPSC waveform is delayed compared to the EPSC waveform during preferred-direction motion but arrives earlier and coincides better with EPSCs during null-direction motion (Fried et al. 2002, Taylor

& Vaney 2002). The delayed preferred-direction inhibition reflects the spatiotemporal offset of the DSGC's inhibitory RF relative to the excitatory RF owing to the spatially asymmetric wiring of SAC-DSGC GABAergic synapses (Fried et al. 2002, Sethuramanujam et al. 2016) (**Figure 4**). At a shorter timescale, motion-evoked EPSCs and IPSCs of a DSGC have been measured near-simultaneously by rapidly alternating the holding potentials during voltage clamp recordings (Cafaro & Rieke 2010). This method reveals that synaptic noise correlation is stronger in the null direction and weaker in the preferred direction. Modeling suggests that stimulus-dependent noise correlation further enhances the direction selectivity of the DSGC by minimizing its firing in the null direction.

The direction-selective spiking response of a DSGC can be evoked by a local motion stimulus restricted to a subregion of the DSGC RF, which can span as little as 1/10 of the RF in the rabbit (Barlow & Levick 1965). These direction-selective subunits within the RF imply the functional independence of DSGC dendritic subdomains. They also indicate that direction-selectivity mechanisms can operate at a spatial scale much smaller than the size of the DSGC RF, presumably corresponding to individual SAC branches that densely tile the DSGC dendritic field. Interestingly, DSGC direction-selective subunits are reminiscent of the RF structure of direction-selective neurons in the primate cortical area MT, which consist of local direction-selective subunits without global, cross-subunit interaction (Hedges et al. 2011).

Furthermore, many postsynaptic mechanisms influence the robustness of direction selectivity, as discussed in the next section.

3.2. Mechanisms that Preserve Direction Selectivity Under Diverse Visual Conditions

The direction-selective circuit reliably reports the direction of motion for both bright and dark moving stimuli of different sizes, brightness, contrasts, and speeds and even in the presence of visual noise. How is direction selectivity maintained while moving objects and their environments vary broadly and dynamically in the operating range of the circuit? Recent studies have begun to address this question by identifying neural mechanisms that are selectively engaged by specific features in the visual stimuli to preserve direction selectivity.

3.2.1. Maintenance of direction selectivity across contrast levels. Directional tuning of On-Off DSGC inhibition is preserved over a broad range of contrast. In rabbits and guinea pigs, null-direction IPSCs exhibit highly nonlinear contrast sensitivity and saturate at low contrast (Lipin et al. 2015), leading to strong suppression of the null-direction response starting at a low contrast threshold. Contrast-invariant direction selectivity of SAC dendrites has also been investigated. In the mouse retina, pharmacological blockade of GABA-A receptors is shown to reduce the direction selectivity of SAC dendrites, particularly under high contrast conditions (Ding et al. 2016). However, genetic deletion of GABA-A receptors from SACs does not affect the direction selectivity of On-Off DSGCs over a range of contrast levels (Chen et al. 2016), suggesting that the effect of GABA receptor antagonists may arise from inhibition of bipolar axonal terminals presynaptic to SACs. As discussed in the previous section, the direction selectivity of SAC dendrites is implemented by a diverse set of synaptic and intrinsic mechanisms, which probably act in concert to preserve direction selectivity across contrast levels.

In the mouse retina, the excitation/inhibition (E/I) balance of On-Off DSGCs has been shown to remain stable over a broad contrast range (Poleg-Polsky & Diamond 2016b). Computational modeling suggests that this feature is important for reliable direction selectivity. Notably, the glutamatergic inputs to SACs exhibit higher contrast sensitivity than those to On-Off DSGCs

(Poleg-Polsky & Diamond 2016b) owing to different types of presynaptic bipolar inputs (Poleg-Polsky & Diamond 2016b) and differential postsynaptic receptor compositions in SACs and On-Off DSGCs (Sethuramanujam et al. 2017). The high-sensitivity glutamatergic inputs onto SACs undergo a nonlinear input-output transformation, resulting in reduced contrast sensitivity of acetylcholine (ACh) and GABA release from SACs to DSGCs to match that of glutamatergic excitation onto DSGCs (Poleg-Polsky & Diamond 2016b). A different scenario is reported by another study (Sethuramanujam et al. 2016), in which the relative contributions of cholinergic versus glutamatergic inputs are contrast dependent, with cholinergic excitation dominating at low contrast. It is noteworthy that the background light intensities and the contrast ranges differ in these two studies, which may contribute to the differences in the results. In both scenarios, the overall excitation of DSGCs is scaled with inhibition across contrast levels.

3.2.2. Mechanisms that compute direction selectivity for dark versus bright moving stimuli. Direction selectivity for bright and dark moving objects is processed in separate sublaminae of the IPL. Both On and Off SAC dendrites show centrifugal direction selectivity and asymmetric wiring with DSGCs (Briggman et al. 2011, Chen et al. 2016, Fransen & Borghuis 2017). Therefore, directional inhibition of On-Off DSGCs during On and Off stimuli is provided by On and Off SACs, respectively. Consistent with separate inhibitory inputs to DSGCs at the On and Off layers, blocking On bipolar cell signaling with the mGluR6 agonist AP4 does not abolish directional tuning of DSGC Off spiking in the rabbit retina (Kittila & Massey 1995).

However, similar connectivity patterns from On and Off SACs to DSGCs do not necessitate mirror symmetric circuit organizations in the On and Off pathways. Instead, circuitries presynaptic to On and Off SACs consist of divergent anatomical and functional components. On and Off SAC dendrites are innervated by distinct sets of bipolar cells and amacrine cells (Ding et al. 2016, Famiglietti 1991, Helmstaedter et al. 2013, Kim et al. 2014). When specific types of inhibitory inputs to SACs are genetically disrupted, the direction selectivity of On and Off SACs is differentially affected (Chen et al. 2016).

Interactions of the On and Off pathways dynamically influence the responses of retinal neurons (Geffen et al. 2007, Pearson & Kerschensteiner 2015, Tikidji-Hamburyan et al. 2014). On/Off interactions in the direction-selective circuit have been observed in multiple studies during pharmacological manipulations or during specific visual stimulation conditions. In the rabbit retina, crossover inhibition between On and Off dendritic layers of On-Off DSGCs has been reported for temporally close motion stimuli (Stasheff & Masland 2002). Blocking GABAergic transmission unmasks directionally tuned Off responses in gap junction–coupled On DSGCs (Ackert et al. 2009). In the mouse retina, blocking On bipolar cells reduces the direction selectivity in the Off pathway by reducing Off SAC excitation (Rosa et al. 2016). When ambient luminance level increases, a subset of On-Off DSGCs change from On-dominated response to Off-dominated response but maintain their directional tuning (Pearson & Kerschensteiner 2015). An adaptation protocol with repeated stimulation using drifting gratings lead to a polarity switch of On and Off SAC responses (Vlasits et al. 2014), which may contribute to the reversal of the preferred direction of On-Off DSGCs under the same stimulus condition (Rivlin-Etzion et al. 2012). Together, these findings add to increasing examples of On/Off channel asymmetry and interaction in the retina and higher visual system (for example, Buldyrev & Taylor 2013, Chichilnisky & Kalmar 2002, Turner & Rieke 2016, Zaghloul et al. 2003, Ratliff et al. 2010, Komban et al. 2014, K.-S. Lee et al. 2016, Nichols et al. 2013, Rekauzke et al. 2016). The detailed synaptic circuitries that mediate these interesting observations and how these mechanisms are used for motion detection under natural conditions remain to be uncovered.

3.2.3. Mechanisms that preserve direction selectivity for noisy motion stimuli. Naturalistic motion stimuli are often obscured by nonmotion features embedded in the moving object and its background. Preventing the degradation of motion detection in complex visual environments is of ecological importance. To investigate the mechanisms underlying noise resilience of direction selectivity, additional features have been incorporated into conventional laboratory motion stimuli. As discussed in the previous section, noise in the motion background engages lateral inhibition of On SACs to prevent the deterioration of direction selectivity in the On pathway (Chen et al. 2016). Noise resilience is also implemented by DSGC dendritic mechanisms. When the intensities of the moving bar and the featureless background vary randomly and independently, NMDA receptor signaling in DSGCs plays a role in amplifying correlated excitation and improves the fidelity of direction selectivity (Poleg-Polsky & Diamond 2016a). By contrast, NMDA receptor blockade has no effect on direction selectivity during noise-free moving bar stimuli (Kittila & Massey 1997, Poleg-Polsky & Diamond 2016a).

3.2.4. Mechanisms that preserve direction selectivity over a range of motion speeds. In the null direction, strong inhibitory inputs to DSGCs need to be generated in time to sufficiently cancel cholinergic and glutamatergic excitation over a range of motion speeds. The direction-selective temporal relationship between DSGC excitation and inhibition is a built-in feature of the circuit architecture among SACs, bipolar cells, and DSGCs. Before a moving object activates bipolar cell inputs onto a DSGC, it first activates SACs that are laterally connected to the DSGC earlier in the motion trajectory (Koren et al. 2017). SACs on both null and preferred sides of the DSGC form cholinergic synapses with the DSGC, while only the SACs on the null side are wired to DSGCs with GABAergic synapses (Briggman et al. 2011, Fried et al. 2002, Lee et al. 2010, Pei et al. 2015). Therefore, in the preferred direction, DSGCs receive leading lateral cholinergic excitation from the centrifugally activated SAC dendrites but receive minimal and delayed inhibition from the centripetally activated SAC dendrites later in the motion trajectory (**Figure 4**). By contrast, in the null direction, DSGCs receive simultaneous cholinergic excitation and GABAergic inhibition owing to the corelease of GABA and ACh from the centrifugally activated SAC dendrites (**Figure 4**). Therefore, GABAergic and cholinergic inputs in the null, but not the preferred direction, are highly correlated at all speeds. In rabbits and guinea pigs, inhibitory inputs onto DSGCs show steep saturation, which also contributes to speed-invariant null-direction inhibition (Lipin et al. 2015).

In the preferred direction, endogenous mGluR2 signaling in SACs is required for maintaining the preferred-direction firing of DSGCs at higher speed. When mGluR2 is blocked, strong centrifugal response in one SAC dendritic sector shows enhanced backpropagation to the centripetally activated sector and causes excessive preferred-direction inhibition of DSGCs. The timing of backpropagated SAC dendritic signals during mGluR2 blockade depends on the speed of linear motion across SAC dendrites. At faster motion speed, enhanced preferred-direction inhibition caused by mGluR2 blockade arrives early enough to interact with DSGC excitation, resulting in a reduction of preferred-direction firing (Koren et al. 2017). Therefore, maintaining electrotonic isolation of SAC dendrites is of particular importance for direction selectivity at higher motion speeds.

3.3. Summary and Outlook on Direction-Selectivity Mechanisms of Individual DSGCs

The pursuit of neural mechanisms underlying direction selectivity has been a tour de force that leverages an almost exhaustive list of cutting-edge methods in neural circuit analysis. Recent studies showcase how the powers of functional, connectomic, and modeling approaches are harnessed

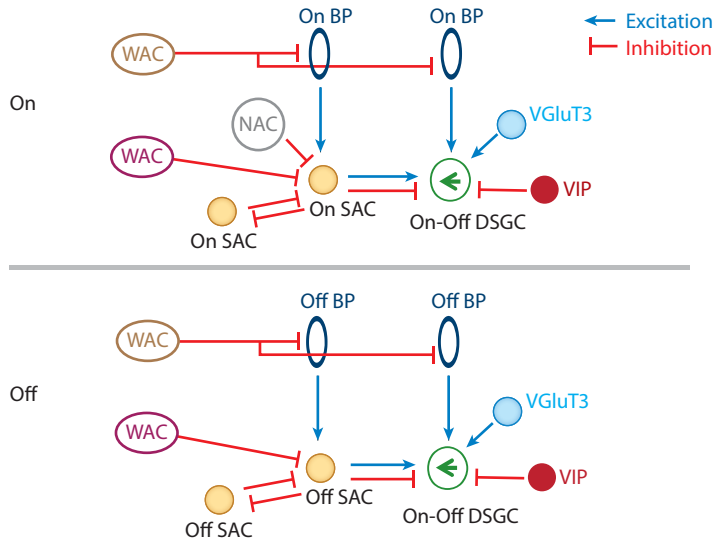

Figure 5

Schematic of anatomically and functionally identified connections in the On and Off pathways of the direction-selective circuit. Abbreviations: BP, bipolar cell; NAC, narrow-field amacrine cells; SAC, starburst amacrine cell; VGluT3, vesicular glutamate transporter type 3; VIP, vasoactive intestinal polypeptide-expressing amacrine cell**;** WAC, wide-field amacrine cells. Figure adapted from Chen & Wei (2018).

and integrated to tackle outstanding questions in this classic example of neural computation. An emerging theme from these studies is that multiple synaptic and intrinsic mechanisms jointly implement direction selectivity of SACs and DSGCs in a stimulus-dependent manner. Varying or adding specific visual features such as contrast, luminance, and noise to the standard moving bar and drifting grating stimuli have revealed previously unknown mechanisms and synaptic loci of direction selectivity. Stimulus-dependent circuit function may contribute to the different results and discrepancies in the current literature. Future research will benefit from the use of diverse motion stimuli and a deeper understanding of stimulus-dependent mechanisms upstream of SACs and DSGCs.

State-of-the-art anatomical and functional approaches are pivotal to the identification of cellular and synaptic substrates of direction selectivity. These approaches have uncovered distinct sets of new amacrine cell types that are synaptically connected with SACs and DSGCs (summarized in **Figure 5**). Connectomic reconstruction reveals distinct types and fractions of wide-field and narrow-field amacrine cells that receive inputs from and release neurotransmitters to On and Off SACs (Ding et al. 2016). Functional mapping, including targeted recordings and optogenetic activation of genetically labeled amacrine cells, had led to the identification of two new amacrine types that are not reported in connectomic studies. The first type, Vglut3-positive amacrine cells, which corelease both glycine and glutamate, provide glutamatergic but not glycinergic inputs to On-Off DSGCs (S. Lee et al. 2016). The second type are the narrow-field vasoactive intestinal polypeptide (VIP)-positive GABAergic amacrine cells that inhibit On-Off DSGCs (Park et al. 2015). The functions of both cell types in the direction-selective circuit are yet to be elucidated.

Notably, all of these newly identified cell types exhibit dendritic stratification patterns that are distinct from the narrow stratification seen in SACs and DSGCs at S2 and S4 in the IPL. Instead, the dendrites of these various amacrine cell types either diffusely encompass S2 and S4

or are in close proximity to them. Therefore, functional connectivity is not strictly confined by costratification of neurites in the IPL.

4. MECHANISMS OF DIRECTION CODING BY DSGC POPULATIONS

At a given visual space, multiple DSGCs with different preferred directions collectively encode motion direction. Theoretical analysis indicates that both singe-cell properties and population activity of On-Off DSGCs are important for coding performance (Fiscella et al. 2015). A population-level feature, synchronous firing among neighboring DSGCs, may improve feature encoding (Amthor et al. 2005). In the transient type of On DSGCs in the rabbit retina, synchronous firing among neighboring cells during motion stimuli is mediated by gap junction coupling and is selectively reduced by GABAergic inhibition during null-direction motion (Ackert et al. 2006). In the superior subtype On-Off DSGCs in the mouse retina, the combined action of electrical and chemical synapses is involved in increasing firing synchrony between neighboring DSGCs of the same subtype (Trenholm et al. 2014). In contrast, the other three subtypes of On-Off DSGCs do not contain electrical synapses. The ethological significance of selective gap junction coupling within the superior subtype On-Off DSGCs in visual processing is an unanswered question for future exploration.

Another population-level response feature is stimulus-dependent noise correlation of spiking activity among On-Off DSGCs. Using a combination of whole-cell patch clamp recordings and modeling, Zylberberg et al. (2016) show that stimulus-dependent noise correlation can be explained by a network model in which a common source of synaptic noise to multiple DSGCs is modulated by stimulus-dependent gain. Enhanced direction coding through stimulus-dependent noise correlation is supported by several metrics of coding performance and may represent a general strategy to improve information coding at the population level by other brain circuits.

Population-level analysis also advances our understanding of the organizational principle of DSGC preferred directions. In a study by Sabbah et al. (2017), the preferred directions of On and On-Off DSGCs in the mouse retina are systematically mapped throughout retinal locations and then compared with the corresponding spherical geometry of optic flow in the animal's visual space. The authors find that rather than adhering to a fixed cruciform axis pattern across the retina, the four preferred directions of both On and On-Off DSGCs align with the cardinal translatory optic flow along the forward-backward motion axis and the up-down gravitational axis. This finding provides new insights into how downstream circuits integrate DSGC population responses to detect translatory and rotatory body movements.

5. CONTRIBUTIONS OF RETINAL DIRECTION SELECTIVITY TO HIGHER MOTION PROCESSING

The well-accepted role of On DSGCs in optokinetic nystagmus is supported by their selective projection to the AOS (Dhande et al. 2013, Yonehara et al. 2009) and by their speed tuning that matches the operating range of the optokinetic response (Oyster 1968, Sivyer et al. 2010, Wyatt & Daw 1975). Furthermore, mice that lack retinal direction selectivity exhibit impaired optokinetic reflex (Amthor et al. 2002, Hillier et al. 2017, Yonehara et al. 2016, Yoshida et al. 2001), although selective disruption of direction selectivity in On, but not On-Off, DSGCs has not been performed. In a major AOS nucleus, MTN, that mediates vertical optokinetic reflex (Simpson 1984, Sun et al. 2015), On DSGCs preferring upward and downward directions have been found to project to the dorsal and ventral subdivisions of the MTN, respectively (Yonehara et al. 2013). How the inputs from On DSGCs and the recently discovered anteriorly tuned On-Off DSGC subtype (Dhande et al. 2013) are processed in the AOS nuclei is unknown.

In the mouse retina, On-Off DSGC axons terminate in the upper layer of stratum griseum superficiale (SGS) of SC (Huberman et al. 2009, Kay et al. 2011, Rivlin-Etzion et al. 2011), where direction-selective collicular neurons are most prevalent (Inayat et al. 2015). Direct in vivo whole-cell recordings from direction-selective collicular neurons show that they receive directionally tuned inputs from the retina (Shi et al. 2017). When direction selectivity of DSGCs is selectively disrupted without affecting the responses of other RGC types, the direction selectivity of collicular neurons is impaired (Shi et al. 2017). These results demonstrate that direction selectivity in the SGS is inherited from direction selectivity computed in the retina.

Another major target of On-Off DSGCs is the outer shell of dLGN (Huberman et al. 2009, Kay et al. 2011, Rivlin-Etzion et al. 2011). Direction-selective geniculate neurons have been found in this region (Cruz-Martín et al. 2014, Marshel et al. 2012, Piscopo et al. 2013). However, unlike a direct causal relationship between retinal and collicular direction selectivity, a more complex picture of signal transformation has been revealed in the retinogeniculate pathway. Recent studies demonstrate that dLGN features sophisticated convergence and divergence of multiple retinal input types rather than a simple relay station (Hammer et al. 2015, Litvina & Chen 2017, Morgan et al. 2016, Rompani et al. 2017). Retinal direction selectivity is multiplexed with other visual features from the retina that collectively contribute to diverse RF properties of dLGN neurons (Liang et al. 2018). Even more complex is the relationship between retinal and cortical direction selectivity. Hillier et al. (2017) examined the direction selectivity of layer 2/3 cells in the primary visual cortex (V1) in transgenic mouse lines with deficits in retinal direction selectivity. They found that cortical direction selectivity in these mice is not abolished but rather altered because of a selective loss of tuning in the posterior direction at higher speed. Another study on layer 4 neurons shows that their direction selectivity can be computed in the cortex de novo from untuned thalamic inputs (Lien & Scanziani 2018). A complete understanding of how retinal direction selectivity contributes to visual processing in the cortex still awaits future investigations at all levels of the retino-geniculo-cortical pathway. Recently, a behavioral assay has been developed for motion direction discrimination in the mouse (Marques et al. 2018), which opens up opportunities to link retinal motion channels to conscious behavior.

The search for DSGCs in primates remains challenging owing to technical hurdles such as limited tissue availability and a lack of molecular and genetic markers. While primate DSGCs are still elusive, an intriguing link has been reported between the gene *FRMD7*, which is involved in idiopathic congenital nystagmus in humans, and retinal direction selectivity in mice (Yonehara et al. 2016). *FRMD7* is enriched in cholinergic amacrine cells in both mouse and monkey retinas. Mutations of *FRMD7*, which selectively disrupt the directional tuning of DSGCs on the horizontal axis in mice, lead to deficits in horizontal, but not vertical, optokinetic reflex in both mice and humans (Yonehara et al. 2016). These findings suggest that retinal direction selectivity is a highly evolutionarily conserved mechanism for optokinetic reflex in vertebrates, including primates (Masseck & Hoffmann 2009).

6. BEYOND DIRECTION SELECTIVITY: CONTEXTUAL EFFECTS OF MOTION STIMULI ON THE RESPONSES OF MULTIPLE RGC TYPES

Besides the dedicated circuit for computing motion direction, the neural network in the inner retina differentially modulates the responses of multiple RGC types according to specific motion contexts. A study on the rabbit retina has reported contextual modulation of On-Off DSGCs using compound drifting grating stimuli (Chiao & Masland 2003). The preferred-direction response of On-Off DSGCs shows stronger suppression by global uniform gratings than by compound gratings with unmatched center and surround grating patterns (Chiao & Masland 2003). The

underlying neural mechanisms of this contextual modulation, and whether similar modulations of DSGCs are present in other species, is completely unknown.

Motion contextual modulation is also highlighted in mouse transient Off-alpha ganglion cells, which are characterized by their large somas, dendritic stratification in the Off sublamina, and transient bursts to light decrements (Sanes & Masland 2015). Traditionally, they are not classified as motion-encoding cells. However, these cells exhibit several different patterns of contextual tuning when they are presented with specific motion stimuli. An expanding black spot centered on their RFs produces stronger responses than a contracting one. This preference for so-called approaching motion involves rapid inhibition through the AII amacrine cell–bipolar cell pathway during nonapproaching motion (Münch et al. 2009). In another study using rapidly and globally shifting stimuli that mimic retinal image shift during saccadic eye movements, these transient Off-alpha cells exhibit a delayed response only when the new image after the shift closely matches the image right before the shift. This property, termed image-recurrence sensitivity, can be modeled by serial inhibition of GABAergic and glycinergic cells in the circuitry presynaptic to the ganglion cells (Krishnamoorthy et al. 2017). In a third study using bars moving irregularly over the visual field, a single type of transient Off ganglion cells identified in multi-electrode array recordings, which are likely to be the same transient Off-alpha ganglion cells as above, encode bar position within the RF center but bar speed in the RF surround (Deny et al. 2017). Interestingly, a disinhibition circuit motif that resembles the serial inhibition model for the image-recurrence-sensitive response is proposed to underlie the multiplexed computations during the irregular bar stimulation (Deny et al. 2017). Therefore, activation of the same circuit motif by different motion contexts may result in distinct patterns of feature encoding by a single RGC type.

Another form of motion-related contextual effect, object-motion sensitivity (OMS), has been observed in multiple RGC types in salamander and mammalian retinas. These OMS cells preferentially respond to relative motion between the center and surround of their RFs and are suppressed by full-field global motion (Ölveczky et al. 2003). The mammalian RGC types that meet this definition include On brisk transient cells, local edge detectors (LEDs), high-definition type 1 cells and On-Off DSGCs (Chiao & Masland 2003, Jacoby & Schwartz 2017, Ölveczky et al. 2003). The synaptic circuitry underlying OMS has been investigated in more detail in W3 retinal ganglion cells, a type of LED, in the mouse retina (Zhang et al. 2012). OMS responses of W3 cells require excitatory inputs from vesicular glutamate transporter type 3 (VGluT3)-expressing amacrine cells and inhibitory inputs from tyrosine hydroxylase promoter-driven (TH2)-amacrine cells (Kim & Kerschensteiner 2017, Kim et al. 2015, Krishnaswamy et al. 2015, Lee et al. 2014, S. Lee et al. 2016). VGluT3 cells are themselves sensitive to object motion and release more glutamate to W3 cells during local motion, while TH2-amacrine cells release more GABA to W3 cells during global motion. The synaptic circuitry for other mammalian OMS cell types is less understood.

Responses of multiple RGC types exhibit higher sensitivity to moving stimuli than to stationary stimuli (Marre et al. 2012). A study on mouse bipolar cell circuits revealed an underlying mechanism in the On pathway. Extensive gap junction coupling among On bipolar cells through AII amacrine cells leads to supralinear integration of motion signals in On bipolar cells, which in turn enhance the glutamatergic inputs to On RGCs for moving stimuli (Kuo et al. 2016). Parasol, but not midget cells, in the primate retina also exhibit pronounced motion sensitivity across contrast and speeds (Manookin et al. 2018). Whole-cell recordings from whole-mount primate retinas show that motion reduces inhibitory inputs to parasol cells and enhances excitatory inputs through a gap junction–dependent mechanism similar to that in mice (Manookin et al. 2018).

Other examples of motion-related contextual effects are documented in the mammalian retina. One of them is motion anticipation. In a population of Off RGCs, the spatiotemporal RF properties and a dynamic gain control mechanism have been proposed to cancel the phototransduction

and synaptic delays to improve the timing of RGC response. The resulting activity pattern of RGCs extrapolates rather than reports the motion trajectory (Berry et al. 1999). In another example, when a moving stimulus suddenly reverses direction, a large fraction of RGCs in the mouse show a synchronous burst of spikes to signal motion reversal (Schwartz et al. 2007). In contrast to object motion in the visual field, stimuli mimicking saccadic eye movements generate a transient suppression of spiking activity in multiple RGC types (Roska & Werblin 2003). The detailed synaptic circuitry underlying these phenomena remains to be elucidated.

7. CONCLUSION AND FUTURE ISSUES

Direction selectivity has been under the spotlight for several decades and is arguably the best-understood neural computation in the brain at the cellular and synaptic levels. Indeed, the null-direction inhibition model of direction selectivity by Barlow and Levick can now be well explained by a precise functional wiring diagram of SACs and DSGCs. However, this diagram is not sufficient when we attempt to explain reliable implementation of direction selectivity for simple stimuli such as moving bars and drifting gratings across their respective parameter space or to explain the contextual effects of DSGC responses during complex or natural motion stimuli (Chiao & Masland 2003, Im & Fried 2016). A comprehensive understanding of this fundamental computation requires connecting SACs and DSGCs to the rest of the retinal neural network, since the visual responses of these cells are dictated by the intricate inner and outer retinal circuitries that process visual inputs in the vast range of stimulus configurations in natural environments.

Even more unanswered questions remain about the neural mechanisms underlying motion encoding in broader RGC populations. These questions will become more amenable to investigation with the development of more tools to target and manipulate specific cell types and microcircuit motifs.

Finally, a better understanding of natural image statistics will aid the design of visual stimulation for studying motion processing. Image statistics in natural stimuli have been shown to reveal distinct RF properties and engage synergistic or novel mechanisms that evade detection when traditional artificial stimuli are used (David et al. 2004, Felsen & Dan 2005, Felsen et al. 2005, Im & Fried 2016, Turner & Rieke 2016). Analysis of signature characteristics of natural scenes may give us hints of what and how ecologically relevant parameters can be included in the standard stimulus repertoire. This can serve as a tractable first step for uncovering mechanisms and functions of retinal circuits in natural environments.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

I thank Marla Feller from University of California at Berkeley and members of my lab for helpful comments on the manuscript. This work was supported by the National Institutes of Health Grant (R01 EY024016) and McKnight Scholarship Award.

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