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Impact of Photoreceptor Loss on Retinal Circuitry

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Abstract

Our sense of sight relies on photoreceptors, which transduce photons into the nervous system's electrochemical interpretation of the visual world. These precious photoreceptors can be disrupted by disease, injury, and aging. Once photoreceptors start to die, but before blindness occurs, the remaining retinal circuitry can withstand, mask, or exacerbate the photoreceptor deficit and potentially be receptive to newfound therapies for vision restoration. To maximize the retina's receptivity to therapy, one must understand the conditions that influence the state of the remaining retina. In this review, we provide an overview of the retina's structure and function in health and disease. We analyze a collection of observations on photoreceptor disruption and generate a predictive model to identify parameters that influence the retina's response. Finally, we speculate on whether the retina, with its remarkable capacity to function over light levels spanning nine orders of magnitude, uses these same adaptational mechanisms to withstand and perhaps mask photoreceptor loss.

Keywords

retina; photoreceptors; degeneration; retinal disease

1. INTRODUCTION

Advancements in gene therapy (Duncan et al. 2018, Hardcastle et al. 2018, Takahashi et al. 2018, Trapani & Auricchio 2018, Wood et al. 2019) and technology for retinal prosthetics (Palanker & Goetz 2018, Yue et al. 2016) have allowed retinal function to be rescued in animal models with photoreceptor disruption; however, the effectiveness of these therapies in ongoing human clinical trials remains unknown (Roska & Sahel 2018). The disconnect between functional rescue and the translational effectiveness of therapies may be due to our lack of understanding of the biological mechanisms active in a retina with photoreceptor disruption. In this review, we examine what has been learned about the state of the neurons within the retinal circuit after photoreceptor disruption using animal models, which allows for insight into neural mechanisms. We review this literature from a neurocentric view and with an outstanding question in mind: Are there conditions under which the remaining retinal circuit is better primed to regain function?

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We begin by providing an overview of the healthy retina's structure and function. We summarize the types of manipulations that have been used to disrupt photoreceptor function and the assessment methods used to evaluate changes in the remaining retinal circuit. Then we analyze observations across a body of literature on photoreceptor disruption to generate a statistical model that predicts the state of the remaining retinal circuit after the disruption. We use this predictive model to identify trends in how specific parameters of the manipulation, timing, extent of death, and photoreceptor type may influence the state of the retinal circuit, i.e., whether it loses or regains function. Finally, we discuss the retina's ability to function over a large range of stimulus conditions and speculate on whether the retina may use some of these same mechanisms to withstand photoreceptor loss and retain function.

2. OVERVIEW OF RETINAL CIRCUITRY

2.1. Structural Organization

The retina is precisely organized along its surface and depth. In depth, i.e., the axis at which light enters the eye, nuclear and synaptic laminae segregate the major cell classes (Figure 1a). Within each of the major cell classes, there are multiple cell types (Demb & Singer 2015, Wässle 2004). Photoreceptors divide into rods and cones with specific opsin expression (Figure 1a). The mouse retina has 15 types of bipolar cells (Helmstaedter et al. 2013, Shekhar et al. 2016), an estimated 35 types of amacrine cells (Diamond 2017), and 12 to >35 types of ganglion cells based on molecular and functional definitions (Baden et al. 2016, Sanes & Masland 2015, Seung & Sümbül 2014).

Along the retinal surface, i.e., the axes that define the spatial positions of light, each of these cell types tiles the retina in a regular mosaic (Figure 1b). These mosaics are the basis for segregating cell types in the retina (DeVries & Baylor 1997, Gauthier et al. 2009, Masland 2012, Wässle et al. 2009).

2.2. Functional Organization

These cell types communicate via excitatory, inhibitory, gap junctional, and neuromodulatory pathways (Diamond 2017, Massey 1990, Vaney 1994). The transduction cascade of photoreceptors releases glutamate in darkness. Photon absorption causes channel closure and lowers glutamate release (Supplemental Figure 1). Rod bipolar cells and half of cone bipolar cells use metabotropic glutamate receptors, which invert the polarity of photoreceptor light responses and initiate the ON pathway (Nakajima et al. 1993, Slaughter & Miller 1981) (Figure 1c, i). The other half of cone bipolar cells use ionotropic glutamate receptors, which preserve the polarity of photoreceptor light responses and initiate the OFF pathway (Borghuis et al. 2014, DeVries 2000, Puller et al. 2013) (Figure 1c, i). Ganglion cells all use ionotropic glutamate receptors; this results in ON, OFF, or ON–OFF ganglion cells, depending on which bipolar cells provide input.

The excitatory feedforward pathway among photoreceptors, bipolar cells, and ganglion cells is modulated by inhibition, provided by horizontal cells in the outer retina and amacrine cells in the inner retina (Figure 1a).

In addition to excitation and inhibition, the retina signals via gap junctions (O'Brien & Bloomfield 2018, Vaney 1994) (Figure 1a), slower neuromodulation (Daw et al. 1989, Dowling 1991, Roy & Field 2019), and acetylcholine (Taylor & Smith 2012, Wei 2018, Wei & Feller 2011).

Such precise organization serves the retina's computations. In this section, we summarize how the retinal circuitry contributes to encoding the basic parameters of photons: number, location, timing, and wavelength.

The retina detects changes in the relative—as opposed to absolute—number of photons over space and time, allowing rods and cones, in conjunction, to detect single to billions of photons. The retina achieves this primarily by employing three mechanisms: adaptation, center-surround spatial organization, and the division of ON and OFF pathways. Adaptation within each photoreceptor's transduction cascade and within the retinal circuit allows dynamic signaling across stimulus statistics, e.g., adapting to the mean or deviations from the mean number of photons from the mean (Demb 2008, Kastner & Baccus 2014, Weber et al. 2019) (Figure 1c, ii). The mosaic arrangement of retinal neurons allows the locations of photons to be preserved up to the resolution of receptive fields of individual cells or their inputs, if distinguishable (Demb et al. 1999, 2001; Enroth-Cugell & Robson 1966; Freeman et al. 2015; Schwartz et al. 2012). These receptive fields are generally organized into center and surround components, which give rise to opposite polarity responses within a single neuron (Figure 1c, iii), allowing for the comparison of the location of photons within a single receptive field and giving rise to greater spatial sensitivity (Turner et al. 2018). ON and OFF pathways that arise from distinct channel expression at bipolar cell dendrites exhibit differences in response kinetics (Chichilnisky & Kalmar 2002), allowing for paired channels to discern the relative timing and location of photon arrival (Gjorgjieva et al. 2014, Gollisch & Meister 2008) (Figure 1c, i).

Wavelengths of photons are also encoded in a relative manner by comparing photoreceptors with different spectral sensitivities in the center versus the surround of a receptive field; however, discerning colors requires further comparison in higher visual areas (Chang et al. 2013, De Valois 1965, Horwitz 2020, Joesch & Meister 2016).

Specific microcircuits also give rise to computations that involve combinations of the basic photon properties, such as the detection of motion (Kuo et al. 2016, Manookin et al. 2018, Matsumoto et al. 2019, Ölveczky et al. 2007) and direction (Wei 2018, Wei & Feller 2011). Whether such computations occur by the level of the ganglion cell across mammalian species remains under investigation (Huberman & Niell 2011).

2.3. Species Differences

Before devoting the remainder of this review to rodent and rabbit models of photoreceptor loss, we want to acknowledge species-specific specializations in the mouse and primate retina. The primate retina has three related specializations that are distinct from the mouse retina: (*a*) the fovea, (*b*) spatially segregated regions of high cone or rod densities, and (*c*) dedicated circuitry for high-acuity vision.

In primates, the first specialization, the fovea, is a region in the central 500 μm that is structurally distinct from the rest of the retina. The fovea contains tightly packed smaller cones that send their axons away from the center to create an unobstructed path for light to strike photoreceptors (Bringmann et al. 2018). This defines the region used for high-acuity vision. Related to the fovea, the second specialization is the segregation of rods and cones, with highest cone density in central retina and high rod density in peripheral retina (Østerberg 1937). The third specialization is the midget pathway, which is a privileged communication line among one cone, one OFF, and one ON midget cone bipolar cell and their respective OFF and ON midget ganglion cells (Lee et al. 2010). The midget pathway confers higher acuity than other retinal pathways that pool inputs across more than one photoreceptor. All other pathways have multiple photoreceptors converging onto each bipolar cell and multiple bipolar cells converging onto each ganglion cell (Boycott & Dowling 1969, Field & Chichilnisky 2007).

The mouse retina has its own related specializations. Though it lacks a true fovea, the central region has a higher density of photoreceptors (Volland et al. 2015), and though rods and cones are not segregated, the distribution of cone opsins is spatially segregated (Applebury et al. 2000). Accumulating evidence suggests that, although the mouse retina lacks a single fovea with a high-density midget system, specific ganglion cell types have higher densities in different retinal regions and may confer perceptual specializations for different regions of the visual field (Bleckert et al. 2014, El-Danaf & Huberman 2019). Furthermore, the central region of the mouse retina has characteristics similar to the human macula, e.g., photoreceptor densities, thinner Bruch's membrane, and phagocytic load of the retinal pigment epithelium (Grünert & Martin 2021, Volland et al. 2015).

Given these differences between the primate and mouse retina, identical genetic mutations could cause the mouse retina to undergo processes unlike those that occur in human disease, especially in the fovea. However, the structure of the retina outside of the central region is largely conserved between primate and mouse, and the basic cellular and synaptic changes that ensue following photoreceptor degeneration may use similar mechanisms despite occurring in different cell types or retinal regions.

With regard to the fovea, species with cone-rich retina, e.g., tree shrews (Müller & Peichl 1989) and zebrafish (Angueyra & Kindt 2018), serve as better models of foveal cone density. In another cone-rich species, the thirteen-lined ground squirrel, cone structure and function can be studied simultaneously using noninvasive techniques such as adaptive optics and optical coherence tomography (Sajdak et al. 2016). Although models of retinal disease in cone-dominant animals are becoming more prevalent with the advent of techniques for gene manipulation across species, there is a paucity of degeneration models available in cone-rich retina. Therefore, although the mouse retina is rod dominant, an understanding of cellular processes following photoreceptor degeneration in the mouse could guide future research to understand nonfoveal retinal circuitry.

3. OVERVIEW OF PHOTORECEPTOR LOSS MANIPULATIONS INCLUDING METHODS OF ASSESSMENT

3.1. Genetic Manipulations

Photoreceptor disruption in rodents occurs by either spontaneous mutations or directed mutagenesis. In a tour de force review by Collin et al. (2020), 230 gene mutations causing photoreceptor death were curated by their contributions to specific biological functions. For example, one category of visual transduction involves genes essential for photoreception (Supplemental Figure 1A). These elements are similar in rods and cones, but each photoreceptor type utilizes specific genes or proteins to catalyze the multiple steps of the phototransduction cascade (Supplemental Figure 1B). Mutations in a subset of these genes affect photoreceptor function and survival. A detailed description of the effects of these gene mutations and the diseases that they cause can be found in reviews dedicated to this topic (Collin et al. 2020, Pfeiffer et al. 2020, Veleri et al. 2015).

3.2. Acute Death: Chemical Ablation, Photocoagulation, and Diphtheria Toxin Receptor

The majority of genetic manipulations cause photoreceptor death during retinal development; however, in humans, macular degeneration and most inherited retinal degenerations cause photoreceptor death after retinal development. To disentangle remodeling triggered by photoreceptor loss from normal developmental plasticity, four techniques have been used to ablate photoreceptors after retinal maturation: (*a*) chemical ablation of photoreceptors (Chen & Nathans 2007, Nagar et al. 2009); (*b*) light damage to photoreceptors in albino animals (De Vera Mudry et al. 2013, Montalbán-Soler et al. 2012, Richards et al. 2006); (*c*) the photocoagulation method, in which the laser causes a focal lesion to the retinal pigment epithelial cells and the photoreceptor layer, indiscriminately ablating rods and cones (Beier et al. 2017, 2018, Sher et al. 2013); and (*d*) the expression of the simian diphtheria toxin receptor under a promoter for either rod or cone opsin genes in the mouse, in which systemic injection of diphtheria toxin determines the timing and degree of cell death by inducing death selectively in either rods or cones (Care et al. 2019, 2020; Shen et al. 2020). While none of these methods of acute death causes the combined apoptotic and necrotic pathways that occur with slower degenerative diseases, all of them allow for precise control over the timing of the perturbation. By inducing death in the mature retina, these manipulations eliminate the confounds of developmental plasticity and thereby better recapitulate a subset of retinal conditions. Among these systems, however, only the genetically encoded diphtheria toxin receptor allows for selective ablation of rods or cones, isolating the contribution of each pathway.

3.3. Assessment Methods

Common methods of assessing the retina following photoreceptor perturbations involve characterization of retinal structure and function. Structural assessments include examination of gross lamination; quantification of remaining cells; morphological evaluation of individual cells; and, providing the greatest detail, quantification of synaptic proteins between pre- and postsynaptic partners at the levels of light and electron microscopy. Functional assessments include examination of the electrical potential across the retina using

the electroretinogram (ERG), which can distinguish responses from different cell classes but cannot distinguish responses from cell types beyond activity in the ON and OFF pathways. With greater resolution, multielectrode array (MEA) recordings can examine extracellular spikes across a large population of ganglion cells (Wong et al. 1993). The finest resolution of examination is provided by single-cell recordings of known types (Hellmer & Ichinose 2018). The culmination of cellular and circuit mechanisms working in concert is represented by the visual behaviors, which include the optokinetic reflex to test visually evoked eye movements, the visual cliff to test contrast detection and depth perception, and the water maze to test visual sensitivity in rodents (Koskela et al. 2020, Nagar et al. 2009, O'Steen et al. 1995, Shen et al. 2020, Simpson 1984). Even when studies perform the assessment methods mentioned above in conjunction, each study contributes only a glimpse of a grand landscape that encompasses the effects of photoreceptor loss on the rest of the retina across different manipulations, within specific cell types and their microcircuits, and as a function of time. Part of the goal of this review is to compile data across studies and across assessment methods to identify trends in the studies to date.

3.4. Summary of the Dominant Stages of Retinal Degeneration

Given the wide array of manipulations and assessment methods, one question is whether there are meaningful trends across manipulations and studies. In one respect, the process of retinal degeneration can be described as an escalating involvement of more cell types and greater chaos, as has been observed across various studies (for a review, see Pfeiffer et al. 2020). In seminal work from Jones and colleagues (2003), extensive anatomical characterization of rod degeneration in humans and animals revealed that the sequences of retinal degeneration exhibit common stages of (*a*) cell death, (*b*) relocation of surviving neurons, (*c*) neurite sprouting, (*d*) increasing involvement of Müller cells, and (*e*) disruption of blood vessels. In this view, the remaining retinal circuit follows the same course to degeneration, and the details of the insult only affect the time scale. In another respect, the remaining retinal circuit enters different states en route to degeneration, e.g., remains stable or compensates for input loss; these different states may be promising points for treatment. Recognizing these states and their etiology may become relevant for determining the most effective treatments in each state.

3.5. How Experimental Design Influences Observations of Retinal Outcomes

In this section, we discuss a handful of studies to highlight how the observed state of remaining retinal circuits, i.e., retinal outcome, may depend not only on the time of assessment, but also on the methods of assessment and perturbation.

The Royal College of Surgeons (RCS) rat, in which the receptor tyrosine gene necessary for phagocytosis of photoreceptor outer segments by the retinal pigment epithelium is mutated, is a classic animal model of rod death used to define the stages of retinal degeneration (Jones et al. 2003). In this model, Jones et al. observed at late time points that cell bodies were mislocalized across lamina, demonstrating a retinal outcome of degeneration. However, at early time points, other groups observed bipolar cell dendrites exhibiting both atrophy and extension toward surviving presynaptic partners, demonstrating a potential retinal outcome of compensation (Cuenca et al. 2005, Peng et al. 2003). These studies highlight how, for

the same genetic mutations, whether the retinal outcome is observed to be degeneration or compensation can depend on the time of assessment.

Observed retinal outcomes of the same genetic mutation may differ based on how the remaining retinal circuit is assessed. For example, the *rd1* mouse, in which phosphodiesterase is mutated, was observed to have misplacement of rod bipolar and amacrine cell bodies (Jones et al. 2003). In the same mouse, Strettoi et al. (2002) revealed a combination of shrinking rod bipolar cell axons and dendrites, as well as horizontal cell processes that both sprouted and lost complexity at a single time point, illustrating that individual neuronal classes respond differently to photoreceptor death. The differences between excitatory and inhibitory neurons in stages of retraction or sprouting are incorporated into the dominant stages of retinal degeneration (Pfeiffer et al. 2020). When O'Brien et al. (2014) examined the same *rd1* mouse with a focus on cell types, morphological analysis revealed that, at a single time point, specific ganglion cell types had dendrites that sprouted, remained stable, or shrunk. These findings demonstrate how multiple outcomes can coexist across cell types and how different structural assessment methods influence which retinal outcome is observed. Type-specific differences within a single class of retinal neuron are still under exploration and are not yet part of a generalized understanding of the stages of degeneration.

Similarly, for the same genetic perturbations of cone function, retinal outcome can vary in structural versus functional methods of assessment. In the *CNGA3* knockout, in which the cone photoreceptor cyclic nucleotide-gated channel lacks a critical subunit, Haverkamp (2006) demonstrated that cone bipolar cell dendrites extend beyond the disrupted cones and form ectopic synapses with functional rods, potentially compensating for lost input. When Xu et al. (2012) examined the same *CNGA3* model, retinal layers were thinner, and rod- and rod bipolar cell–mediated components of the ERG were reduced, suggesting degeneration. From these two studies, conclusions about *CNGA3* cone disruption include both structural rewiring of cone bipolar cell dendrites with the potential to bolster rod input (Haverkamp 2006) and functional evidence demonstrating that, instead, the rod-mediated ERG is compromised (Xu et al. 2012). These studies highlight how the method of assessment can lead to differing conclusions about the retinal outcome. Retinal degeneration beginning with cone disruption has yet to be incorporated into a definitive sequence of retinal degeneration, especially for the processes that may be distinct from rod-initiated disruption.

Finally, in another class of photoreceptor perturbation, acute photoreceptor death is induced by laser in a process called photocoagulation. In response to photocoagulation, rod bipolar cell dendrites initially lose synapses and then sprout and form ectopic synapses with surviving rods (Beier et al. 2017). The same group observed new functional connections between migrating photoreceptors and bipolar cells, resulting in the recovery of ganglion cell scotomas (Sher et al. 2013). These results provide evidence for the ability of the mature retina to undergo synaptic formation and compensation, which has not been as easily discoverable with genetic perturbations. Understanding the conditions under which synaptogenesis can occur remains an active area of exploration across photoreceptor perturbations (Wang et al. 2019), highlighting how methods of perturbation may affect the retinal outcome.

Across the few studies highlighted, we find that retinal outcome is contingent upon (*a*) the time of assessment, (*b*) the method of assessment, and (*c*) the method of perturbation. To resolve these potential confounds, a literature analysis is required. Insight could be gained from the periodic synthesis of findings across studies, e.g., from grouping common outcomes and examining the experimental details, manipulations, etc., that might have been causal to that outcome. For example, one common observation is the sprouting of dendrites that was observed following genetic mutations in the rods (*rd1*) and cones (*CNGA3*) and following photocoagulation. Are there common causes leading to that outcome across studies? In the following section, we group studies according to their outcomes to identify trends that may perhaps be missed if studies are assessed according to time alone, as has been done previously.

4. LITERATURE ANALYSIS GENERATES A PREDICTIVE MODEL FOR THE STATE OF THE RETINAL CIRCUIT AFTER PHOTORECEPTOR LOSS

4.1. Scope

In this section, we compile data across studies and across assessment methods to find trends. To do so requires some degree of categorization across individual studies that may blur certain distinctions. We recognize the challenges of reducing studies to numbers, of categorizing results across different methods, and of attempting to collapse data to lower dimensionality. However, despite these challenges, we make this attempt to identify common trajectories that the retinal circuit may take in response to photoreceptor disruption. The compilation of observations from the literature is used to generate a predictive model for the retinal circuit's outcome given the specific experimental conditions.

4.2. Definition of Retinal Outcomes and Parameters of Photoreceptor Disruption

We consider the studies highlighted in the previous section to be representative of the variety of outcomes following photoreceptor disruption. From these possible outcomes, we identify three general categories. We begin by categorizing observations from the literature into one of three outcomes that describe the state of the remaining retinal circuit: (*a*) stable, (*b*) degenerated, or (*c*) compensated (Figure 2; Supplemental Table 1).

The stable outcome includes results that show no additional cell death in the retinal circuit beyond the initial photoreceptor death; the predicted loss in number of inputs to postsynaptic cells; and functional linear propagation of the input loss, e.g., if half of the inputs have been lost, then the output is halved (Figure 2a). For example, following rod loss in the *rd1* mouse, a specific ganglion cell type had dendrites that remained stable and therefore presumably retained their presynaptic inputs (Supplemental Table 1).

The degenerated outcome includes results that show cell death beyond that which was originally induced and functional output that is worse than predicted from the degree of photoreceptor loss alone (Figure 2b). For example, fewer and shorter bipolar and/or horizontal cell dendritic processes were observed in the RCS rat following rod loss (Supplemental Table 1).

The compensated outcome includes results that show more than the predicted total number of inputs, e.g., because of neurite sprouting and new synapse formation, and functional output that is better than predicted from the linear propagation of photoreceptor loss alone (Figure 2c). For example, the *rd1*, *CNGA3*, and photocoagulation studies all demonstrated dendritic sprouting across neuronal classes (Supplemental Table 1).

Once a result has been placed in one of these three outcome categories, we assess the parameters that lead to the outcome. Parameters can either be categorical or numerical. Categorical parameters include (*a*) the biological processes affected by single gene mutations and (*b*) the identity of photoreceptors affected. Numerical parameters include (*a*) the age of photoreceptor disruption, (*b*) the interval between photoreceptor disruption and the observation time point, and (*c*) the percent of total photoreceptor death.

4.3. Method of Analyzing Data Across Studies to Generate a Predictive Model

Using the outcomes and parameters defined above, we have collected observations from 151 original research studies. Among these studies, we included a subset referenced by Collin et al. (2020) that compiled monogenic mutations in mice that caused photoreceptor disruption. The subset of studies that we included satisfied the following criteria: (*a*) Inner retinal structure and/or function was characterized, along with a description of photoreceptor disruption, and (*b*) causative genes were expressed in photoreceptors. In addition to these studies, we included studies that used methods of acute photoreceptor ablation and involved characterization of the effects on the retina of the mouse, rat, and rabbit (Supplemental Table 2). To categorize the causative genes associated with photoreceptor disruption, we used the framework established in the comprehensive review from Collin et al. (2020). If a single study made observations using more than one time point or assessment method, i.e., structural or functional analyses, then we categorized each observation separately. In total, there were 466 outcomes consisting of 222 observations from structural analyses and 244 observations from functional analyses. We used this framework to identify trends in what happens to the rest of the retinal circuit after photoreceptor loss.

We generated a statistical model to predict the probabilities of outcomes for various parameters of the observations. Statistical analyses and predictions were implemented using R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Generated code and reports are available at https://github.com/lucadellasantina/degeneration. For each of the parameters, we first examined frequency distributions to determine if the data had sufficient variability to calculate probabilities (Github and Supplemental Figure 2). With parameters that occurred with sufficient variability of observations with respect to the three possible outcomes, we determined how often the value of a parameter was associated with a particular outcome. In other words, could the value of a parameter predict a specific outcome? Multinomial logistic regression was used to predict the probability of three outcomes (i.e., stability, degeneration, compensation) by estimating the log odds of each category based on a linear combination of the parameters (i.e., gene mutations, photoreceptor type, etc.). We employed the log-linear model from R package nnnet, including outcome phenotype as a function of the parameters.

To generate predictions of phenotypic outcome, we used two simplified models in which either the photoreceptor type or the biological process affected by the gene mutation was the only categorical variable alongside the numerical variables.

4.4. Predictions from Gene Mutations and Photoreceptor Types: Most Roads Lead to Degeneration

First, we examined the predictions for the categorical parameters: gene mutations and photoreceptor types. For these predictions, we held numerical parameters fixed at their average values. To understand if the cause of photoreceptor disruption and/or death influenced the fate of the rest of the retina, we classified gene mutations in terms of the biological process that they disrupt. We defined four categories: phototransduction; signaling; trafficking; and other, which includes gene mutations with low variability of observations (<5% or >95%) (Collin et al. 2020) (Figure 3a). The probability that one of these four categories of photoreceptor disruption could predict the outcome is displayed in a pie chart and table (Figure 3a; Supplemental Figure 2A). Each category of gene mutation predicts degeneration with greater probability than stability or compensation. Only mutations affecting signaling had a lower probability of degeneration compared to other categories of gene mutation. These results reflect how some of these signaling molecules interfere with intercellular communication rather than cell survival. The majority of these gene mutations disrupt proper function and compromise viability of photoreceptors indiscriminately, albeit potentially on different time scales, which we examine further below. The photoreceptor type was ignored when predicting each category of gene mutation.

Next, we considered how the photoreceptor type that is perturbed influences the outcome. We categorized the outcomes by the population of photoreceptors that was primarily affected by the manipulation: rods, cones, or both. Manipulations included gene mutations and physical methods. In all three categories of photoreceptor types, degeneration was the most likely outcome; it was most common when rods alone (0.56) were the primary target and occurred less often when rods and cones (0.52) or cones alone (0.43) were the primary target (Figure 3b). In fact, among the studies that induced disruption and/or death in cones specifically, there are examples of cone bipolar cell dendritic sprouting and potentially synaptogenesis (Haverkamp 2006, Shen et al. 2020), which we categorized as structural compensation. Functional assessments also demonstrated compensation (Care et al. 2019).

Taken together, predictions of retinal outcome based on gene manipulations and photoreceptor types suggest that most roads lead to degeneration, especially when rods or phototransduction pathways are affected, at least when the parameters of timing of photoreceptor disruption and degree of death were held fixed at their averages.

4.5. Predictions from Age: Delayed Photoreceptor Disruption Allows the Retina to Remain Stable

In this section, we examine the predictions for numerical parameters starting with age when disruption occurred, e.g., during development or in maturity. To understand how the timing of photoreceptor disruption might influence the outcomes, we examined the probability of predicted outcomes when disruption occurred at different ages relative to

retinal development. We collected results from species with different timelines of retinal development. To scale the timelines, we normalized the age of photoreceptor disruption by the age at which the retina is considered mature in that species. Specifically, the mouse retina was considered mature at postnatal day (P) 21, when excitatory synaptic densities peak (Tian 2004), while the rat and rabbit retina were considered mature at P30, when light responses and retinal structures reach maturation (Gorfinkel et al. 1988, Wachtmeister 1998, Yamagiwa et al. 2020). Disruptions occurring during development were normalized to ≤1, and disruptions occurring in maturity were >1. In considering numerical parameters across a range, we categorized this range into two groups for visual display: early and late time points, although predicted probabilities were calculated across the entire range (Figure 4a; Supplemental Figures 3A and 4A). Across photoreceptor types, developmental (early) photoreceptor disruption predicts degeneration in the rest of the retina with the highest probability (Figure 4a, internal pie chart; Supplemental Figure 2B). In contrast, when photoreceptor disruption occurs in the mature retina (late), stability has the highest predicted probability (Figure 4a, external pie chart). These results indicate that the longer photoreceptor disruption is delayed, the more stable the rest of the retina is. These findings hold whether one or both types of photoreceptors are disrupted.

The finding of different outcomes as a function of age at photoreceptor disruption suggests that there exists a time point at which the probability of degeneration is surpassed by the probability of stability, i.e., the tipping point. For rods only and cones only, the tipping points occur at normalized ages of 1.1 and 1.9 (Supplemental Figures 4A). This demonstrates that the retina is less likely to degenerate in response to input loss when photoreceptors become disrupted after retinal development. For disruption of rods and cones together, the tipping point occurs at the normalized age of 2.2, which is delayed relative to the tipping points with single-photoreceptor-type disruption. This demonstrates that disruption in both rods and cones is more likely to lead to degeneration of the rest of the retina for a later period than disruption of single photoreceptor types.

4.6. Predictions from the Interval Between Disruption and Observation: Both Short and Long Intervals Lead to Degeneration

Across studies, while the same photoreceptor manipulation may be used, the observation time point may vary. To determine the contribution of intervals of examination on the outcomes observed, we categorized the outcomes by the interval between the age when disruption began and the observation time point. Again, we normalized intervals by species-specific retinal maturation age, as described above. When the observation was made at a short interval after photoreceptor disruption, the statistical model predicted degeneration as the most likely outcome (Figure 4b, *internal pie chart*; Supplemental Figure 2C). The same prediction was made at longer intervals (Figure 4b, *external pie chart*). Although the extent of structural and functional changes may differ between intervals, these results suggest that secondary cell death begins upon the onset of photoreceptor disruption, lending support to the idea that most roads lead to degeneration. However, the model revealed that, when the perturbation was cone specific, compensation was predicted with nearly equal probability as degeneration (Figure 4b, *middle, internal pie chart*). Probabilities of degeneration and compensation with early cone disruption differed by only 0.05 and 0.01

for the age of disruption and intervals, respectively (Supplemental Figure 3A,B). In contrast, compensation had the lowest predicted probability for rod-specific disruption (Figure 4b, *left*). For rod and cone disruption together, the dominant outcome for either short or long intervals between disruption and observation was degeneration (Figure 4b, *right*). Taken together, these differences in outcome probabilities across intervals demonstrate that retinal responses can be influenced by the photoreceptor type that is disrupted. This difference may reflect the proportion of photoreceptors affected in these rod-dominated retina, which comprise all of the observations. We explore this difference further in the next section.

4.7. Predictions from Percent of Photoreceptor Death: Differential Impact of Photoreceptor Type and Degree of Death on Retinal Circuitry

To further understand how the degree of photoreceptor death contributes to different outcomes, we categorized the observations by photoreceptor types and compared the proportion of photoreceptor death to the total number of photoreceptors, e.g., 0% includes no to minor photoreceptor loss and 97% (rod) and 3% (cone) includes major to complete loss. Across varying severity of rod loss, degeneration was predicted with the highest probability (Figure 4c, *left*). In contrast, for both mild and severe degrees of cone loss, compensation had the greatest predicted probability (Figure 4c, *middle*). Similarly, when both rods and cones experienced minor loss, compensation had the greatest predicted probability (Figure 4c, *right, internal pie chart*).

Why are retinal circuits more likely to exhibit compensation when the loss of cones occurs along with that of rods? Most observations of both rod and cone death in genetic models are the results of late-stage global photoreceptor degeneration; however, more local lesions of photoreceptors have been performed with laser photocoagulation, which ablates approximately 10% of the total photoreceptor population in the mature retina. In these photocoagulation studies, the retinal circuit showed evidence of restoring structure and function (Beier et al. 2017, Sher et al. 2013). Our data set had limited observations with a mild degree of both rod and cone death, thus potentially biasing mild photoreceptor loss to reflect the compensation outcome of the photocoagulation studies. At severe photoreceptor death for both rods and cones, degeneration became the prevalent outcome. The tipping point between compensation and degeneration occurs at 8% total photoreceptor loss (Supplemental Figure 4C). Taken together, these results indicate that rod loss predicts degeneration, cone loss predicts compensation, and cone loss coupled with mild rod loss predicts compensation.

4.8. Summary of the Predictive Model

Above, we introduce a predictive model that provides insight into how different (*a*) defunct biological processes, (*b*) photoreceptor types, (*c*) timelines, and (*d*) degrees of photoreceptor death influence the retina's outcome after photoreceptor disruption. When we focused on gene mutations and specific photoreceptor types across the average of the latter two parameters, we found that degeneration was the most likely outcome (Figure 3). When we focused on time points of photoreceptor disruption, we found that retinal circuits are more prone to degenerate in response to developmental perturbations and are expected to be more resilient when the perturbations occur after retinal development (Figure 4a).

When we focused on intervals between photoreceptor disruption and observation time points, we found a tendency for the retina to degenerate at both short and long intervals; however, when only cones were affected, compensation was predicted with only slightly less probability than degeneration at both short and long intervals (Figure 4b). Lastly, the predicted outcomes from different degrees of photoreceptor death indicate that retinal circuits respond differentially to type-specific photoreceptor loss (Figure 4c). Because our predictive model is based on a limited data set dominated by rodent studies, we cannot rule out the possibilities that these findings are a result of (*a*) the rod-dominant retina; (*b*) the paucity of literature cited with cone-specific manipulations; (*c*) studies that may miss stability or compensation because of experimental design; and/or (*d*) the list of observations that we chose to highlight, which is by no means exhaustive. Therefore, the value of this predictive model has the potential to grow with additional observations using more diverse photoreceptor manipulations, analyzing more parameters, and extending the definitions of outcomes beyond the three we defined. Ultimately, it would be useful to know if additional studies, especially those with cone-specific manipulations in cone-dominant species, would allow this predictive model to accurately determine how photoreceptor loss impacts the human retina.

5. PHOTORECEPTOR LOSS AS PART OF THE RANGE OF VISUAL CONDITIONS: INSIGHTS FROM PHOTORECEPTOR INPUT LOSS FOR EARLY DETECTION OF DISEASE

5.1. Psychophysics: Discerning the Visual System's Robustness or Vulnerability to Photoreceptor Loss

Our analysis of the literature demonstrates that photoreceptor disruption most likely leads to the degeneration of the rest of the retina. Thus, the most effective way to rescue the retina is to prevent degeneration in the first place. Therefore, early diagnosis is key. However, the difficulty with early diagnosis is that humans do not notice vision loss until approximately half of the photoreceptors are already dead. In a seminal study combining psychophysics with adaptive optics live imaging of cones in human patients, Ratnam et al. (2013) reported that visual sensitivity and acuity in patients are not appreciably different from those of control subjects until the density of cones has decreased to the level that would remain after, on average, 40–60% cone loss (see also Foote et al. 2018, Geller et al. 1992). Normal variation in cone numbers in healthy control subjects makes the percentage potentially more elusive. In the future, a longitudinal study of the same subjects would provide more accurate numbers than are currently available (Bensinger et al. 2019). Results from this work suggest the following possibilities: (*a*) The visual system is able to actively compensate for input loss; (*b*) current measurements of visual sensitivity and acuity are not sensitive enough to detect photoreceptor loss below 40–60%; and/or (*c*) human vision is robust to input loss up to a certain threshold, for example, through redundancy. We comment on the possibility of compensation above.

While we can only speculate about the lack of sensitivity in conventional measurements of visual sensitivity and acuity, it is clear that advances in this field, for example, in adaptive

optics imaging, have provided valuable direct photoreceptor quantification. Breakthroughs in detecting early photoreceptor loss have the potential to increase the likelihood of reversing blindness. We suggest new avenues for solving the problem of early diagnosis below.

In considering the robustness of the visual system, one must acknowledge the wide range of inputs that our visual system handles to provide visual perception throughout the day (Simoncelli & Olshausen 2001). Given that our visual system has the capacity to function over light intensity levels spanning 10^9 (Shapley & Enroth-Cugell 1984) and that a single visual scene can contain luminance changes ranging over 10^4 (Frazor & Geisler 2006), it would be reasonable to assume that the visual system's mechanisms of adapting to light levels could also serve to keep the visual system robust against photoreceptor loss. To test this possibility, one might ask whether the visual system can distinguish between a case of fewer environmental photons and one of fewer available photoreceptors to transduce those photons. A few psychophysical and physiological studies have asked this question, and we discuss these findings in the next section.

The human psychophysical study by Seiple and colleagues (1995) aimed to distinguish between the effects of dropping pixels from letter representations and photoreceptor loss in retinitis pigmentosa. More than 80% of the pixels had to be eliminated before letter discrimination dropped below 20/40 in the Snellen acuity metric, a minor change in acuity. At the time that this study was done, live imaging of photoreceptors was not yet possible (Liang et al. 1997, Marcos et al. 2017), but one interpretation of this result was that photoreceptor loss alone could not account for the loss in visual acuity reported in patients. In other words, visual acuity loss was a combination of photoreceptor loss and deficits in other parts of the visual system, which we would categorize as the degeneration outcome. Whether the original conclusion of this study will be supported by simultaneous and longitudinal photoreceptor imaging remains to be seen. In later studies, when photoreceptors could be directly imaged by adaptive optics, similar changes in acuity were only detected when photoreceptor loss was estimated to be greater than 40–60%, a result consistent with the Seiple et al. study. These studies show that photoreceptor loss must reach a threshold to noticeably impact acuity, allowing for the possibility that mechanisms that make the visual system robust to wide ranges of light also make it robust to wide ranges of photoreceptor inputs.

5.2. Physiology: Distinguishing Between Stimulus and Photoreceptor Inputs

Inspired by the findings of Seiple et al. (1995) and Ratnam et al. (2013), we also sought to answer the question of whether the retinal circuit could distinguish between a case of fewer environmental photons and one of fewer available photoreceptors. To avoid unknown contributions from higher stations in the visual system, we answered this question by measuring physiological responses from retinal neurons. Changes in photons or photoreceptors contribute to differing signal-to-noise ratios, for which there are clear predictions about the responses of retinal neurons. Experimental (Enroth-Cugell & Freeman 1987) and theoretical work based on the efficient coding hypothesis (Atick & Redlich 1990) provides predictions for how spatiotemporal processing may change under different

signal-to-noise ratios. Specifically, at lower signal-to-noise conditions, e.g., at low light levels, retinal neurons have wider spatial receptive fields and slower response kinetics, which increase spatiotemporal integration, whereas at higher signal-to-noise conditions, e.g., at higher light levels, retinal neurons have narrower and faster spatiotemporal responses (Figure 5a). These effects have been demonstrated at different light levels, and we wondered whether the same efficient coding hypothesis could be applied under different degrees of input. To study this, we compared ganglion cell responses under three conditions: full spatial stimulation of the photoreceptors in a control retina, half spatial stimulation of photoreceptors in a control retina, and full spatial stimulation of photoreceptors in a mouse where half of the cones or rods are dead (Care et al. 2019, 2020) (Figure 5).

For the condition of half cone ablation, we found that the resulting spatial receptive field modifications, specifically, center width narrowing and surround width widening, could not be mimicked by half stimulation of a control retina. To understand the retina's response to lost photoreceptors, we examined the results through the lens of the efficient coding hypothesis, which predicts that fewer photoreceptor inputs would lead to lower signal-to-noise ratios and thus increased (i.e., wider and slower) spatiotemporal integration. Half cone loss caused ganglion cell responses to slow, consistent with predictions of lower signal-to-noise ratios. However, half cone loss also caused ganglion cells to show spatial receptive field profiles that were more consistent with higher signal-to-noise ratios. This discrepancy illustrates that there may be multiple retinal mechanisms engaged in processing input after cone loss. A potential key difference between half stimulation and photoreceptor loss is the adaptation state of the retina. In full and half stimulation conditions, baseline transmitter release from cones (i.e., in the dark) is constant, thus keeping the adaptation state constant (Figure 5b). Following half cone loss, the absence of cones and, therefore, the absence of transmitter release, barring any homeostatic changes in transmitter release from surviving cones, could be interpreted by the retina as light. Thus, the narrower center and wider surround, which are inconsistent with lower signal-to-noise ratios, may be consistent with receptive field changes for a light-adapted retina under greater signal-to-noise ratios (Figure 5c).

Similarly, in the condition of half rod ablation, we found that modifications in rod-mediated light responses could not be mimicked by half stimulation of a control retina, suggesting that the retina can differentiate between loss of photons and loss of photoreceptors in the rod system. Light responses at rod light levels are better characterized by their amplitude, sensitivity, and kinetics than by their spatial profile, so to understand these light responses, we examined their intensity–response curves. Light responses after rod death were greater than expected based on an assumption of linear propagation of photoreceptor input loss (i.e., our definition of stability), suggesting that there are additional neural mechanisms contributing to these light responses. As in the cone system, rods signal darkness with a resting rate of glutamate release. Following half rod loss, the absence of rods, and therefore the absence of transmitter release, could be interpreted by the retina as light (Figure 5d,e). Thus, one interpretation is that the retina missing half of the rods is more light-adapted than the retina receiving half of the photons. In a light-adapted retina, rod-mediated responses in ganglion cells would be expected to exhibit faster kinetics, smaller amplitudes, and greater half-maximum intensities compared to dark-adapted retina. While the half rod deletion

retina does have faster responses and smaller response amplitudes, the half maximum intensities are lower than those of a control retina (i.e., the half rod deletion retina could be more sensitive) (Figure 5f). The retina uses mechanisms other than those that occur with light adaptation to compensate for lost rod inputs.

These physiological studies show that mechanisms within the retina can recover light responses after photoreceptors die. This is incongruent with the psychophysical study by Seiple et al. (1995), which suggested that mechanisms within the visual system exacerbate vision loss. However, it is congruent with the study by Ratnam et al. (2013) of simultaneous cone imaging and psychophysics. Together, these studies also demonstrate that the mechanisms of resilient visual function may be numerous and differ even across photoreceptor circuits.

Returning to the question introduced in Section 5.1, these findings highlight the fact that, while photoreceptor deletion shares similar response signatures observed in different light adaptation states, photoreceptor deletion also evokes mechanisms that are distinct from adaptation. This insight into the state of the retinal circuit after half photoreceptor loss suggests that there may be other avenues to detect early photoreceptor loss. If photoreceptor loss below 40–60% is undetectable by conventional methods of testing acuity and sensitivity, then perhaps this photoreceptor loss can be revealed by testing kinetics and sensitivity across light levels. For example, changes in kinetics and sensitivity because of light adaptation may have different signatures than changes accompanied by early photoreceptor disruption.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SUMMARY POINTS

1. The timing of photoreceptor disruption influences the outcome of the retina. Developmental photoreceptor disruption causes retinal degeneration, whereas mature photoreceptor disruption causes retinal stability.
2. In general, photoreceptor disruption will eventually lead to retinal degeneration; however, the retina deviates from this fate with specific manipulations of photoreceptor types and different degrees of photoreceptor death.
3. Photoreceptor loss and the linear propagation of its effects are insufficient to explain vision loss reported in human patients when it involves less than 50% of photoreceptors.
4. The retina's ability to respond over a large range of stimulus conditions by adaptation and its reaction to photoreceptor loss are similar in some respects but not equivalent.

FUTURE ISSUES

1. The predictive model should be extended to include a greater body of literature, more parameters, and different definitions of retinal outcome.
2. Further investigation of retinal outcomes and rescue should be conducted in aged animals with photoreceptor disruption to simulate conditions of human retinal degeneration and to test more accurately the receptivity of the mature retina to treatment.
3. Efforts should be made to discover anatomical or functional signatures of early photoreceptor decline that can be tested in humans before they experience enough vision loss to be detected by conventional measures.
4. Efforts should be made to determine if the observed variability in response to current treatments of retinal degeneration among patients depends on the state of the retina at the time of treatment.

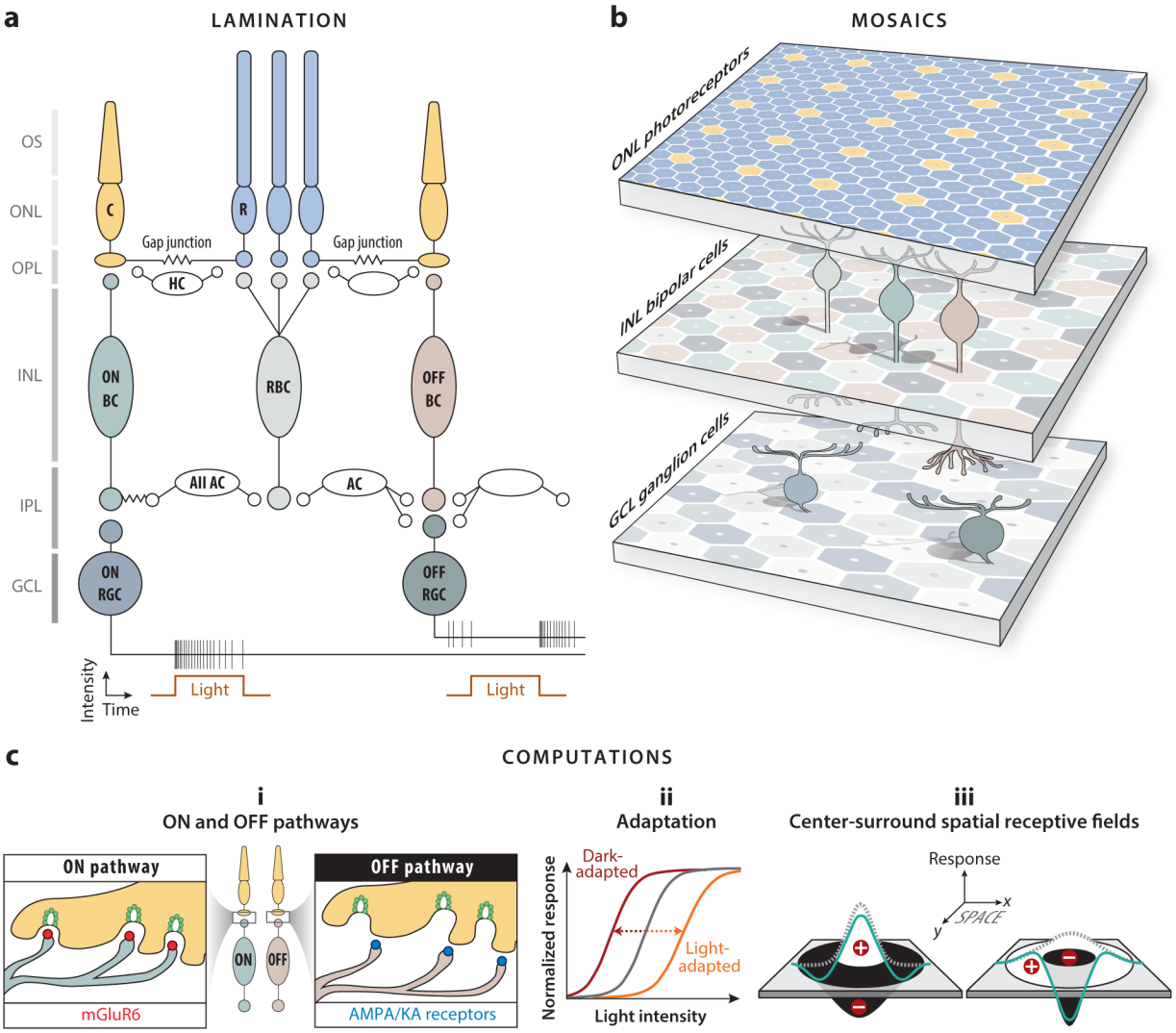


Figure 1.

Basic retinal organization and function. (*a*) Organization of retinal depth into layers: outer segments (OS), outer nuclear layer (ONL), outer plexiform layer (OPL), inner nuclear layer (INL), inner plexiform layer (IPL), and ganglion cell layer (GCL). A basic retinal circuit, including photoreceptors, bipolar cells (BCs), retinal ganglion cells (RGCs) in the excitatory pathways (*colors*), and inhibitory modulation by horizontal cells (HCs) and amacrine cells (ACs) (*white*), is shown. Gap junctions are illustrated by jagged lines. The direct cone pathway leads from cones (C), to ON or OFF cone BCs, to ON or OFF ganglion cells. At the lowest light levels, signals traverse the retina through the primary rod (R) pathway: from rods; to rod BCs (RBCs); to the AII AC, which is coupled through a gap junction to ON cone BCs; and then to ON RGCs; alternatively, the AII AC provides a glycinergic synapse to OFF cone bipolar cells and then to OFF RGCs. (*b*) Organization of cell types. Shown is a schematic of how single cell types tile the retina in a regular mosaic: (*top*) cone (*yellow*) and rod (*blue*) and examples of (*middle*) BC and (*bottom*) RGC mosaics. Relative ratios of cell classes are not shown to scale (Jeon et al. 1998). (*c*) Basic functions of the retina include (*i*) the division of ON and OFF pathways that is conferred by either metabotropic glutamate

receptors (mGluR6) in ON BCs or ionotropic glutamate receptors [AMPA and kainite (KA)] in OFF BCs, (*ii*) light adaptation that centers responses within a dynamic range by shifting the intensity–response relationship to either lower light levels (dark-adapted) or brighter light levels (light-adapted), and (*iii*) center-surround spatial receptive fields.

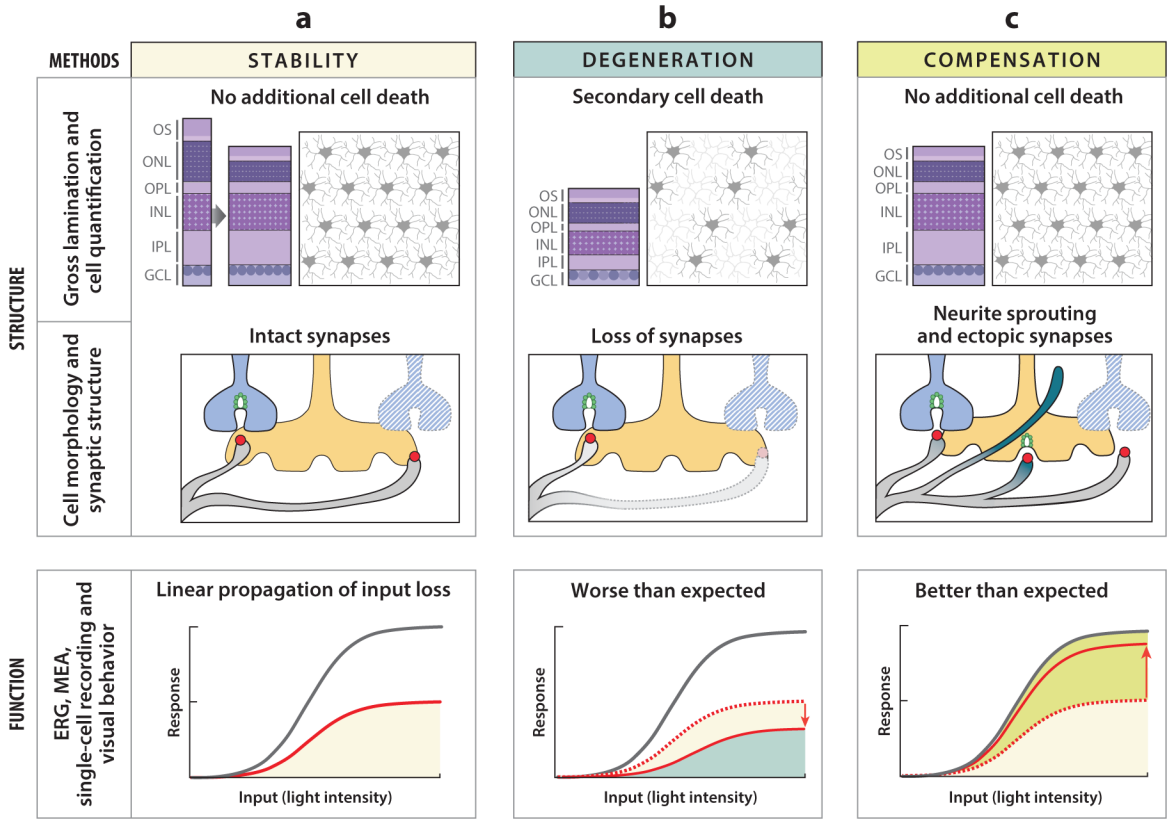
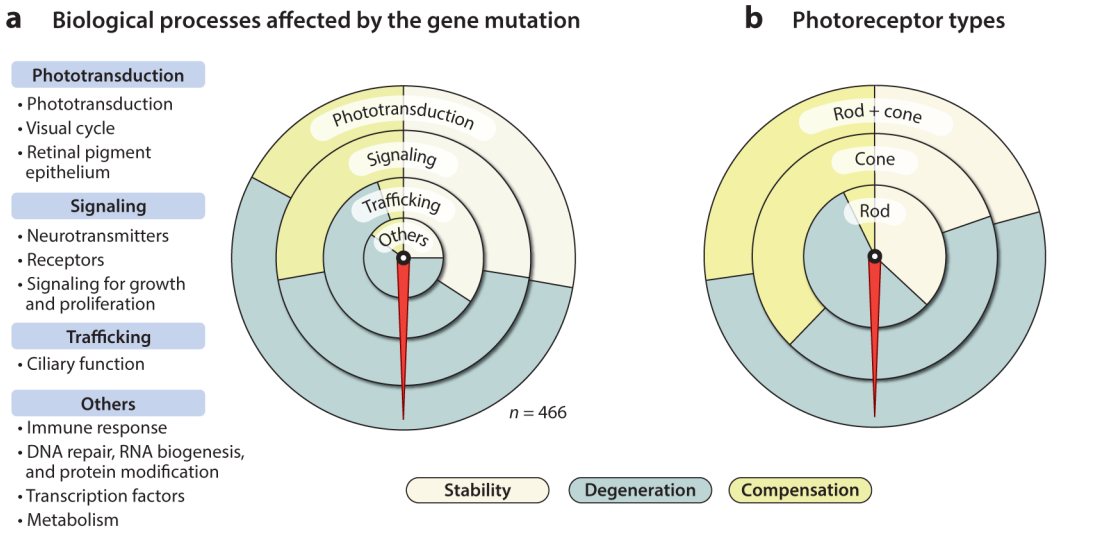


Figure 2.

Possible effects of photoreceptor loss on the remaining retinal circuit. In our analysis of observations across studies, we place the possible effects of photoreceptor loss on the retina in three possible outcomes: stability, degeneration, and compensation. Common methods of analysis are described on the left. (*a*) Stability is defined structurally as no additional cell death beyond the initial photoreceptor loss (a schematic of retinal layers and an example of an intact mosaic are shown) and intact synapses in the remaining retinal circuit. Stability is defined functionally as a linear propagation of input loss by the retinal output. (*b*) Degeneration is defined structurally as additional cell death and loss of dendrites, axons, and synapses and functionally as a worse-than-linear propagation of input loss, i.e., below the dotted intensity–response curve. (*c*) Compensation is defined structurally as no additional cell death beyond initial photoreceptor loss, sprouting of dendritic and/or axonal processes, and the formation of new synapses and functionally as better-than-expected retinal output for a linear propagation of inputs, i.e., above the dotted intensity–response curve. Abbreviations: ERG, electroretinogram; GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; MEA, multielectrode array; ONL, outer nuclear layer; OPL, outer plexiform layer; OS, outer segment.



Predicted outcomes of retinal circuits

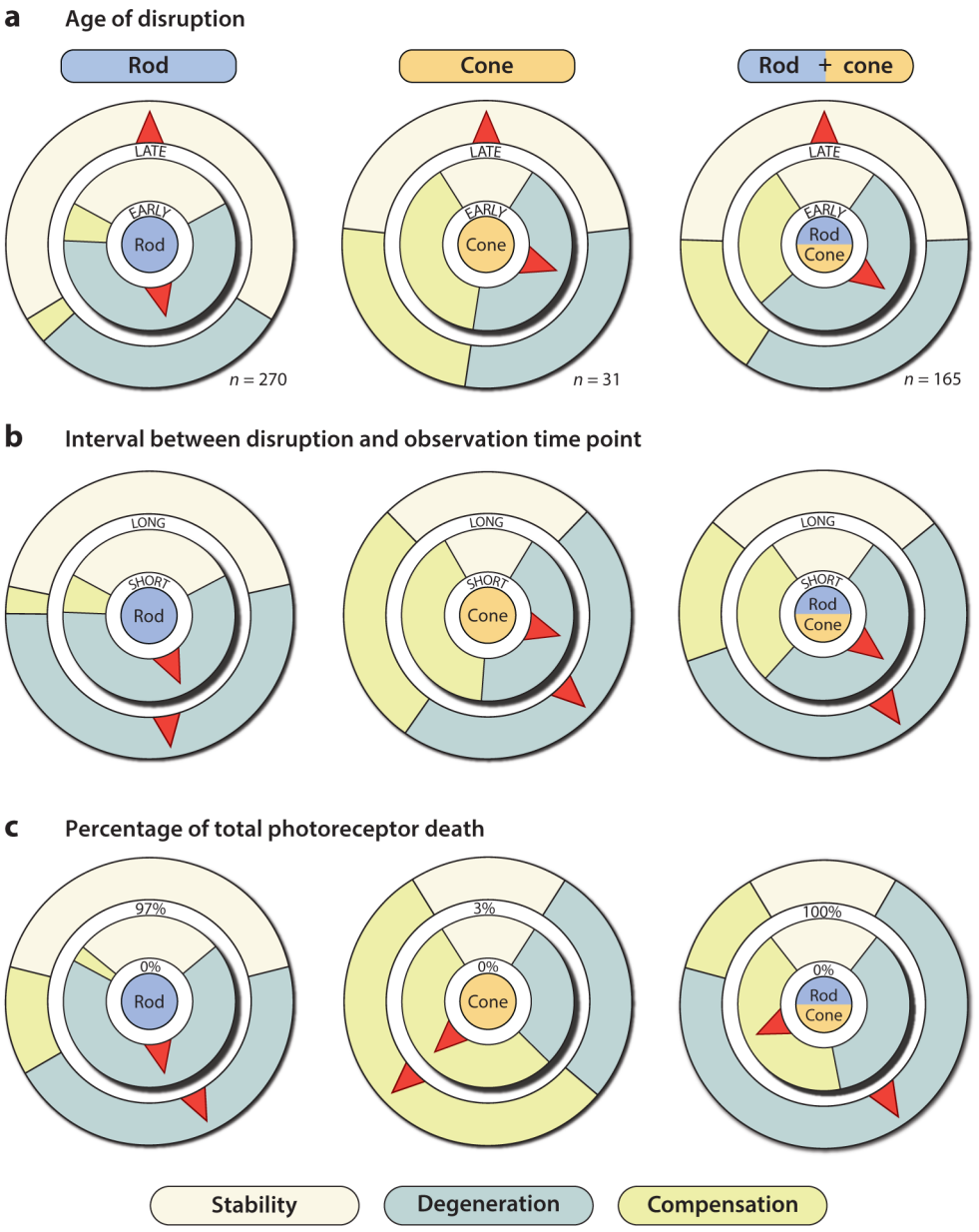
Parameters	Stability	Degeneration	Compensation
Phototransduction	0.28	**0.55**	0.17
Signaling	0.28	**0.45**	0.28
Trafficking	0.34	**0.60**	0.05
Others	0.25	**0.60**	0.15

Predicted outcomes of retinal circuits

Parameters	Stability	Degeneration	Compensation
Rod	0.37	**0.56**	0.07
Cone	0.20	**0.43**	0.38
Rod + cone	0.21	**0.52**	0.27

Figure 3.

Predicted probabilities for categorical parameters: gene mutations and photoreceptor types. The pie charts show the predicted probabilities that the process affected by (*a*) gene mutation or (*b*) photoreceptor type would result in one of the three outcomes: stability, degeneration, and compensation. Gene mutations were placed in categories based on the disrupted process: phototransduction cascade, signaling molecules, trafficking proteins, and other. Photoreceptor types were categorized by manipulations that primarily affected rods, cones, or both rods and cones. Processes affected by each of the gene mutations and types of photoreceptors predict degeneration for the remaining retina (*red needle*) for average values of the numerical variables. Predicted probabilities are displayed in the tables. The number of observations used to derive the predicted probabilities is denoted by *n*.



(Caption appears on following page)

Figure 4.

Predicted probabilities for numerical parameters: age of disruption, interval between disruption and observation, and percent of total photoreceptors. The pie charts show the predicted probabilities for the outcomes of stability, degeneration, and compensation at low (*internal pie chart*) and high (*external pie chart*) values for each numerical parameter. (*a*) Age of disruption describes the age at which the manipulation renders the photoreceptors nonfunctional, although not necessarily dead. (*b*) Interval describes the time between disruption and observation. (*c*) Percent of total photoreceptors describes the proportion of photoreceptors that have died from the manipulation compared to the total number of photoreceptors. Predicted probabilities are made for the death of rods (*left*), cones (*middle*), and both rods and cones (*right*). Red arrows point to the outcome with the greatest predicted

probabilities for low values (*internal arrow*) and for high values (*external arrow*) of the parameters. The number of observations used to derive the predicted probabilities is denoted by *n*.

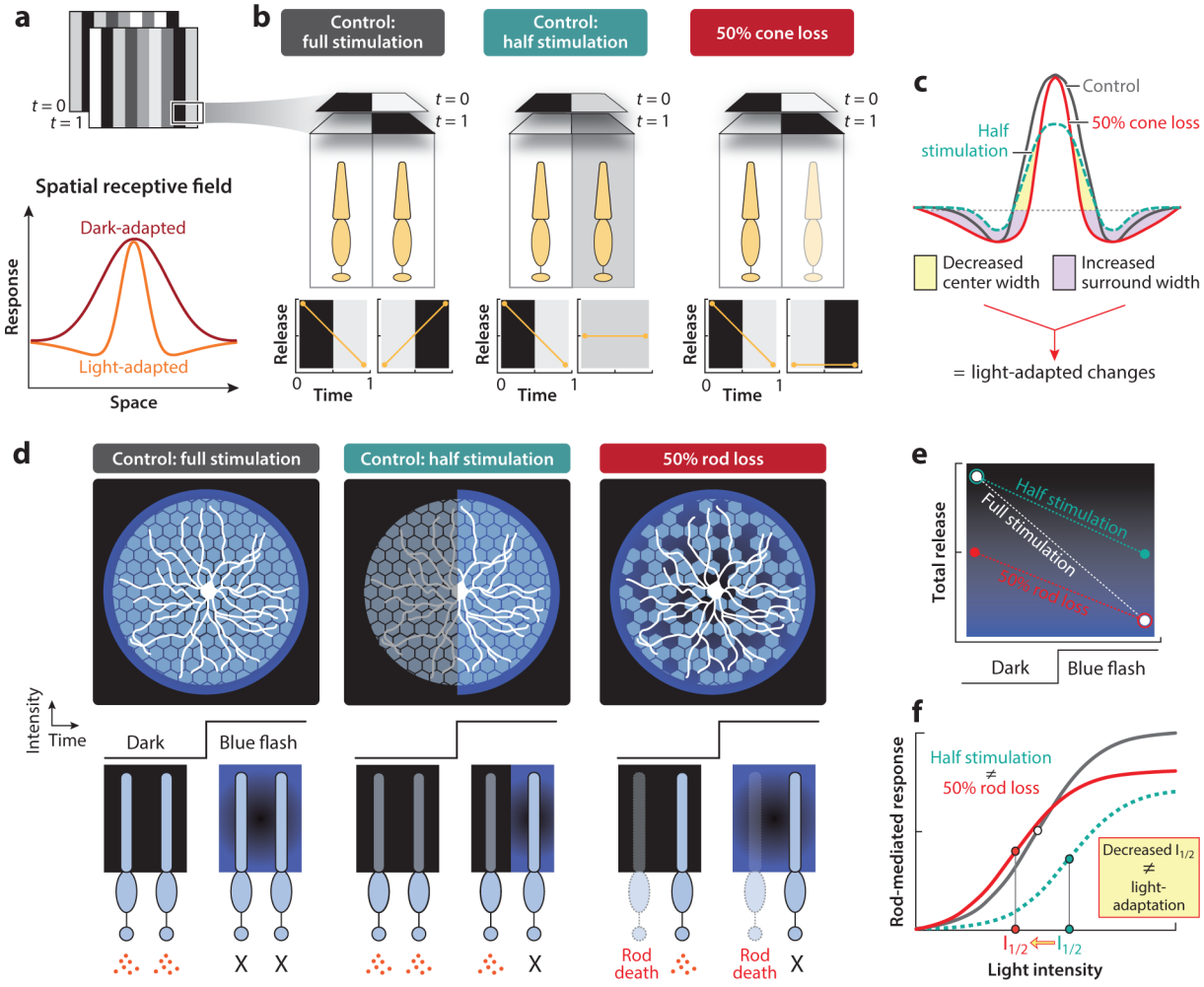


Figure 5.

Predictions for the light-adaptational state of the retina under conditions of half stimulation versus conditions of half photoreceptor loss. (*a*) In response to a stimulus where the intensity of each bar at each time point is drawn from a Gaussian distribution, ganglion cells exhibit spatial receptive fields with center and surround components. In a dark-adapted retina, the receptive field's shape maximizes spatial integration at low signal-to-noise ratios. In a light-adapted retina, receptive fields sharpen at greater signal-to-noise ratios. (*b*) Full stimulation of a control retina would trigger each cone to release glutamate in its full range. Half stimulation holds the intensity of alternating bars fixed at a mean; half of the cones would release glutamate in their full range, while the other half would release the mean rate of glutamate without fluctuation. Following 50% cone ablation, only half of the cones are available to signal the full range of glutamate. The absence of glutamate release from the missing cones potentially signals light. (*c*) Predicted spatial receptive field shapes from half stimulation of a control retina with smaller weights on both center and surround. The predicted spatial receptive field shape if 50% cone loss induces light adaptation matches the measured result. (*d*) Light responses mediated by rods. From darkness, full stimulation of a control retina would cause rods to decrease glutamate release during the flash. Half stimulation of control retina would cause half of the rods to decrease glutamate release

because the other half of the rods would not be stimulated. Following 50% rod ablation, only half of the rods are available to release glutamate. This condition with half the total glutamate could be interpreted as a light-adapted retina. Following the flash, only half of the rods signal a decrease in glutamate release. (*e*) Predicted glutamate release from rods in darkness and in response to the flash. (*f*) Intensity–response functions and their intensity at half maximum ($I_{1/2}$). 50% rod loss does not match the half stimulation of control retina, nor the expectation for a light-adapted retina.