Trends in Neurosciences

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Review

Flexible Neural Hardware Supports Dynamic Computations in Retina

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The ability of the retina to adapt to changes in mean light intensity and contrast is well known. Classically, however, adaptation is thought to affect gain but not to change the visual modality encoded by a given type of retinal neuron. Recent findings reveal unexpected dynamic properties in mouse retinal neurons that challenge this view. Specifically, certain cell types change the visual modality they encode with variations in ambient illumination or following repetitive visual stimulation. These discoveries demonstrate that computations performed by retinal circuits with defined architecture can change with visual input. Moreover, they pose a major challenge for central circuits that must decode properties of the dynamic visual signal from retinal outputs.

Highlights

The retinal code is more dynamic than originally thought.

Visual context can significantly alter encoding properties of individual retinal circuits. These alterations expand beyond classic adaptation, as they result in changes in the core computations of the circuit.

Signals originating in the rod and cone photoreceptors traverse the retina through multiple parallel pathways. Dynamic computing largely originates from interactions between these parallel circuitries.

Dynamic Computing: Stretching the Limits of Adaptation

An impressive array of computations supports visual perception and visually guided behavior. The majority of these computations, particularly the more sophisticated ones, are often assumed to arise in the visual cortex. In this view, the retina provides an initial encoding of visual inputs and implements several general purpose computations to ensure that this encoding is efficient. One example is filtering signals in space and time to reduce correlations in the inputs, such as those present between nearby spatial locations in natural scenes (reviewed in [1]). A second example is adjusting signaling gain to make effective use of the range of available neural responses, e.g. so that retinal computations are invariant to changes in luminance (reviewed in [2–4]). Recent findings, however, demonstrate that some retinal computations are much more complex. Here, we focus on one aspect of this complexity: stimulus-dependent changes in the core computations performed by retinal neurons.

Adaptation provides a well-studied example of the dependence of retinal signaling on stimulus history. Classically, adaptation is viewed as a sacrifice in sensitivity for one aspect of the input (e.g., mean light intensity) to maintain sensitivity to another (e.g., fluctuations about the mean) (reviewed in [2,4]). But recent work has highlighted numerous examples of stimulus-dependent alterations in retinal computation that extend well beyond classic adaptation. Here, we describe examples that range from extensions of established retinal adaptation to unexpected findings that challenge basic concepts of retinal processing. As appropriate, we will discuss what is known about the mechanisms underlying dynamic encoding, and speculate on its functional importance. These findings require revisiting the view of the retina as a relatively rigid, invariant computational front-end for vision.

Parallel Processing of Rod and Cone Signals

Signals originating in the rod and cone photoreceptors traverse the retina through multiple parallel pathways (Box 1). The parallel retinal pathways do not operate in isolation, but instead interact extensively via lateral connections mediated by horizontal and amacrine cells. Thus, both divergence of inputs into separate cell types and pathways and convergence of signals

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Box 1. Parallel Pathways Convey the Photoreceptors Signal

Parallel processing of visual signals begins in the photoreceptors, with rods mediating nighttime (or scotopic) vision, and cones mediating daytime (photopic) vision. Both rods and cones contribute to vision at intermediate (mesopic) light levels (e.g., dawn and dusk). Photoreceptor signals traverse the retina through several pathways. Cone signals are transmitted to On and Off retinal ganglion cells (RGCs, the retinal output neurons) through ~12 cone bipolar cell types which depolarize either at light onset or at light offset. In rodents and other mammals, rods can transmit their signals to the same On and Off RGCs via three distinct pathways (reviewed in [60]; Figure I). In the 'primary' pathway, rods project via rod bipolar cells onto AII amacrine cells, which then contact On cone bipolar cells via gap junctions and Off cone bipolars and RGCs via inhibitory glycinergic synapses. This pathway dominates at low light levels such as starlight. In the 'secondary' pathway, rods form gap junction connections directly with cones, thus allowing rod signals to use all of the retinal circuitry typically used by cones (e.g., cone bipolar cells, horizontal cells). In the 'tertiary' pathway, rods make direct glutamatergic synapses onto the dendrites of a subset of Off cone bipolar cells. Rod and cone circuits culminate in the responses of 20 to 30 subtypes of RGCs, each of which encodes a unique aspect of the visual scene [44,45].

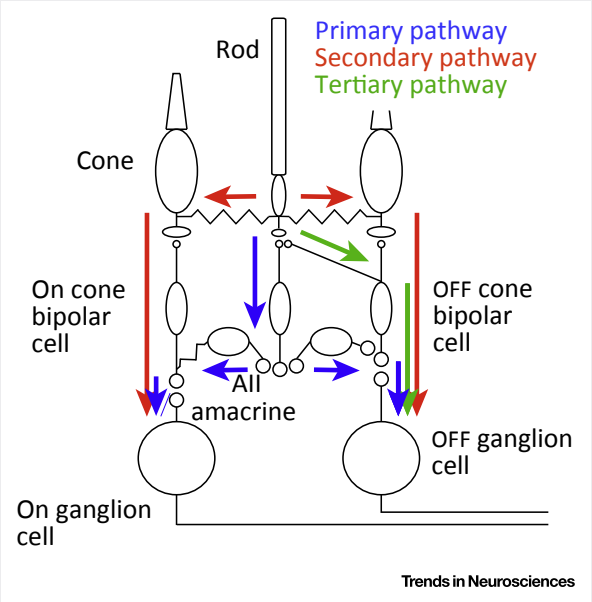

Figure I. Pathways By Which Rod-Derived Signals Can Traverse the Retina. Two alternatives to the 'primary' rod bipolar pathway have been identified: (i) the 'secondary' pathway, in which rod signals are conveyed directly to cones via rod–cone gap junctions; and (ii) the 'tertiary' pathway in which rods provide direct synaptic input to a subset of Off cone bipolar cells.

from multiple pathways contribute to the functional differences between distinct retinal ganglion cell (RGC) types. Notably, the strength and nature of the interactions between the pathways can vary with lighting conditions, resulting in alterations of RGC function. Below we first discuss two examples of flexible computation that are close to classic ideas about adaptation; we then turn to phenomena that are harder to fit into this classic framework.

From Single Photon Detection to Contrast Coding

Rod photoreceptors mediate low-light vision, and contribute substantially to retinal signaling over roughly half of the ~12 log units of mean luminance encountered over the course of a day (i.e., in 'natural' day/night environments). The challenges facing the retinal readout of rod signals change substantially across this range. In starlight, amplification within the rod bipolar pathway causes the absorption of a single photon in just one of the thousands of rods within a RGC receptive field to trigger one or more spikes in the RGC output [5–7]. If unchecked, this amplification would saturate the ganglion cell output signals at moderate light levels – e.g. at 1

R*/rod/s (isomerizations per rod per second), RGCs would be spiking at ~1 kHz; such saturation is prevented by adaptive gain control mechanisms that match the available range of retinal signals to the range of visual inputs.

One particularly important site of gain control within the primary rod pathway is the synapse between rod bipolar cells and AII amacrine cells [8,9]. But preventing saturation is not the only job of this synapse. At light levels from 1 to 250 R*/rod/s, the gain of rod signals in the AII amacrine cell responses scales inversely with luminance (known as Weber's law); this scaling causes AII amacrine cells to generate near-equal responses to a given change in contrast, independent of the luminance level (Figure 1). This is important because contrast is poorly defined in darkness, but emerges as a fundamental image statistic once there is sufficient illumination. The reduction in gain of the AII responses in part reflects changes in synaptic gain (e.g., via vesicle depletion) at the rod bipolar-AII synapse [8,10]. Moderate steady illumination also leads to a high level of tonic synaptic release at the rod bipolar output synapse, which in turn allows the synapse to transmit responses, via a change in release rate, to both positive and negative changes in rod bipolar membrane voltage.

The change in operation of the rod bipolar pathway, from the high gain needed to encode weak single-photon responses to the specific gain control needed for luminance-invariant contrast encoding, provides our first example of retinal hardware acting flexibly for luminance-dependent computations.

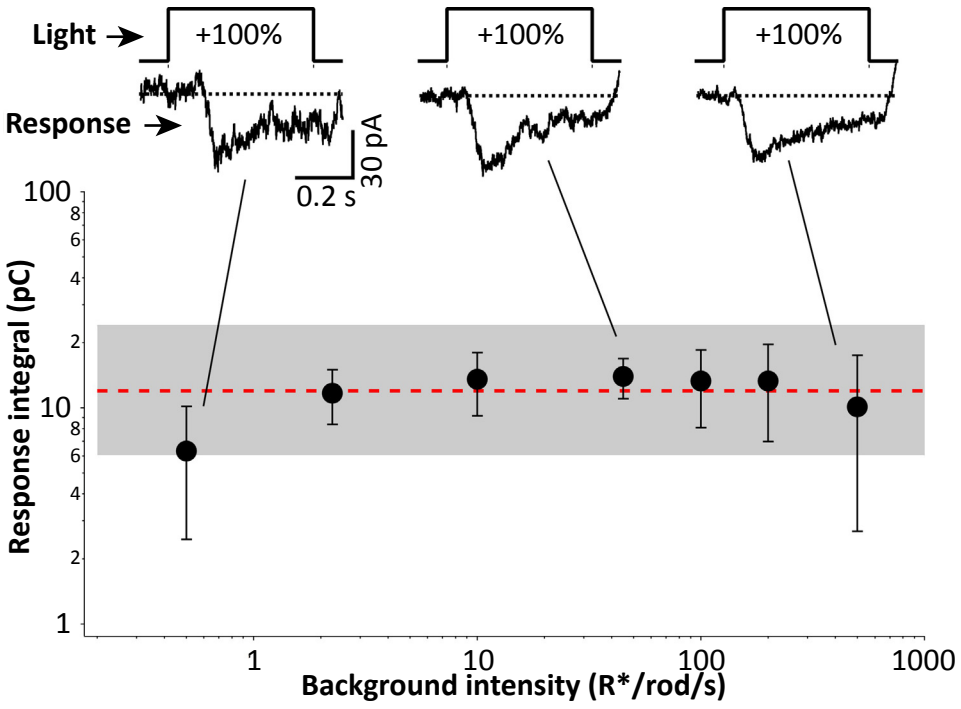

Figure 1. The Synaptic Inputs to AII Amacrine Cells Obey Weber's Law. Responses to 100% contrast light steps (0.5 s) exhibit a constant amplitude at background intensities between ~1 and 500 R*/rod/s. Top: Example traces of light-evoked signals recorded from a voltage-clamped AII amacrine cell (holding potential equal to the chloride reversal potential) in response to 100% contrast at three different levels of mean luminance (0.5, 45, and 500 R*/rod/s). Bottom: Response integral (absolute values) as a function of background luminance (n = 6 cells; mean ± standard deviation). Adapted from [27].

Center-Surround Receptive Field Organization Changes with Luminance

The center-surround receptive field is a fundamental concept in visual neuroscience [11,12]. On-center RGCs respond to light increments in the center of their receptive fields, but are inhibited by light increments in the periphery or surround. Off-center RGCs display a similar center-surround antagonism. This receptive field structure is not fixed; instead, at low light levels the antagonistic surround is weak or absent [13–17]. This change in center-surround organization of the RGC receptive fields has a clear functional role. Minimal receptive field surrounds at low light levels enhance spatial averaging and sensitivity to weak inputs. The emergence of a more substantial surround as light levels increase sharpens the RGC receptive field, increasing sensitivity to fine spatial structure.

Recent work shows that the surround in some RGCs increases in strength abruptly ('switch-like') at a critical light level [18,19]. This behavior was first described by Farrow and colleagues, who found that surrounds of On and Off alpha RGCs strengthened when visual stimuli crossed a critical light level (~10 R*/rod/s) (Figure 2; [18]). Surround recruitment was mediated by wide-field spiking amacrine cells with dendritic arbors much larger (>1 mm diameter) than those of On alpha RGCs (~300 μm diameter). As a result, excitatory input to an On alpha RGC reaches a plateau for stimulus sizes matching the cell's dendritic field, while inhibitory input from wide field amacrine cells continues to increase with stimulus size. Thus, an antagonistic surround is evoked in response to stimuli that exceed the area of the On alpha RGC dendritic field.

Farrow *et al*. proposed that at low light levels (<10 R*/rod/s) rod signals from the primary rod bipolar pathway fail to drive the wide field amacrine cell across the spike threshold. At higher light levels (>10 R*/rod/s), cone bipolar dendritic inputs are recruited and combined with axonal input from AII amacrine cells; these conditions provide sufficient input to depolarize the spiking amacrine cell past threshold. Thus, at low light levels, the wide field amacrine cell provides little or no inhibitory input to an On alpha RGC; but at higher light levels, when cone bipolars start to receive additional dendritic input (e.g., via the secondary rod pathway), the wide field amacrine cell is recruited to inhibit the On alpha RGC.

The surprising switch-like transition of center-surround organization likely serves a nuanced role in visual function since it occurs in some but not all RGC types. Understanding this issue will require more complete information about which cells exhibit this switch-like transition and how those cells participate in visually guided behavior.

We now turn to examples of retinal dynamic computations that deviate more dramatically from the classic picture of retinal adaptation.

Mode of Spatial Integration of Visual Inputs Depends on Mean Luminance

In 1966, Enroth-Cugell and Robson, using extracellular recordings from the cat optic-tract, discovered two types of RGCs that display distinct spatial encoding properties. 'X' RGCs exhibit linear spatial integration, such that if the center of their receptive field is presented with a stimulus composed of regions of equal positive and negative contrast, the responses to light and dark regions cancel and no response is evoked (Figure 3A, left). 'Y' RGCs exhibit nonlinear spatial integration, so that responses to positive and negative regions of the same stimulus never fully cancel [15]. The mode of spatial integration is often used as a distinguishing feature of specific RGC types, and the physiologically characterized X and Y cells were later shown to be the equivalent to the morphologically characterized beta and alpha RGCs, respectively [20–22]. The homologs of the alpha type have been found in many mammalian species, including mouse, where anatomically and functionally identified On and Off alpha RGCs both can exhibit

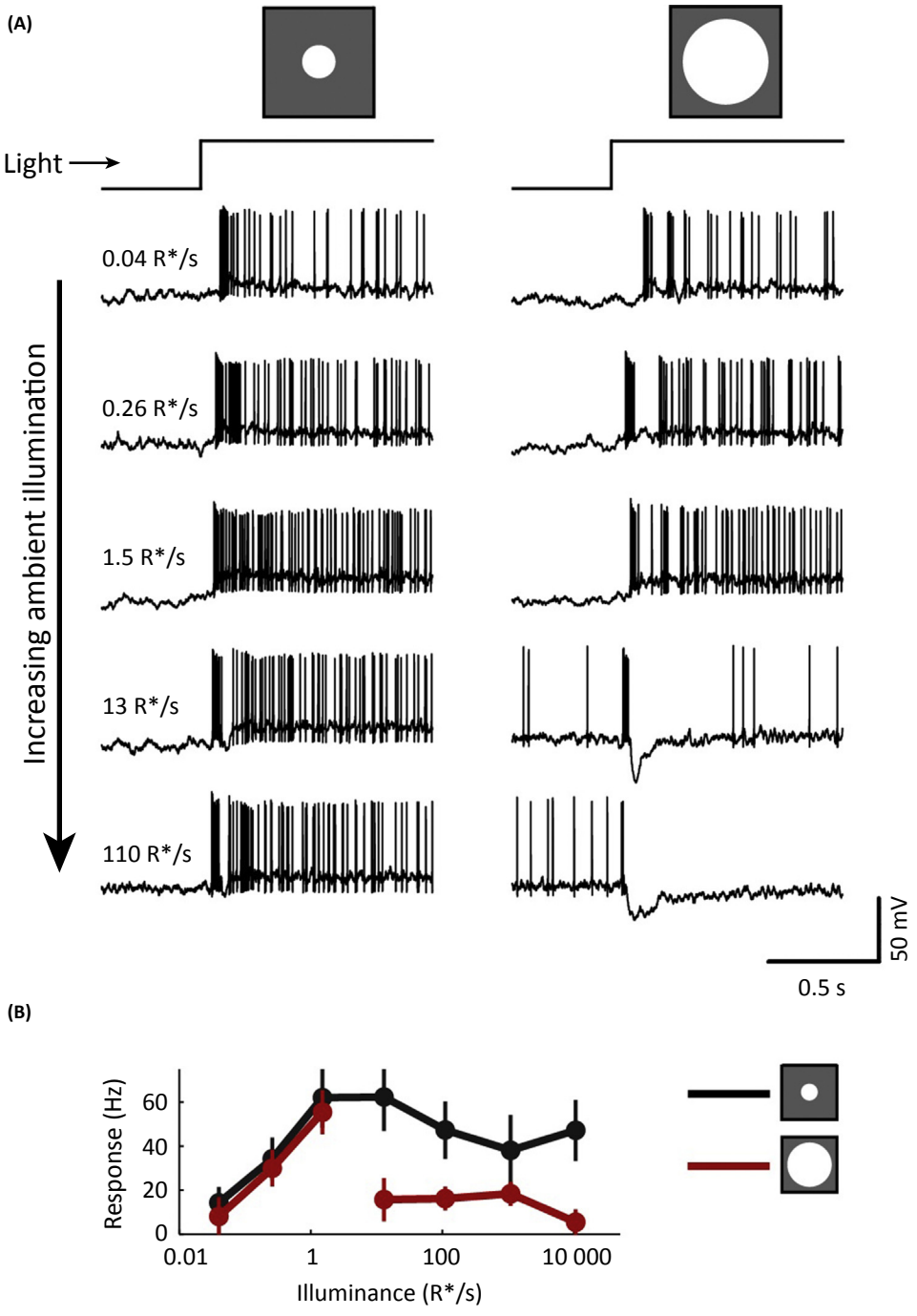

Figure 2. Switch-like Recruitment of Antagonistic Surround in On Alpha Retinal Ganglion Cells. (A) Current-clamp recordings of an example On alpha retinal ganglion cell in response to 400 μm (left) and 1000 μm (right) spots across five log units of light intensity. The Michelson contrast at each light level was 0.9993. (B) Summary of responses (firing rates) to 400 μm (black) and 1000 μm (red) spots of various light intensities. Values indicate mean firing rate ± standard deviation during the first 1.5 s of the spot presentation (n = 12 cells). The break in the red curve represents the abrupt surround recruitment, resulting in a significant reduction in the spiking activity of the cells. Adapted from [18].

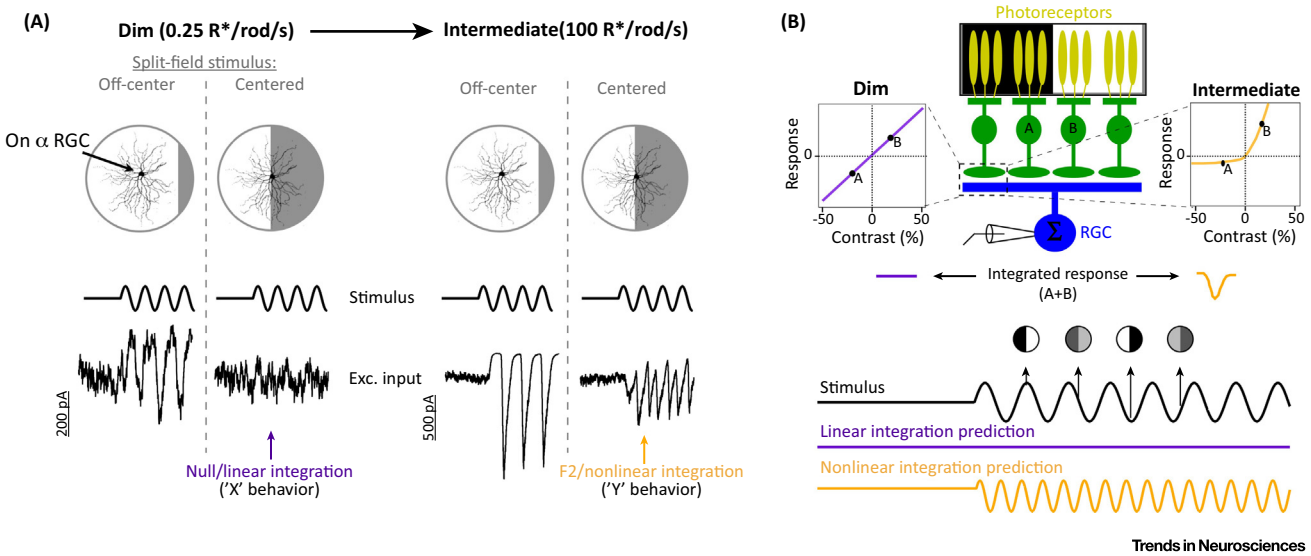

Figure 3. Spatial Integration Properties of On Alpha Retinal Ganglion Cells Depend on Mean Luminance. (A) A temporally modulated split-field grating can be used to determine how a retinal ganglion cell (RGC) integrates visual signals across its receptive field. If the 'split' between (equal and opposite) light and dark sides of the grating is far from the receptive field center (i.e., the stimulus is uniform across the receptive field) the cell responds at the stimulus frequency. The 'split' between light and dark halves can then be shifted into the center of the RGC's receptive field. RGCs that integrate linearly over space (left) will now exhibit a null point because the mean luminance over space is held constant. RGCs that integrate nonlinearly over space (right) are unable to be nulled, and instead produce a frequency doubled (F2) response when the split is centered over the receptive field. Grimes and colleagues [27] found that On alpha RGCs in mice perform linear spatial integration under dim lighting conditions and non-linear spatial integration under intermediate lighting conditions. (B) RGCs integrate signals from tens to hundreds of bipolar cells that tile the retinal surface. If these bipolar cells transmit visual signals linearly to RGCs then signal integration from many bipolar cells in response to a centered split-field grating stimulus will null the RGC's response to temporal modulation. If bipolars only transmit signals in response to increments or decrements (i.e., are rectified) then integration over space will lead to a response on every half cycle (i.e., the response frequency is doubled compared with the stimulus). Adapted from [27].

nonlinear spatial integration [23–25]. Bipolar cells, and rectification of the bipolar synaptic output, provide the substrates for this nonlinear spatial integration [26] (Figure 3B).

Surprisingly, Grimes and colleagues found that the mode of spatial integration in On alpha RGCs in mice changes with ambient light level; these cells integrate signals linearly over space (like X cells) at low illumination levels (~0.5 R*/rod/s) and nonlinearly (like Y cells) at higher illumination levels (≥100 R*/rod/s) [27] (Figure 3A). The change in spatial integration was accompanied by a change in rectification: at low illumination levels, positive and negative contrasts elicited responses of similar magnitude in On alpha RGCs. At higher illumination levels, positive contrasts elicited larger responses than negative contrasts (i.e., positive rectification). This rectification mediates nonlinear integration across space at high illumination (Figure 3B).

What mechanisms underlie this change in rectification with changes in light level? Positive rectification was present in the RGC excitatory synaptic inputs, indicating that it is a property of the bipolar output. Positive rectification, however, was absent in the voltage responses of the cone bipolar cells that provide input to On alpha RGCs; hence the major rectification must occur in the conversion of bipolar voltage to synaptic output. Indeed, increases in mean light level led to a sustained hyperpolarization (rather than the depolarization expected for On retinal cells) in electrically coupled On cone bipolar cells and AII amacrine cells. This hyperpolarization appeared to result from a reduction in tonic release at the rod bipolar-AII synapse. Hyperpolarization in turn shifts the On cone bipolar synapse to a more nonlinear region of its operating range.

What is the functional consequence of the change from linear to nonlinear spatial integration? At low (but nonzero; see [7]) light levels, On alpha RGCs respond to the total light flux within their receptive field center, irrespective of how that light is distributed spatially. At higher light levels, the cells become sensitive to the distribution of light across space, and hence become sensitive to spatial patterns or texture [23]. Consequently, the visual information carried by On alpha RGCs is fundamentally different at low and high light levels. Whether and how these differences impact visually guided behavior remains to be determined.

Reversal of Directional Preference in Direction-Selective Ganglion Cells

One of the most interesting and well-known retinal computations is the encoding of directed motion (i.e., direction selectivity). Direction-selective retinal ganglion cells (DSGCs) fire robustly in response to motion in one (preferred) direction, and poorly to motion in the opposite (null) direction. Since their discovery over 50 years ago [28], the neuronal circuit underlying this computation has been studied extensively. Physiological, anatomical, and computational methods all indicate that a circuit architecture based on asymmetric inhibitory connections mediates direction selectivity [29–32]. This inhibition arises via starburst amacrine cells (SACs), as SACs located on the null side, but not preferred side, of the DSGC form strong GABAergic connections onto its dendrites [30] (Figure 4A). This is a beautiful example, in which anatomical connectivity and function go hand in hand.

Despite the apparent completeness of the circuit operation described above, On–Off DSGCs in the mouse retina have recently been shown to reorient their directional tuning by 180 degrees following short repetitive visual stimulation at high light intensities (Figure 4B) [33]. High photopic light intensities ($\geq 10^5$ R*/rod/s) and a few minutes of repetitive stimulation could produce long-lasting reversal in directional preference.

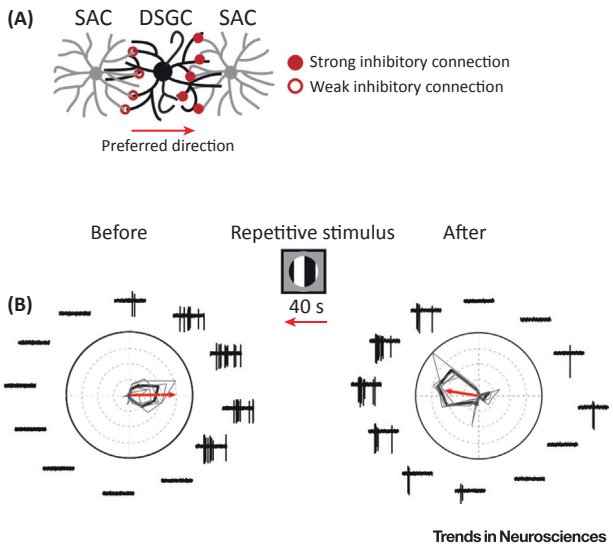

Figure 4. Direction-Selective Retinal Ganglion Cells Reverse Their Directional Preference Following Repetitive Stimulation. (A) Cartoon of the anatomical connections that underlie the directional responses in direction-selective retinal ganglion cells (DSGCs). DSGC receives strong inhibitory connections from starburst amacrine cells (SACs) located on its null, but not preferred, side. (B) Directional tuning of a DSGC before (left) and after (right) stimulation with 40 seconds of drifting grating (shown in center), revealing reversal of directional preference following repetitive stimulation. Polar plot represents number of spikes in response to 3 second gratings drifting in 12 different directions. The outermost rings correspond to 72 spikes. The black tuning curve shows the mean response (five repetitions), while the gray curves show the responses for each repetition; the red arrow indicates the vector sum of the responses. Traces show the response data for the first 0.5 seconds of grating stimuli. Adapted from [33].

What mediates the reversal of the direction-selective computation? GABA blockade has been shown to trigger a reversal of directional preference in DSGCs [34,35]. However, Rivlin-Etzion *et al*. [33] showed that the reversed directional tuning requires GABAergic inhibition, similar to the original directional tuning. Moreover, the inhibitory synaptic input to DSGCs, which is typically very large (four times larger than excitatory input) in response to motion in the null direction, changes following repetitive stimulation and strengthens in response to motion in the original preferred direction (two and a half times larger than excitatory input), thus creating a new null direction. Whether this inhibition arises from SACs is unknown.

The asymmetric inhibitory synapses between SACs and DSGCs, which are thought to be fundamental for the computation, are not expected to change within a few minutes of stimulation. As opposed to the cortex, little evidence exists for large and rapid changes in synaptic strength within the retina. Another possibility is that repetitive stimulation alters the directional preference of individual SAC processes, resulting in reversal of DSGCs. Prior to strong stimulation, SACs are thought to release more GABA in response to centrifugal motion (i.e., motion away from the soma) [36,37], which corresponds to the null direction of the DSGC they innervate [32]. As a result, GABA release onto DSGCs increases sharply during object motion in the null direction. Since the centrifugal preference in SAC processes is supported by intrinsic properties of the cell and by synaptic mechanisms [38–42], changes in any of these properties could reverse SAC, and hence DSGC, directional preference. These findings highlight the importance of functional studies even as we gather more information about neural connectivity, because even with fixed anatomical connections, the final computation of a circuit may be altered substantially by changes in external input.

Reversal of the directional preference of DSGCs occurs in preparations in which the retina is detached from the pigment epithelium. Under these conditions, recovery of saturated rods is prevented [43]. The sustained rod saturation caused by the high illumination levels may therefore explain the long duration of motion reversal. Whether reversal of DSGCs has a physiological relevance remains to be determined, but this finding can be used to shed new light on the mechanisms underlying the computation of motion direction.

Polarity Preference of Some Retinal Ganglion Cells Change with Mean Luminance

RGC light responses are functionally diverse and can be divided into 20–30 subtypes [44,45], but on a simpler level most RGCs can be classified into three groups based on their polarity preferences: On, Off, and On–Off. The polarity preference generally matches the morphology of RGCs: On and Off RGCs stratify exclusively in the On and Off layers of the inner plexiform layer, respectively, whereas the dendrites of On–Off RGCs stratify in both layers. This functional organization is a fundamental aspect of retinal signaling, and the response polarity is often used as an identifying feature of specific RGC types.

Recent multielectrode array recordings from mouse retina show that the polarity preference of some RGCs can change with ambient light levels [46,47]. These changes in polarity preference were revealed by exposing the retina to full-field positive or negative contrasts steps at mean light levels ranging from 1 to 10^4 R*/rod/s. Some RGCs that exclusively responded to either positive or negative contrasts at one light level (i.e., a pure On or a pure Off response) responded to both positive and negative contrasts at other light levels (On–Off responses; Figure 5). These changes in response properties were not caused by antagonistic surround activation, as they persisted when only stimulating the receptive field center [46,47]. The two studies describing these polarity changes differ in the percentages of RGCs that altered their

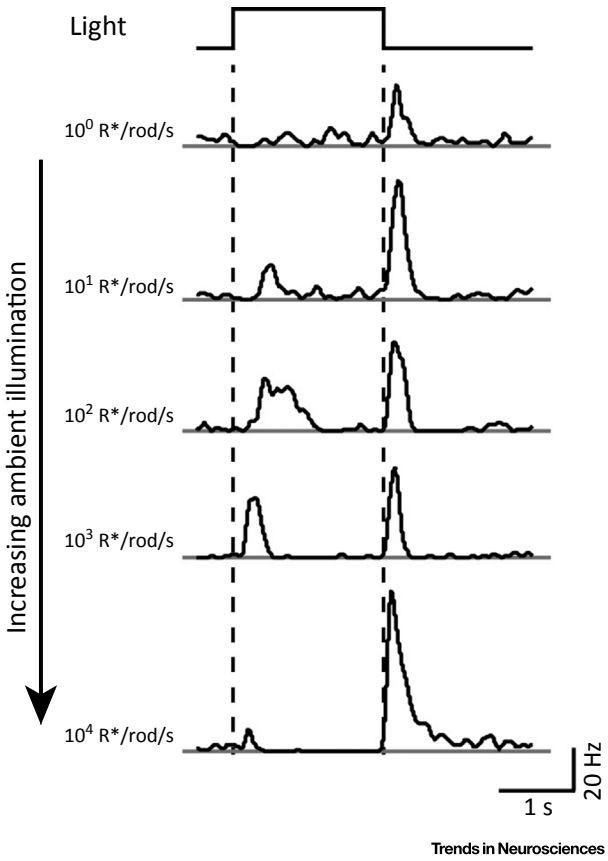

Figure 5. Retinal Ganglion Cells Change Polarity Preference with Mean Light Level. Responses (firing rate) of a single Off retinal ganglion cell (RGC) to full-field positive contrast steps (average firing rate to 45 stimulus repeats at each of five different light levels). The Weber contrast at each light level was 0.66. Adapted from [46].

polarity preference, and reported different light levels that maximize the effect; but these studies unequivocally show that the strict affiliation of retinal neurons as either On or Off is incomplete. Potentially related, SACs were shown to reverse their polarity preference following repetitive stimulation, with On-SACs losing their On response and gaining an Off response, and Off-SACs doing the opposite [48].

Since multielectrode array recordings identify RGC types by light response alone, the possibility that RGC types with altered polarity preferences exhibit On–Off morphology cannot be excluded [49]. Patch recordings combined with cell fills in several RGCs demonstrated that monostratified cells can display increased firing rates in response to both positive and negative contrasts [46]. The observation that both amacrine cells [48] and RGCs can exhibit altered polarity preference with background level challenges the view of parallel processing using distinct, static, On, and Off channels with strictly defined stratification patterns.

Potential Mechanisms of Dynamic Computing

Interactions between parallel rod and cone pathways appear to play a central role in several of the examples of dynamic computing described above in the mouse retina. At very low light levels, only the rod bipolar pathway functions [50]. As background intensities increase, two other rod pathways are recruited, and cones begin to function [51–53]. The recruitment of these

pathways by itself does not necessarily cause the changes in computation, but it is clear that intrinsic changes in the rod bipolar pathway and in its interactions with other parallel pathways can lead to fundamental changes in retinal processing.

The rod bipolar pathway classically is assumed to function only in very dim light. Recent work, however, demonstrates that mouse rod bipolar cells receive direct input from cone photoreceptors, and indeed the rod bipolar pathway can respond across a broader range of intensities than previously thought [10,48,54–57]. Adaptation at the rod bipolar output synapse [10,27] extends its operational range and permits it to modulate downstream circuit components that control RGC stimulus selectivity. The change in RGC spatial integration described above is one specific example.

In the following sections we discuss additional mechanisms that potentially contribute to dynamic encoding.

Rod–Cone Interactions via Horizontal Cells and Gap Junctions

Both rod and cone photoreceptors are depolarized in the dark and continuously release glutamate. At high light levels ($>10^3$ R*/rod/s), rods saturate and can no longer transduce incident light into an electrical response. Nevertheless, rods can continue to respond to electrical and chemical input. Specifically, horizontal cells transmit cone-driven surround inhibition to rods at high light levels [54]. As a result, rods switch their response polarity and depolarize in response to light increments in bright conditions [48,54]. This inversion in rod response polarity could contribute to alterations in polarity preference reported in some RGCs [47] and SACs [48] at high background illumination.

Gap junctions play a central role in transmitting rod and cone signals through the retina. They are found in each of the five major retinal neuron types, and provide key connections between the rod and cone pathways. This includes connections between rods and cones themselves [58] and between AII amacrine cells and On cone bipolar cells (see Figure I in Box 1). In bright light, gap junctions can transmit signals from On cone bipolar cells to AII amacrine cells, and contribute to disinhibition of the Off pathway in response to negative contrast stimuli [59–61].

Electrical coupling strength can be regulated by light level [62,63]. This modulation of coupling strength likely controls the relative contribution of each of the retinal parallel pathways, and the interactions between them. Hence, the signaling arising from rod and cone pathways is highly dynamic, and depends on the lighting conditions. The change in coupling strength, which is expected over the course of a day, may also contribute to flexibility in retinal computation [64–66].

Masked Synaptic Inputs

Several studies have identified robust changes in polarity preference in On and Off RGCs following blockade of GABAergic inhibition [35,67,68]. These emergent responses were evoked in response to stimuli restricted to the receptive field center (i.e., excluding the surround). Anatomical considerations (i.e., stratification lamina in the inner plexiform layer) make it unlikely that On RGCs receive direct input from Off bipolar cells. Thus, emergent responses are likely to originate from excitatory or inhibitory cross-over mechanisms [35,59,68–75].

Blocking dendritic input to On bipolar cells can also unmask anomalous responses in both On and Off RGCs. Off RGCs can produce a delayed On response following blockade of the On pathway [76]. The delayed On response persisted when inhibition was blocked, and is thought to originate within the Off pathway. This emergent On response may normally be masked by

inhibition coming from the On pathway. Similarly, some On RGCs can exhibit large Off excitatory synaptic input upon the block of signaling in On bipolar cells; these responses are eliminated when the tonic level of activity in On bipolar cells is maintained while modulated activity is eliminated [77]. Importantly, inhibitory masking of synaptic inputs is highly context-dependent (e.g., [78,79]), and hence these masked inputs can contribute to physiology signaling under certain stimulus conditions. Taken together, these findings suggest that excitatory/inhibitory input balance at various points within the retinal circuitry may rapidly change with changes in the visual environment, contributing to alterations in circuit function.

Concluding Remarks

Stimulus-dependent functional changes occur in many brain regions, especially the cortex and hippocampus. Conversely, primary sensory organs such as the retina are conventionally thought to stably and reliably process visual information, and therefore are not expected to exhibit substantial stimulus-dependent changes in function. Recent evidence regarding flexible hardware and dynamic encoding in the retina requires revisiting some of the basic assumptions about visual processing, including the differential activation of rod and cone circuits at low and high light levels and the distinction between On and Off pathways. These studies also identify common features of neural circuits that can lead to rapid changes in computation with changing environments.

Why Have These Encoding Dynamics Been Missed in the Past?

The simple answer is that dynamic computing has not, in fact, been missed. We consider hardware flexibility to play an integral part of adaptation, and the latter is well known to play a central role in retinal processing. Changes in RGCs' center-surround organization were discovered almost 60 years ago [13–17], and temporary changes in polarity preference of RGCs were reported following surround stimulation more than a decade ago [49]. Advances in genetically based cell identification and multielectrode array recordings have improved the ability to target specific cell types and to make long-lasting recordings from cell populations. These technical advances have contributed to the ability to identify dynamic coding features exhibited by some but not all RGCs.

Dynamic Computing and Retinal Connectomics

Recent advances in microscopy, imaging, and genetics, allow us not only to expand our knowledge of brain function, but also to recognize fine details of its anatomy, even at the level of single synaptic connections. Serial electron microscopy has led to the connectomics approach for revealing brain function, that is, that knowledge of circuit structure in the form of a complete wiring diagram can predict function. The retina is particularly appealing for this purpose, due to its highly organized and laminar structure. Indeed, retinal computations are often predicted by the anatomical organization (e.g., On and Off neurons stratify in different layers within the inner plexifom layer, and DSGCs' dendrites are asymmetrically wired to SACs). Pioneering connectomic studies have confirmed longstanding hypotheses that were based on physiological data and computational theories, and have also revealed new cell types and new predictions regarding unknown connections within the retina [32,80].

Retinal connectomics alone, however, does not provide a complete description of retinal function [81,82]. The examples of flexible computation described here do not require changes in connectivity, as the change in function often occurs immediately following a change in stimulus conditions (e.g., light level), or within a few minutes of repetitive stimulation (i.e., likely to be too rapid for fundamental changes in the underlying synaptic connectivity to occur). Thus, dynamic encoding emphasizes the significance of combining multiple approaches in studying

Outstanding Questions

How does dynamic computing shift the entire population of retinal output signals? Are such shifts beneficial for coding?

Is dynamic computing shared across species?

What neural mechanisms alter the retinal code? Do other brain regions exhibit similar changes in dynamics? If so, do they rely on similar mechanisms?

How do downstream visual circuits handle a dynamic retinal code? How do we maintain our visual perception in a constantly changing representation of the visual world?

neural circuits, as different architectures may achieve the same functional implementation, and a given architecture can support multiple activity patterns [83].

Physiological Relevance of Dynamic Retinal Computations

It is increasingly clear from work in rodents and amphibians that the retina extracts specific features of the visual inputs rather than just providing veridical information about the visual field [84]. These new studies provide some of the most surprising examples of the complexity of retinal computation and its potential influence on downstream visual processing. Indeed, if, and how, the changes in computations of retinal neurons are integrated and interpreted along the visual pathway remains an open question.

Notably, Tikidji-Hamburyan and colleagues, who demonstrated changes in the RGC polarity preference with differing background illumination, also detected similar changes *in vivo* in the dorsal lateral geniculate nucleus (dLGN) of anesthetized mice. Their findings suggest that changes in polarity preference are transferred to a primary retinal target [46]. Yet, this study did not resolve whether all changes in retinal encoding translate to the dLGN, or if some compensation is achieved at the dLGN level. There are many additional unanswered questions that evolve from these findings (see Outstanding Questions). Perhaps the most intriguing is how one maintains a stable visual perception in a constantly changing representation of the visual world. These difficult questions remain to be resolved in future studies. We think, however, that the evidence presented here implies that a conceptual change is needed in how we see the retina and its computational role in visual processing.

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