Published in final edited form as:

Trends Neurosci. 2011 December ; 34(12): 638–645. doi:10.1016/j.tins.2011.08.002.

Organization and development of direction selective circuits in the retina

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Abstract

The direction selective circuit in the retina extracts the directional information of image motion in the visual scene. It is a classic model for neural circuit analysis because its input and output are well-defined and accessible to physiological measurements. However, the neural basis of direction selectivity is still not fully understood. Indeed, this ostensibly simple computation arises from a collection of complex neural mechanisms at all levels of circuit organization. In this review, we describe recent advances in genetic, imaging and optogenetic techniques that have improved our understanding of the synaptic organization and development underlying retinal direction selectivity.

Introduction

The direction selective circuit of the retina is arguably one of the most tractable neural circuits in the brain. The input of the circuit is a patterned sequence of photons that activates the photoreceptors in the outer retina. These signals are then transmitted via excitatory interneurons called bipolar cells into the inner part of the retina, where the direction of image motion is computed and subsequently encoded in the spiking patterns of the output neurons called the direction selective ganglion cells (DSGCs) (Figure 1). DSGCs generate a maximum number of spikes when the image is moving in their preferred direction, but fire minimally for the opposite, or the null, direction.

Since DSGCs were identified in rabbit^{1,2}, rigorous investigation has been directed towards resolving the underlying circuit. Earlier work focused on a complete characterization of the receptive field properties of DSGCs. More recently, work has focused on the synaptic conductances that are activated on DSGCs during visual stimulation (for reviews, see^{3,4,5}). From these elegant studies the predominant model for retinal direction selectivity has emerged, in which activation of potent inhibitory mechanisms during null-direction motion prevent the DSGC from firing action potentials. This null-direction inhibition, and therefore the directional response of DSGCs, is critically dependent on a retinal interneuron, the starburst amacrine cell (SAC). Detailed characterization of intrinsic and network properties of the SACs has greatly advanced the construction and modeling of hypothetical wiring diagrams underlying retinal direction selectivity. Recent studies provide several exciting insights into the functional and anatomical organization of synapses between the SACs and DSGCs, thereby providing critical experimental evidence for the synaptic basis of the null-direction inhibition. Furthermore, state-of-the-art genetic and optogenetic tools offer

unprecedented opportunities for exploring the diversity and early development of the direction selective circuit.

Synaptic mechanisms of direction selectivity in DSGCs

Here we focus primarily on understanding the circuit basis of the most well-studied type of DSGC, the ON-OFF DSGC. ON-OFF DSGCs respond to both light onset and offset with a transient burst of spikes (Figure 1c), consistent with their bistratified arbors in the ON and OFF sublamina of the inner plexiform layer (IPL) (Figure 1a). The classical receptive field of the ON-OFF DSGC exhibits center-surround structure, with the size of the receptive field center matching well with its dendritic diameter^{6–8}. When presented with a moving bar visual stimulus, both the ON and OFF components of the spike response are direction selective over a wide range of movement velocities⁹. Furthermore, motion stimuli restricted to a small fraction (< 20% in rabbit) of the receptive field can produce directional spiking of ON-OFF DSGCs, indicating that direction selective mechanisms are present in local dendritic computational subunits that repeat in an array over the DSGC dendritic arbor¹. Interestingly, a nondiscriminating zone where motion-evoked spiking is nondirectional has been found on the preferred side of the DSGC's receptive field in the rabbit retina^{1,10}. It has been well-established that the directional spiking of the ON-OFF DSGC is due to null-direction inhibition. GABA_A receptor antagonists abolish the directional response and lead to uniform spiking to all directions of motion^{11–14}. Furthermore, the null-direction inhibition acts independently in the ON and OFF pathways, since blocking ON bipolar cell signaling with the metabotropic glutamate receptor 6 (mGluR6) agonist APB abolishes the ON response but spares the direction-selective OFF response¹². When a GABA_A receptor antagonist was added in addition to APB, the OFF component showed equal firing to all directions, thereby losing its directional tuning.

The directional spikes from ON-OFF DSGCs inevitably arise from the precise integration of its synaptic conductances during image motion. Indeed, careful analysis of synaptic conductances has revealed that robust direction selectivity results from synergistic actions of multiple synaptic mechanisms:

1. *The amplitude of the inhibitory input is larger during null-direction motion.* This observation is supported by multiple studies^{13,15–18} in rabbit and mouse retina, with the GABAergic input during null-direction motion being about 3–5 times larger than that during the preferred-direction stimulation.
2. *The amplitude of the excitatory input is smaller during null-direction motion.* This is also a robust feature of the DSGC, although the difference between preferred and null direction excitatory input is in general smaller than that of the inhibitory input^{13,15–18}. A recent study dissected the excitatory and inhibitory input to DSGCs¹⁹. Both the cholinergic and NMDA receptor-mediated input is facilitated for stimuli moving in the preferred direction and suppressed for stimuli moving in the null direction, while the non-NMDA receptor mediated glutamatergic input is symmetrical. In addition, this directional modulation of excitatory input is abolished by the GABA_A receptor antagonist SR95531/gabazine, suggesting that

presynaptic inhibition impinges on the excitatory input to DSGCs during image motion in the null direction.

3. *Temporal offset between inhibitory and excitatory inputs.* During null-direction motion, the inhibitory conductance coincides with the excitatory conductance, effectively shunting the excitatory input. During preferred-direction motion, the inhibitory conductance is delayed relative to the peak of the excitatory conductance and fails to inhibit the light-evoked excitation. This difference in timing might be due to a spatial offset between excitation and inhibition^{15,16}. It has been reported that in the rabbit retina, the spatial offset inhibition is more commonly detected for the OFF component of the ON-OFF DSGCs, while the ON response often lacks this feature¹⁷. Note, the extent of this variability in the ON response, or its source, is not clear^{16,19}.
4. *A role for synaptic noise correlation in direction selective tuning.* In addition to light-evoked synaptic input, synaptic noise correlation has been implicated in direction selective tuning. In a study that examined covariation of the excitatory and inhibitory inputs to an ON-OFF DSGC during image motion²⁰, the synaptic noise from the two sources was found to be 3–4 times more correlated during null-direction motion than during preferred-direction motion. This suggests that enhanced noise correlation sharpens the tuning of the ON-OFF DSGCs by preventing noise-dependent firing during null-direction motion.

Starburst amacrine cells are a critical component of the direction selective circuit

SACs are remarkable retinal interneurons that release both GABA and acetylcholine. Two mirror symmetric populations of the SAC somas reside in the inner nuclear layer (INL) and ganglion cell layer, and send their monostratified processes to S2 and S4 of the IPL, respectively (Figure 1a). SACs are highly abundant, providing at least twenty-fold coverage of the retina in both rabbit and mouse^{21–24}. As the name suggests, SACs have thin, radially symmetric processes (Figure 1b). Bipolar cell inputs occur along the entire length of SAC processes, while the distal (outer) third of the SAC processes have varicosities containing synaptic vesicles indicative of neurotransmitter release sites^{25–28}. The processes of the SACs at the same strata cofasciculate to form a meshwork-like cholinergic plexus and are immunopositive for choline acetyltransferase (ChAT) or vesicular acetylcholine transporter (VAChT)^{23,24,29}. These cholinergic strata are the precise sublaminae that host the dendritic arbors of ON and ON-OFF DSGCs^{23,30–33}. Indeed, SACs are the only known cell type that form GABAergic synapses with the two types of DSGCs. Furthermore, ablation of SACs eliminates the directional preference of DSGCs and the optokinetic reflex mediated by ON DSGCs^{34,35}, making the SAC the top candidate for generating the null-direction inhibition in both ON and ON-OFF DSGCs.

Like many retinal neurons, SACs exhibit center-surround receptive fields^{36–38}. However, SACs do not generate action potentials in adult rabbits³⁹, but use their electrotonically, semi-isolated distal processes to compute light-evoked signals locally. In a study using two-photon calcium imaging during visual stimulation, centrifugal stimulus motion generates

larger calcium transients than centripetal stimulus motion at the distal processes⁴⁰. These observations strongly suggest that centrifugal motion drives more GABA release than centripetal motion, though this has not yet been directly demonstrated. The centrifugal preference is consistent with earlier modeling studies based on the morphological and electrotonic properties of SACs^{41,42}. In addition, several other intrinsic properties such as a gradient-distribution of chloride cotransporters^{43,44}, voltage-gated membrane conductances⁴⁵ and tetrodotoxin (TTX)-resistant sodium channels⁴⁶ have been indicated to contribute to SAC's directional preference.

The directional preference in SAC processes is present when GABA or glycine receptors are blocked⁴⁵, indicating that the inhibitory network is not required for the directional preference. However, SACs form GABAergic synapses with each other in the adult retina to form an interconnected network. This reciprocal inhibition has been proposed to contribute to the centrifugal preference of SACs by creating a spatially offset inhibition³⁷, which is particularly relevant when the image originates from regions outside the SAC's receptive field center towards the distal processes.

The synaptic organization between SACs and DSGCs

Since SACs are radially symmetric neurons, how are SAC and DSGC connected to generate asymmetric inhibition? The centrifugal directional preference of SAC dendrites poses a possible source for an asymmetric pattern of inhibition to DSGCs. However, this model requires an asymmetric wiring between SAC dendrites and DSGCs. Anatomical studies at the limited resolution of light microscopy have found little evidence for any asymmetry -- immunostaining for pre- and postsynaptic markers for GABAergic and glutamatergic synapses in filled SACs and DSGCs has suggested a symmetric pattern of labeling across the dendritic arbors⁴⁷⁻⁴⁹. While one study reported an increased dendritic cofasciculation between null-side SACs and DSGCs¹⁵, other groups have found a similar pattern of cofasciculation between the two cell types for all orientations^{30,50}.

Evidence for an asymmetry in the wiring between SACs and DSGCs was first reported in a pioneering study, in which dual recordings between SACs and DSGCs were performed in rabbit retina¹⁵. GABAergic inputs were detected only from SACs located at the null side of the DSGC, but not from SACs located at the preferred side. Recently, the synaptic conductances between SACs and DSGCs were characterized in detail¹⁹. Dual recordings were performed between SACs and DSGCs whose processes overlap with about half of the DSGC's dendritic field. Consistent with previous findings, the GABAergic input from the null-side SACs are much larger than those from the preferred-side SACs. Similar asymmetry was also found in the mouse retina, with one significant difference in that the preferred side SAC consistently provides a weak GABAergic input to the subtype of DSGCs that prefer motion along the nasal retinal axis (nDSGCs)⁵⁰. Indeed, in adult mice, SACs form synapses with nDSGCs with a high probability. More than 90% of the SAC-nDSGC pairs with overlapping dendritic arbors showed detectable GABAergic connections, regardless of the relative orientations of the SACs⁵⁰. Assuming a similar asymmetric wiring pattern between SACs and each of the four subtypes of ON-OFF DSGCs⁵¹, the presynaptic machinery of the SAC is remarkably specific and robust since each SAC needs to provide asymmetric

inhibition along the null-preferred axis for all four ON-OFF DSGC subtypes. How such subcellular specificity is established is an intriguing question for future exploration.

Unlike GABAergic input, the monosynaptic cholinergic input from SACs is symmetric on all sides of the DSGCs in rabbit¹⁹. In contrast to the previous notion that GABA and acetylcholine (ACh) are co-released from the same pool of synaptic vesicles, GABAergic and cholinergic currents in DSGCs exhibit different sensitivities to N and P/Q type calcium channel blockers¹⁹, indicating that these two types of synapses are differentially regulated, and probably distributed in separate microdomains of SAC processes.

The physical connectivity and the specificity between SACs and ON-OFF DSGCs was recently revealed by a landmark study combining functional calcium imaging and serial electron microscopy in the mouse retina²⁵. The majority of SAC-DSGC synapses (equivalent to the SAC varicosities) have been reported to originate from the SAC processes oriented toward the null direction of the DSGCs. On the other hand, each quadrant of the SAC processes along the cardinal axes preferentially forms synapses to one of the four ON-OFF DSGC subtypes (although a small number of synapses are formed between DSGCs and SAC dendrites pointing to the preferred side). These findings are consistent with electrophysiological recordings⁵⁰ and provide the first anatomical evidence for asymmetrical wiring between SACs and DSGCs. It is worth noting that while the cholinergic and GABAergic synapses cannot be distinguished in this study, the preferential formation of synaptic contacts from varicosities in null-direction pointing SAC processes, together with the finding that the monosynaptic cholinergic inputs from SACs are symmetric¹⁹, strongly argues against the notion that ACh and GABA are co-released from the same pool of vesicles. Further studies are needed to understand the intricate specificity of GABA and ACh release at individual varicosities.

Current circuit models of direction selectivity computation

The growing body of knowledge on the properties of DSGCs and SACs and the synaptic interactions between them are essential for improving models of direction selective computation. Here we attempt to use the identified synaptic mechanisms in ON-OFF DSGCs as a blueprint to summarize the current understanding of the synaptic organization of the direction selective circuit and models of retinal DS computation.

1. Presynaptic inhibition: The enhanced inhibition arising during null-direction motion can be explained by a model combining the centrifugal preference of the SAC dendrites and the asymmetric wiring between SACs and DSGCs (Fig 2a). Since the majority of inhibitory conductance comes from null-direction-pointing SAC processes, null-direction motion is centrifugal in these processes and therefore maximally evokes GABA release.
2. Presynaptic excitation: The enhanced excitation arising during preferred-direction motion is known to arise from inhibitory mechanisms upstream of the excitatory input to DSGCs (Fig 2b and c). However, the source of the inhibition is not known. It has been proposed that the glutamatergic input from bipolar cells and the cholinergic input from SACs is modulated by SACs in a pattern similar to the

SAC-DSGC GABAergic synapses¹⁹. Together with the asymmetric presynaptic inhibition (Fig 2a), this creates a push-pull mechanism that enhances inhibitory inputs and reduces excitatory inputs during null-direction motion. However, little evidence is currently available to support this hypothesis. Future studies on the functional and anatomical characterization of the bipolar-DSGC and bipolar-SAC synapses will yield valuable insights into this problem.

3. Temporally offset inhibition: The current model of selective wiring between DSGCs and SAC dendrites oriented in the null direction would account for at least some of the temporally offset inhibition, since the null-direction pointing SAC dendrites might be activated to release GABA before the visual stimulus enters the receptive field of the DSGCs (Fig 2a).
4. Postsynaptic nonlinearities: It is noteworthy that some or all the above DS mechanisms may act at the scale of local dendritic “DS subunits”, which can independently process image motion and lead to directional firing at the DSGC soma¹. It has been proposed that directional spiking is first generated at these local DS subunits before propagating to the cell body to elicit somatic spikes, which is supported by the finding that spikes are initiated at multiple sites within the DSGC dendrites during preferred-direction stimuli⁵². Computational modeling suggests that these dendritic spikes arise from local DS mechanisms and propagate to the soma with a high probability to minimize the attenuation of postsynaptic potentials and enhance the directional tuning at the soma⁵³.

Development of the ON-OFF direction selective circuit

Direction selective responses are established very early in development. In both mice and rabbits, retinal direction selectivity is detectable immediately after eye opening^{7,54,55}. In mouse, the ON-OFF DSGCs have been identified as early as postnatal day 11 (P11) (two days before eye opening), when the light response just begins to emerge⁵⁵. Hence, extensive visual experience is not required for the establishment of direction selectivity.

Insights into the development of direction selectivity prior to eye-opening have been limited by the inability to unambiguously identify DSGCs prior to the maturation of the light response. This problem has been circumvented by the use of transgenic mouse lines that express green fluorescent protein (GFP) in subtypes of DSGCs^{56–59}. Using these mouse lines, characterization of several anatomical features, including mosaic organization, dendritic arborization, and axonal targeting has been carried out for all types of DSGCs^{50,57,59–63} (Table 1). Furthermore, genetic profiling in multiple transgenic lines has revealed deeper complexity among subtypes of ON-OFF DSGCs with respect to their molecular diversity and structure-function relationships, and suggests that distinct sets of molecules are expressed in ON-OFF DSGC subtypes in development before eye opening⁶³.

Critical for studies of development, GFP-expressing mouse lines also allow for targeted recordings from DSGCs prior to eye-opening^{50,60}. The first circuit question addressed was a characterization of the emergence of asymmetric wiring between SACs and DSGCs. The maturation of SAC-DSGC GABAergic synapses⁵⁰ was examined using a double-transgenic

mouse that selectively labels ON-OFF DSGCs preferring nasal-direction motion and SACs. Inhibitory inputs from SACs on the null and preferred side were of similar magnitude in the first postnatal week as measured by the whole cell GABAergic conductance. By the end of the second postnatal week, the synapses between SACs on the null side were significantly strengthened while those on the preferred side did not. Though it is not known from these experiments whether this change in synaptic strength is due to number of synapses or changes in strength at individual synapses, these findings indicate that a subset of GABAergic synapses made between the two cell types are destined to be formed or strengthened during this relatively short time in development.

Among the potential factors that regulate the development of retinal direction selectivity, neural activity has long been a favorite candidate because of its well-documented role in visual development, including eye-specific segregation in the dLGN and retinotopy in the superior colliculus (for a review, see⁶⁴). Indeed, in the week before eye-opening, the retinas are not silent but rather exhibit retinal waves, which provide a strong depolarizing input to DSGCs⁶⁵. There are many compelling reasons to hypothesize that waves may play a role in establishing direction selectivity. First, they correlate the firing between SACs and DSGCs via early cholinergic synapses⁶⁶. Second, waves are directional in their propagation, and therefore function as a directional stimulus prior to vision. Third, there is a directional bias in wave propagation^{65,67} – with more waves propagating nasally than temporally – indicating they carry information about the cardinal axes of the retina.

Despite these facts, several *in vivo* manipulations indicate that waves are not critical for wiring direction selective circuits. Intraocular injections of a voltage-gated sodium channel blocker (tetrodotoxin, TTX), a GABA_A receptor agonist (muscimol), GABA_A receptor antagonists (bicuculline methiodide, SR95531/gabazine), or a cholinergic receptor agonist (epibatidine)^{50,68} all fail to prevent the development of retinal direction selectivity. However the possibility that compensatory activity has been generated during drug treatment cannot be ruled out. In addition, all of these studies measured the circuit output, namely extracellular spiking, in response to directional stimuli but not the synaptic conductances underlying that output. Indeed, it would be interesting to test whether direction selective circuits can compensate for the loss of one synaptic mechanism by enhancing another. Future experiments based on targeted genetic manipulations will allow for addressing more specific hypotheses as to the role of neural activity in the establishment of various aspects of the circuit that mediate direction selectivity.

Synaptic mechanisms and development of other DSGC types

ON DSGCs

ON DSGCs exhibit a sustained response to light onset. Unlike the ON-OFF DSGCs that respond to a broad range of stimulus velocities, the ON DSGCs are tuned to slower velocities of image motion. Within its optimal velocity range, the directional tuning of ON DSGCs is similar to that of ON-OFF DSGCs¹⁸. Like ON-OFF DSGCs, the ON DSGCs cofasciculate with the ON SAC processes at S4^{30,69,70}, and use GABA_A receptor-mediated null-direction inhibition to generate directional spiking^{11,14,71}.

The directional tuning of ON DSGCs has been previously considered to share similar mechanisms with the ON component of the ON-OFF DSGCs, since motion elicits asymmetric excitatory and inhibitory conductances as well as the temporally offset inhibition in ON DSGCs¹⁸. Direct recordings between SACs and ON DSGCs have not yet been reported. Instead, channelrhodopsin (ChR) was expressed in ~60% of the SACs and eight sectors surrounding each ON DSGC were photostimulated⁶⁰. It was found that inhibitory currents in the ON DSGC evoked by photostimulating the null-side sectors were larger than those evoked by photostimulating the preferred-side sectors. The size and location of each stimulated sector relative to the DSGC's dendritic arbor were not reported, but the photostimulation presumably activated a similar number of SAC processes oriented in all directions. Therefore, this result can be interpreted in the following two ways: 1) the GABA_A receptors at the null side of the DSGC dendritic arbor are more densely distributed than those at the preferred side; or 2) the majority of GABA release occurs in SAC processes pointing to the null direction. The ChR-evoked response in ON DSGCs is symmetric at P6 and sharply transitions to an asymmetric pattern at P8⁶⁰.

Additional complexity of the ON DS circuitry has been revealed by recent studies.⁷² A recent study found that application of GABA_A receptor antagonist picrotoxin unmasks an OFF spiking response in ON DSGCs, in addition to disrupting the direction selectivity of the ON responses. Surprisingly, the unmasked OFF response is also direction selective, showing a preferred direction opposite to that of the ON response^{71,72} (but see⁷⁰). The detailed mechanisms underlying the unmasked OFF response are still not clear, but are known to depend on gap junction coupling between ON DSGCs and a class of polyaxonal amacrine cells^{71,72}. Another set of studies^{73,74} imply heterogeneity of ON DSGCs. These reports describe another type of ON DSGCs with a transient response to light onset, which has the same three preferred directions as the sustained ON DSGCs. They postulate that the transient type of ON DSGCs has a different axonal projection pattern than the sustained type, which requires future verification.

OFF DSGCs

More recently, a third type of DSGC, the OFF DSGC, was described in a mouse expressing GFP under the junctional adhesion molecule B (JAM-B) promoter⁵⁷. In contrast to ON and ON-OFF DSGCs, OFF DSGCs in the JAM-B mice have asymmetric dendritic arbors pointing to the superior direction, which is their preferred direction. Although the OFF DSGC dendrites stratify in the OFF sublamina, the cell can respond to both dark and bright moving objects. The directional tuning for dark object is sharper at higher velocities, while the directional response to bright objects occurs only at low velocities. The circuit underlying the OFF DSGC likely uses very different mechanisms from those of ON and ON-OFF DSGCs to generate direction selectivity, for which little knowledge is currently available.

Concluding remarks and future directions

Recent technical developments have led to significant advances in understanding the direction selective circuit. However, the half-a-century pursuit for the mechanism of direction selectivity is far from complete. Indeed, we are just beginning to unravel the

cellular and synaptic substrates that give rise to the directional tuning of DSGCs. While the characterization of the specific wiring between SACs and DSGCs has advanced our understanding of the presynaptic inhibition that arises during null-direction motion, the biophysical properties of the SAC-DSGC synapses and the mechanisms governing the differential release of GABA and ACh is far from clear. Even more mysterious are the mechanisms of presynaptic inhibition. Little is known about the specific bipolar cell types that synapse onto different subtypes of DSGCs. We also lack information about how the bipolar cells, SACs and DSGCs interact with each other, and whether there are additional cell types involved in modulating the excitatory conductances in the DSGCs. Future studies combining cell type-specific targeting, optogenetics and electrophysiology will allow for the characterization of the subcellular DS unit at higher resolution.

Basic questions remain about the circuits that mediate direction selectivity in the different DSGC types. For example, what are the neural mechanisms that encode directions in OFF DSGCs? What accounts for the difference in the ON and ON-OFF DSGC properties? By striving for a complete understanding of these circuits, we will gain valuable insights into the fundamental principles of neural computation.

Acknowledgments

We thank members of Feller lab for careful reading of the manuscript. This work was supported by grants from National Institute of Health (NIH) RO1EY013528 and ARRA EY019498.

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Figure 1. Major cellular components of the ON-OFF direction selective circuit and functional output of an ON-OFF direction selective ganglion cell (DSGC)

(a) Schematic drawings of mammalian retina and the key cell types involved in direction selectivity. ON- and OFF bipolar cells (BP) relay the light-evoked signals from the photoreceptors (PR) to the bistratified dendritic arbors of ON-OFF DSGCs at the sublaminae 2 and 4 (S2 and S4) of the inner plexiform layer (IPL). Two mirror symmetric populations of SACs, whose cell bodies reside in the inner nuclear layer (INL) and ganglion cell layer (GCL), modify forward transmission at S2 and S4 respectively.

(b) NEUROLUCIDA reconstructions of the dendrites from the ON sublamina and side views of the complete dendritic arborizations from a synaptically connected pair of SACs and DSGCs. Dots represent dendritic contacts, with cofasciculation segments coloured white and the rest coloured purple. Scale bar, 25 μ m. (Modified from ⁵⁰).

(c) Spiking responses from loose patch cell recordings of an ON-OFF DSGC to a flashing spot.

(d) Spike traces from loose patch cell recordings and a polar plot showing the response of the same ON-OFF DSGC in (c) to a moving bar in 12 directions, (c) and (d) are modified, with permission, from ¹³.

Figure 2. Schematic model demonstrating the pattern of inhibitory and excitatory input to ON-OFF DSGCs during image motion

For simplicity, only the ON dendritic arbor of the ON-OFF DSGC is illustrated.

(a) GABAergic input is stronger between the DSGC and SAC processes pointing to the null direction, which is opposite to the preferred (Pref) direction^{15, 19, 50}. The enhanced GABAergic conductance may be due to a greater number of synapses and/or to a stronger unitary conductance at each synapse. Arrows: preferred directions (Pref) for the DSGC (grey) and SAC processes (blue).

(b) Cholinergic input is symmetric during direct stimulation via paired recordings, but asymmetric during image motion¹⁹. Black dots represent cholinergic synapses. When the image is moving towards the null direction of the DSGC (red arrows), the cholinergic input is suppressed. The inhibitory circuit that mediates this suppression is currently not known.

(c) Glutamatergic input from bipolar cells is reduced during null-direction motion (red arrows)¹⁹

Table 1

Anatomical, genetic and molecular characterization of DSGC types

^a Directional preferences are given in retinal coordinates

DSGC type	Distribution of preferred directions	Dendritic stratification in IPL	Preferred direction	Molecules enriched	Transgenic markers	Axonal projection
ON-OFF		S4 and S2	Nasal	CART, Mmp17 ⁶³	DRD4-GFP	dLGN, Superior colliculus, vLGN ^{56, 63}
			Temporal	?	W9 ⁶³	?
			Ventral	CART, Col25a1, Cdh6 ⁶³	TRHR-GFP ⁶²	dLGN, Superior colliculus, vLGN, zona incerta ⁶²
			Dorsal	CART, Col25a1, Cdh6 ⁶³	?	?
ON		S4	Temporal	?	FSTL4/Spig1-CreER (BD) ^{59, b} , Cdh6-CreER ⁶³	dLGN, Superior colliculus, vLGN, MTN, NOT ^{59, 63}
			Ventral	?	Cdh6-CreER ⁶³	dLGN, Superior colliculus, vLGN, MTN, NOT ⁶³
			Dorsal	?	?	?
OFF		S1	Temporal	?	FSTL4/Spig1-GFP (knock-in) ⁵⁸	MTN ^{58, 61}
			Ventral	?	?	MTN ⁶¹
			Dorsal	?	?	?
OFF		S1	Ventral	?	JAM-B-CreER ^{57, 59}	dLGN and superior colliculus ⁵⁹
			Dorsal	?	?	?

^a Abbreviations: N: nasal; T: temporal; V: ventral; D: dorsal;; NOT: the nucleus of the optic tract; vLGN: ventral lateral geniculate nucleus; DRD4: dopamine receptor 4; TRHR: thyrotropin-releasing hormone receptor; Cdh6: cadherin 6; CART: cocaine- and amphetamine-regulated transcript; Col25a1: collagen 25a1; Mmp17: matrix metalloproteinase 17; Spig1: a secretory protein; W9: mouse line generated from a vector in which Thy1 regulatory elements drive expression of YFP; CreER: tamoxifen-responsive cre recombinase; MTN: medial terminal nucleus of the accessory optic system; FSTL4: Follistatin-like protein 4; S1–4: sublaminae layers 2–4.

^b The preferred direction of the BD cells matches their dendritic asymmetry.