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Homeostatic plasticity in the retina

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A B S T R A C T

Vision begins in the retina, whose intricate neural circuits extract salient features of the environment from the light entering our eyes. Neurodegenerative diseases of the retina (e.g., inherited retinal degenerations, age-related macular degeneration, and glaucoma) impair vision and cause blindness in a growing number of people worldwide. Increasing evidence indicates that homeostatic plasticity (i.e., the drive of a neural system to stabilize its function) can, in principle, preserve retinal function in the face of major perturbations, including neurodegeneration. Here, we review the circumstances and events that trigger homeostatic plasticity in the retina during development, sensory experience, and disease. We discuss the diverse mechanisms that cooperate to compensate and the set points and outcomes that homeostatic retinal plasticity stabilizes. Finally, we summarize the opportunities and challenges for unlocking the therapeutic potential of homeostatic plasticity. Homeostatic plasticity is fundamental to understanding retinal development and function and could be an important tool in the fight to preserve and restore vision.

1. Introduction

The retina is the part of the central nervous system that lines the back of the eye looking out onto the world. The neural circuits of the retina transform the pixel representations of photoreceptors into the feature representation of ganglion cells, the sole output neurons of the eye (Gollisch and Meister, 2010; Kerschensteiner, 2022; Polyak, 1941).

The retina is extraordinarily diverse, comprising more than 120 different neuron types in mice (Shekhar and Sanes, 2021). While the specific numbers in this section refer to mice, for which most information on homeostatic plasticity is available, the overall plan of the retina is conserved across the species covered in this review (i.e., from zebrafish to primates, Fig. 1) (Baden et al., 2020). In mice, three photoreceptors - rods, medium-wavelength-sensitive (M-) cones, and short-wavelength-sensitive (S-) cones - translate changes in photon flux into changes in glutamate release (Baden et al., 2013; Field et al., 2005; Nadal-Nicolás et al., 2020). Rods and cones differ in their absolute light sensitivities (high and low, respectively) and M- and S-cones in their spectral preferences. A single horizontal cell type provides pathway-specific feedback to the photoreceptors in the outer plexiform layer: horizontal cell axons to rods and horizontal cell dendrites to cones (Chapot et al., 2017; Thoreson and Mangel, 2012). The photoreceptor output is relayed from the outer to the inner retina by 15 bipolar cell types (Ghosh et al., 2004; Helmstaedter et al., 2013; Mataruga et al., 2007; Shekhar et al., 2016; Wässle et al., 2009). One bipolar cell type selectively connects to rods (i.e., rod bipolar cell) and the others connect to cones. Six bipolar cell types (types 1a, 1b, 2, 3a, 3b, and 4) express ionotropic glutamate receptors on their dendrites and depolarize to light decrements (i.e., OFF bipolar cells); nine bipolar cell types (types 5o, 5i, 5t, X, 6, 7, 8, 9, and rod bipolar cells) express metabotropic glutamate receptors on their dendrites and depolarize to light increments (i.e., ON bipolar cells) (Borghuis et al., 2014; DeVries, 2000; Euler et al., 2014; Masu et al., 1995). In addition to luminance contrast (OFF vs. ON), bipolar cells differ in their temporal, spatial, and chromatic tuning (Behrens et al., 2016; Breuninger et al., 2011; Franke et al., 2017; Purgert and Lukasiewicz, 2015). In the inner retina, OFF and ON bipolar cell axons stratify in the outer and inner parts of the inner plexiform layer, respectively (Euler et al., 2014). Amacrine cells are the most diverse retinal neuron class with 63 cell types (Helmstaedter et al., 2013; Yan et al., 2020a). They mediate interactions among bipolar cells, amacrine cells, and ganglion cells in the inner plexiform layer and are critical for visual feature extraction (Diamond, 2017; Grimes et al., 2010; Jacoby et al., 2015; Kim et al., 2020; Kim and Kerschensteiner, 2017; Wei, 2018; Yoshida et al., 2001). More than 40 ganglion cell types encode distinct feature representations of the visual world, which they communicate to specific subsets of over 50 retinorecipient brain areas to guide actions, generate perceptions, and mediate a wide range of influences of light on

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Abbreviations

AMIGO	amphoterin-induced gene and open reading frame
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	brain-derived neurotrophic factor
CNGA3	cyclic-nucleotide-gated channel α3 subunit
ERG	electroretinography
GABA	γ-aminobutyric acid
GluA	AMPA-type glutamate receptor subunit
KCNV2	gene encoding Kv8.2
Kv	voltage-gated potassium channel subunit
M-cone	middle-wavelength-sensitive cone
NMDA	N-methyl-D-aspartate
Rd1	retinal degeneration 1
S-cone	short-wavelength-sensitive cone
sOFFα	sustained OFFα
sONα	sustained ONα
tOFFα	transient OFFα
TNFα	tumor necrosis factor α
UV	ultraviolet

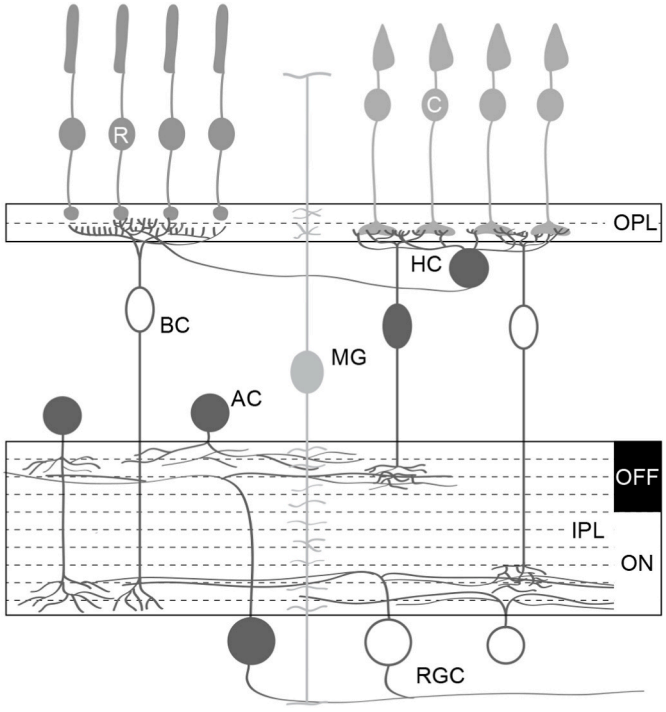

Fig. 1. Retinal cell classes and circuit organization. In the outer plexiform layer (OPL), rod (R) and cone (C) photoreceptors connect to rod and cone bipolar cells (BCs). Rods also receive feedback from horizontal cell (HC) axons and cones from horizontal cell dendrites. Bipolar cells relay the photoreceptor signals from the outer to the inner retina. In the inner plexiform layer (IPL), bipolar cell axons innervate amacrine (AC) and retinal ganglion cells (RGC). Amacrine cells, which receive and send signals via their dendrites, provide input to bipolar cells, other amacrine cells, and ganglion cells. Amacrine cells shape the feature representations that ganglion cell axons communicate to the brain.

physiology (Kerschensteiner, 2022; Lazzerini Ospri et al., 2017; Martersteck et al., 2017). Müller glia span the retinal depth and provide metabolic support, regulate the extracellular space, recycle neurotransmitters and limit their spread, and function as light guides (Franze et al., 2007; Reichenbach and Bringmann, 2020; Vecino et al., 2016; Wang et al., 2017).

The organization of the diverse retinal neurons into specific circuits is facilitated by lamination (Fig. 1) (Masland, 2001; Sanes and Zipursky, 2010; Wässle, 2004). Retinal cell bodies are separated into three layers: the outer nuclear layer (rods and cones), the inner nuclear layer (horizontal cells, bipolar cells, amacrine cells, Müller glia, and a few displaced ganglion cells), and the ganglion cell layer (ganglion cells and many displaced amacrine cells). Synaptic connections form in two layers between the somatic layers: the outer plexiform layer, containing synapses between photoreceptors, horizontal cells, and bipolar cells, and the inner plexiform layer, containing synapses between bipolar cells, amacrine cells, and ganglion cells. Each plexiform layer is further subdivided to support the formation of cell-type-specific circuits.

In addition to vertical lamination, retinal neurons exhibit specific lateral organization (Lefebvre et al., 2015; Masland, 2001; Reese, 2012; Reese and Keeley, 2015; Wässle, 2004). The cell bodies of many neuron types are regularly distributed (i.e., retinal mosaics), and their dendrites and axons cover the retina with cell-type-specific overlap (i.e., coverage factor). Together, these lateral organizing principles evenly distribute the computations implemented by the respective cell types across visual space.

Homeostatic plasticity refers to the drive of a neural system to return its function to a set point following perturbation and the mechanisms by which this goal is accomplished (Davis, 2006; Turrigiano, 2012). In this review, we discuss the events that trigger homeostatic plasticity in the retina, the mechanisms that implement it, and the set points and outcomes it stabilizes. Increasing evidence suggests that homeostatic plasticity can preserve retinal function in the face of major disruptions, including neurodegeneration (Fig. 2). We discuss factors that limit plasticity and the obstacles and opportunities for unlocking the therapeutic potential of homeostatic plasticity in the retina.

2. Triggers for homeostatic plasticity

Homeostatic plasticity stabilizes neuronal activity and circuit function in the retina. Destabilizing perturbations, or triggers, alter retinal activity and circuit function, eliciting homeostatic adjustments back towards stability (Turrigiano, 2012). Triggers do not need to be deleterious. The retina adapts to changes in environmental illuminance and contrast under physiological conditions (Demb, 2008; Demb and Singer, 2015; Rieke and Rudd, 2009), and homeostatic plasticity stabilizes spontaneous activity patterns (i.e., retinal waves) in developing circuits (Wong, 1999). However, many triggers do occur during disease, injury, or abnormal visual experiences (e.g., dark rearing). We consider perturbations in two broad categories: those that primarily affect activity at the synaptic or circuit level and those that primarily affect the retina's cellular composition. We will discuss these two categories of triggers in the context of specific retinal examples and illustrate how they challenge neuronal and circuit homeostasis (Fig. 3). We also note the specific retinal cell types and circuits affected by and responding to the homeostatic trigger (Table 1).

2.1. Activity-dependent triggers of homeostatic plasticity

Many perturbations to the retina can affect its activity in one way or another. In this section, we focus on perturbations that increase or decrease neuronal activity directly. Light-evoked activity is generated by the phototransduction cascade within photoreceptors (Fain et al., 2010; Yau and Hardie, 2009) and propagated through the retina by synaptic transmission (Gollisch and Meister, 2010). Both signaling pathways can be disturbed by changes that occur during development (i.e., developmental triggers), changes in sensory experience (i.e., sensory triggers), by retinal diseases (i.e., disease-related triggers), and by experimental manipulations (i.e., experimental triggers).

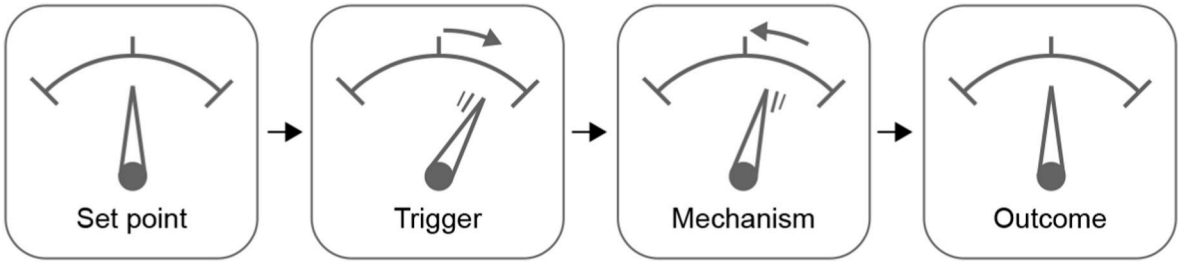

Fig. 2. Homeostatic plasticity nomenclature. Central to the concept of homeostasis are set points from which a system measures deviations and to which it tries to return. Set points in neural systems can relate to the activity of individual neurons, within-type interaction in a neuronal population, circuit functions, and their behavioral outputs. Triggers are events that drive systems away from their set points, eliciting homeostatic responses. Homeostatic responses are implemented by a diverse and coordinated set of mechanisms. Successful homeostatic responses result in the system's return to its set points.

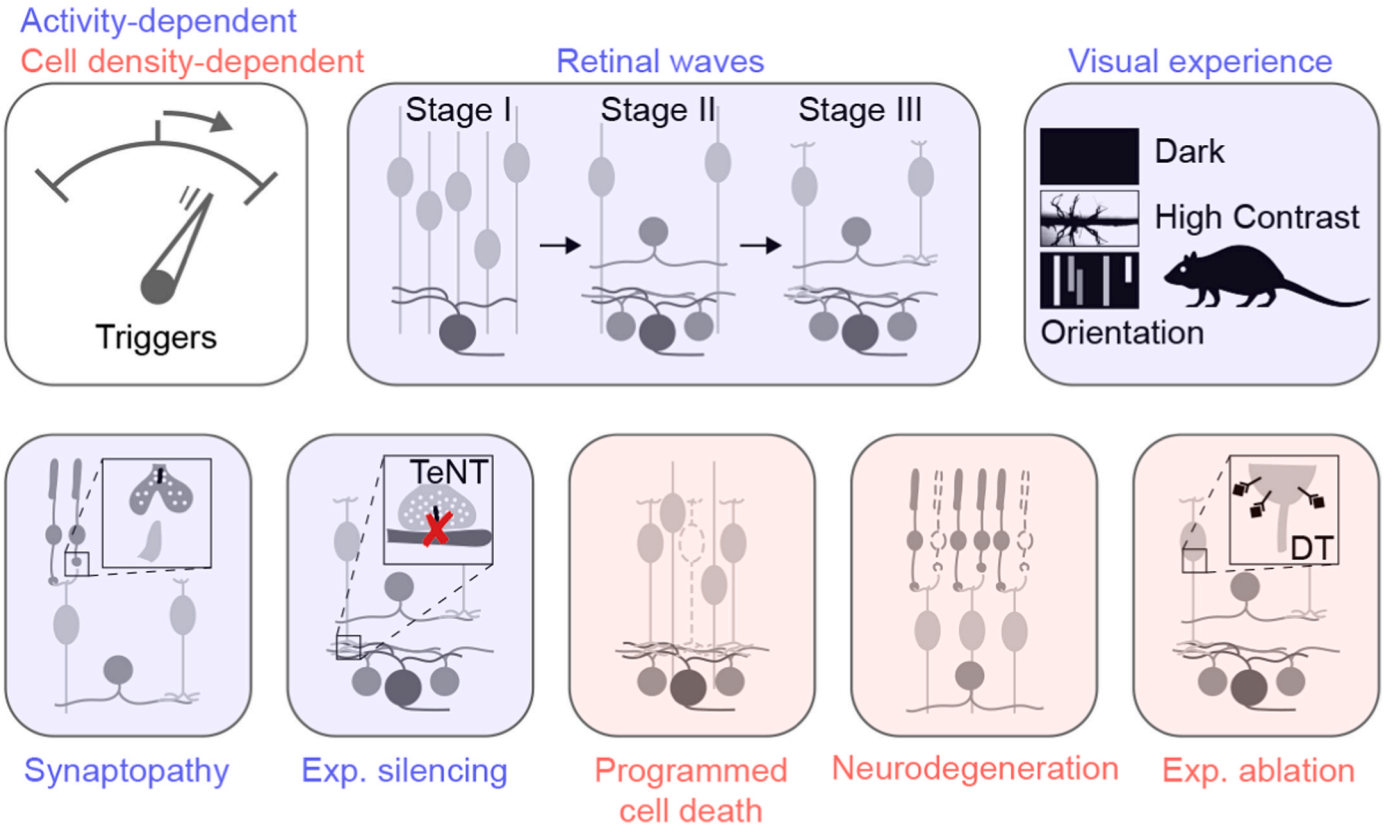

Fig. 3. Triggers of retinal homeostatic plasticity. The retina responds homeostatically to changes in its activity and cellular composition. Activity-dependent triggers (blue) are encountered during development as neurons differentiate and connectivity patterns mature. Despite these changes, the developing retina stably generates spontaneous waves of activity (panel: retinal waves) that propagate through the early visual system. Wave homeostasis relies on the sequential engagement of different generation and propagation mechanisms (stages I-III). At maturity and during development, homeostatic plasticity can be triggered by manipulations of visual experiences, including persistent darkness, high-contrast environments, and environments enriched for particular stimulus orientations or motion directions (panel: visual experience). In inherited retinal degenerations, synaptic dysfunction (panel: synaptopathy) precedes cell death providing a homeostatic challenge to the downstream circuits. Neuronal activity is also a frequent target of experimental manipulations (panel: exp. silencing) to study homeostatic retinal plasticity, including through the expression of the tetanus toxin light change, which blocks neurotransmitter release. During development, cell density-dependent homeostatic plasticity is triggered by naturally occurring programmed cell death (panel: programmed cell death). At maturity and during development, the neuronal populations can be thinned by degenerative diseases (panel: neurodegeneration) and experimental manipulations (panel: exp. ablation), including the expression of the diphtheria toxin receptor and injections of diphtheria toxin.

2.1.1. Developmental triggers

The developing retina generates spontaneous waves of activity (i.e., retinal waves) (Galli and Maffei, 1988; Meister et al., 1991; Wong, 1999). Retinal waves spread laterally among ganglion cells and propagate down their axons to dominate activity in the early visual system (Ackman et al., 2012; Demas et al., 2003; Maccione et al., 2014). Waves first emerge in a retina with few synapses and a large ventricular zone populated by retinal precursor cells (embryonic day 16 in mice) (Bansal et al., 2000; Catsicas et al., 1998) and persist until eye opening (postnatal day 14 in mice), when all neurons have differentiated, and synaptic circuits are nearly mature (Demas et al., 2003; Fisher, 1979; Kerschensteiner, 2020). The need to generate stable activity patterns from diverse cellular complements and connectivity patterns poses a major challenge to homeostatic plasticity. How can a network with continuously changing excitability of its cells (or nodes) and strength of their connections (or edges) generate stable activity patterns? In

Table 1
Selected examples of cell-type-specific homeostatic responses of to triggers.

Cell Type	Triggers
Rod	Development: Nrl knock-out (Strettoi et al., 2004), Disease: P23H mutation and other retinitis pigmentosa (Aleman et al., 2001; Leinonen et al., 2020; Peng et al., 2000, 2003; Scalabrino et al., 2022) Experimental: photocoagulation (Beier et al., 2017; Sher et al., 2013), diphtheria toxin ablation (Care et al., 2020), tetanus toxin (Cao et al., 2015), synaptic connectivity (Beier et al., 2017)
Cone	Disease: CNGA3 knock-out (Haverkamp et al., 2006) Experimental: photocoagulation (Akiba et al., 2022; Beier et al., 2018), diphtheria toxin ablation (Care et al., 2019; Lee et al., 2022; Shen et al., 2020), tetanus toxin (Yoshimatsu et al., 2014), synaptic connectivity (Beier et al., 2018; Care et al., 2019; Shen et al., 2020)
Horizontal Cell	Development: Neurite territories (Huckfeldt et al., 2009; Reese et al., 2005; Soto et al., 2022) Experimental: photocoagulation (Huckfeldt et al., 2009), synaptic connectivity (Yoshimatsu et al., 2014, 2016)
Bipolar Cell	Development: glutamatergic (stage III) waves (Blankenship et al., 2009, 2011), programmed cell death (Johnson et al., 2017; Lee et al., 2011), neurite territories (Johnson et al., 2017; Johnson and Kerschensteiner, 2014) Experimental: diphtheria toxin ablation (Johnson et al., 2017; Okawa et al., 2014; Tien et al., 2017), tetanus toxin (Johnson and Kerschensteiner, 2014; Kerschensteiner et al., 2009; Okawa et al., 2014)
Amacrine Cell	Development: cholinergic (stage II) waves (Blankenship et al., 2009), GABA inhibitory shift (Zhang et al., 2006), neurite territories (Soto et al., 2019)
Ganglion Cell	Development: retinal waves (Bansal et al., 2000; Blankenship et al., 2011; Stacy et al., 2005), GABA inhibitory shift (Barkis et al., 2010; Zhang et al., 2006), mosaic formation (Lin et al., 2004) Sensory: dark-rearing (Tian and Copenhagen, 2001), synapse scaling (Jones et al., 2012), contrast encoding (Care et al., 2019, 2020; Johnson et al., 2017; Tien et al., 2017)

addition to gradual compensatory adjustments, the retina switches the mechanisms of wave generation and propagation in three stages (I-III), relying primarily on gap junctional coupling early on (stage I), followed by cholinergic transmission (stage II) and glutamatergic transmission (stage III) from amacrine and bipolar cells, respectively, which are born and mature sequentially (Blankenship et al., 2009; Catsicas et al., 1998; Feller et al., 1996; Kerschensteiner, 2020; Livesey and Cepko, 2001; Syed et al., 2004; Wong et al., 2000). The transitions between these wave mechanisms pose additional homeostatic challenges, as does the dismantling of waves in favor of light-evoked activity. The retina exhibits light-evoked activity before eye-opening, as light passes through the closed eyelids and engages retinal photoreceptors to modulate wave activity (Arroyo et al., 2016; Renna et al., 2011; Tiriac et al., 2018a). The end of retinal waves coincides with eye opening (Demas et al., 2003). It relies on the maturation of the synapses between photoreceptors and bipolar cells but occurs independently of visual experience (Demas et al., 2003, 2006). However, visual experience plays important roles after eye opening, as changes in sensory environments challenge activity homeostasis.

The need to generate stable activity patterns in networks with changing cells and connections is shared between the retina and other parts of the nervous system, as is the developmental switch from excitatory to inhibitory actions of GABA, which threatens to destabilize activity (Wenner, 2014). During development, GABA switches from excitatory to inhibitory as the cation-chloride cotransporters lower the initially high intracellular chloride concentrations in neurons (Ben-Ari et al., 2007; Blaesse et al., 2009). In the mouse retina, this switch occurs around postnatal day six, during stage II waves (Barkis et al., 2010; Hennig et al., 2011; Maccione et al., 2014; Zhang et al., 2006). Homeostatic adjustments are required to stabilize stage II waves across this switch and the resulting increase in network inhibition.

2.1.2. Sensory triggers

2.1.2.1. Physiological adaptation. Visual scenes are first processed by the photoreceptors, whose signals are divided into parallel rod and cone pathways to distribute phototransduction across luminance regimes. Rods operate in dim light conditions, whereas cones are active in bright light. Rod signals are routed to ganglion cells through three distinct pathways, depending on the background light intensity (Grimes et al., 2018; Volgyi, 2004). Visual adaptation occurs in both photoreceptors, where it maintains linear encoding of luminance increments and decrements across different background light intensities (Fain et al., 2001; Schneeweis and Schnapf, 1999). Retinal circuits add further levels of adaptation to the photoreceptor input, allowing ganglion cells to sensitively detect contrast across different light levels (Dunn and Rieke, 2008; Jarsky et al., 2011; Ke et al., 2014; Oesch and Diamond, 2011). These same circuits not only allow ganglion cells to adapt to mean light intensity (i.e., luminance adaptation) but also to the variations around that mean (i.e., contrast adaptation) (Baccus and Meister, 2002; Dunn and Rieke, 2008; Jarsky et al., 2011). Given that illuminance ($\sim 10^9$) and contrast vary tremendously within and between visual environments (Frazor and Geisler, 2006; Lucas et al., 2014; Reinagel and Zador, 1999; Shapley and Enroth-Cugell, 1984), accurately encoding visual information in the limited output range of ganglion cells ($\sim 10^2$) (Barlow et al., 1957; Enroth-Cugell and Shapley, 1973) is no small feat. The retina has evolved adaptation mechanisms that adjust its input-output transformations to optimally use the ganglion cells' output range to encode the current stimulus distribution. This increases signal-to-noise ratios in dim light and low contrast and reduces the risk of response saturation in bright light and high-contrast environments (reviewed extensively elsewhere, e.g. (Demb, 2008; Demb and Singer, 2015; Fain et al., 2001; Rieke and Rudd, 2009; Schneeweis and Schnapf, 1999; Shapley and Enroth-Cugell, 1984),).

By adjusting the input-output transformations, adaptation stabilizes the activity of retinal ganglion cells. Homeostatic plasticity similarly stabilizes retinal ganglion cell firing rates and adjusts input-output transformations to preserve light sensitivity and contrast encoding in the retinal output (Care et al., 2019, 2020; Johnson et al., 2017; Tien et al., 2017). Despite their common goals, there are key differences between adaptation and homeostatic plasticity. Thus, adaptation acts on faster timescales (milliseconds to minutes) than homeostatic plasticity (minutes to months). In addition, the term adaptation is generally reserved for 'normal' variations in visual scene statistics, whereas homeostatic plasticity describes responses to deviations from the norm (e.g., dark rearing). We include adaptation in our discussion of homeostatic plasticity because of their common goal of stability and because their mechanisms may overlap (i.e., studies of adaptation may provide clues for understanding homeostatic plasticity). For example, just as changes in background illuminance can lead to adaptive changes in photoreceptor input selection (i.e., rod vs. cone activation) and routing to ganglion cells during adaptation, homeostatic changes early in inherited retinal diseases can alter relative rod vs. cone input to ganglion cells while routing those signals through novel, atypical circuits (Haverkamp et al., 2006; Lee et al., 2021; Peng et al., 2000, 2003).

Variations in light intensity induce other qualitative changes in retinal processing and responses (Tikidji-Hamburyan et al., 2017), including luminance-dependent changes in contrast preferences, gain, receptive field size, and center-surround weighting (Atick and Redlich, 1990; Enroth-Cugell and Robson, 1966; Farrow et al., 2013; Grimes et al., 2014; Pearson and Kerschensteiner, 2015). Neuromodulators, particularly dopamine, are released in response to increasing light levels (Pérez-Fernández et al., 2019) and exert broad effects on visual processing and retinofugal information transmission (Jackson et al., 2012; Moya-Díaz et al., 2022). These natural variations provide the physiological context for plasticity, and homeostatic plasticity must maintain stability in the retinal circuitry while simultaneously allowing for the

computational flexibility and complexity offered by the dynamics of visual adaptation (i.e., homeostatic plasticity must preserve physiological adaptation).

2.1.2.2. Abnormal visual experience. While adaptation responds to 'normal' variation in environmental statistics, abnormal variations necessitate a different response (i.e., homeostatic plasticity). Monocular visual deprivation is the most classically studied example of abnormal sensory experience, in which the loss of input from one eye elicits homeostatic compensation by input from the other (Hubel et al., 1977; LeVay et al., 1980; Wiesel and Hubel, 1963). Visual-experience-dependent plasticity plays crucial roles in the development of primary visual cortex (Espinosa and Stryker, 2012; Kaneko and Stryker, 2017), and visual deprivation paradigms demonstrate how and over what timescales homeostatic mechanisms respond to sustained sensory loss (Desai et al., 2002; Hengen et al., 2013; Keck et al., 2013; Maffei et al., 2006; Maffei and Turrigiano, 2008; Mrsic-Flogel et al., 2007). The retina must also contend with input loss during visual deprivation. While retinal waves cease around eye opening (Demas et al., 2003), retinal circuits continue to be refined through light-evoked activity as photoreceptor synapses mature (Demas et al., 2006; Tiriac et al., 2018a). Dark rearing, thus, alters the developing retina (Di Marco et al., 2009; Dunn et al., 2013; Tian and Copenhagen, 2001, 2003; Xu and Tian, 2007). Some of the resulting changes are reversible if juvenile mice are returned to typical light-dark cycling environments (Tian and Copenhagen, 2001), illustrating the adaptive plasticity of the mechanisms underlying these changes. In fact, environmental enrichment with high contrast, visually complex environments can promote the opposite response from deprivation (Landi et al., 2007; Liu et al., 2007; Sale et al., 2007), demonstrating the importance of balance in visual development. This balance is also evident in the toxicity of light and the neuroprotective effect of dark rearing in some models of inherited retinal degeneration (Paskowitz et al., 2006). Furthermore, visual-experience-induced activity may shape and inform specific retinal and cortical circuits (e.g., direction selectivity) (El-Quessny et al., 2020; Li et al., 2006, 2008; Roy et al., 2020; Tiriac et al., 2022; Zhang et al., 2020).

2.1.3. Disease-related triggers

Genetic mutations resulting in inherited retinal diseases are common causes of visual impairment, including blindness (Hanany et al., 2020; Sohocki et al., 2001). Of the diverse genes mutated in these diseases, a substantial fraction support phototransduction and synaptic transmission (Collin et al., 2020; Daiger et al., 2019; Lee et al., 2021), highlighting aberrant activity as an early and potentially causative feature of inherited retinal degenerations. In addition, synapse loss and dysfunction precede cell death even in degenerations not caused by mutations in phototransduction and synaptic transmission genes (Fisher et al., 2005; Jones et al., 2003; Lewis et al., 1998; Marc and Jones, 2003; Pfeiffer et al., 2020b), providing an opportunity for homeostatic intervention. While many changes during retinal remodeling are maladaptive, particularly in the long run (Euler and Schubert, 2015; Jones et al., 2003; Pfeiffer et al., 2020a; Stasheff, 2008), the retinal circuitry can respond homeostatically in the early stages of degeneration. Such changes have been well documented in the common P23H mutation in rhodopsin (Dryja et al., 1990; Sohocki et al., 2001), where the loss of rod function precedes rod degeneration and leads to homeostatic compensation in the retinal circuitry (Aleman et al., 2001; Leinonen et al., 2020; Machida et al., 2000; Sakami et al., 2011). Likewise, mutations affecting rod (e.g., rhodopsin knock-out) or cone (e.g., CNG3A knock-out) signaling can elicit compensatory circuit changes downstream (Biel et al., 1999; Haverkamp et al., 2006; Jaissle et al., 2001).

Modeling the consequences of photoreceptor dysfunction on the retinal circuitry, Lee et al. (2021) suggested that degeneration, stability, and compensation are all possible outcomes, with the probability of each depending on a combination of factors. Interestingly, the probability of compensation as an outcome, which the authors defined as *'results that show more than the predicted total number of inputs … and functional output is better than predicted,'* is highest when photoreceptor perturbations occur in phototransduction or signaling pathways, as compared to other categories of perturbations (e.g., protein trafficking, metabolism, immune response, etc.). Thus, homeostatic plasticity can potentially preserve visual function in the diseased retina. Continued investigation is needed to understand why certain perturbations skew towards compensation, what mechanisms of homeostatic plasticity are employed, and how maladaptive changes can be avoided to preserve and restore vision. Our review of disease-related changes focuses on homeostatic plasticity. Detailed analyses and excellent reviews of maladaptive retinal remodeling are available elsewhere (Jones et al., 2016; Lee et al., 2021; Marc and Jones, 2003; Pfeiffer et al., 2020b; Telias et al., 2020).

2.1.4. Experimental triggers

It can be difficult to study activity-dependent changes in inherited retinal diseases, where the loss of activity is confounded with and overlapped by cellular death, glial reprogramming, and other structural and functional changes (Pfeiffer et al., 2020b). To isolate how perturbations in activity affect retinal circuitry, it is useful to experimentally silence neurons without ablating them. One strategy involves transgenic expression of the tetanus toxin light chain, which proteolytically cleaves vesicle-associated membrane protein 2 (VAMP2) (Schiavo et al., 1992), effectively silencing synaptic neurotransmission. Several studies have employed this technique, using different promoters to specifically express tetanus toxin in rod and/or cone photoreceptors (Cao et al., 2015; Yoshimatsu et al., 2014) or bipolar cells (Johnson and Kerschensteiner, 2014; Kerschensteiner et al., 2009; Okawa et al., 2014). In contrast to the acute effects of chemogenetic inhibitors (Magnus et al., 2019; Roth, 2016), the chronic loss of activity induced by tetanus toxin in one cell type allows time for homeostatic compensation in other cell types. However, acute manipulations may still unmask homeostatic processes in the retina. Application of chemogenetic agents or other drugs targeting membrane channels and receptors could unveil homeostatic mechanisms governing intrinsic membrane excitability (Sonoda et al., 2018a; Weick and Demb, 2011; Wienbar and Schwartz, 2022) or synaptic scaling (Jones et al., 2012; Xia et al., 2007) to shape visual processing. More studies are needed to isolate the effects of activity from those of cell death and demonstrate how and through what mechanisms the loss of retinal activity in disease can be compensated.

2.2. Cell-density-dependent triggers of homeostatic plasticity

Cell loss is both a feature and a bug of the retina. On one hand, proper retinal development requires phases of programmed cell death (Braunger et al., 2014; Buss et al., 2006; Kerschensteiner, 2020), on the other, retinal disease frequently involves neurodegeneration (Collin et al., 2020; Pfeiffer et al., 2020b). Whether in health or disease, cell loss is often followed by homeostatic compensation in the remaining cells. Here, we will review how stable cellular populations can be perturbed through various developmental programs (i.e., developmental triggers), retinal diseases (i.e., disease-related triggers), and direct damage or experimental manipulations (i.e., experimental and injurious triggers).

2.2.1. Developmental triggers

Programmed cell death proceeds in two phases of retinal development (Braunger et al., 2014; Kerschensteiner, 2020). The first involves the death of undifferentiated retinal progenitor cells through an adaptive process (Blaschke et al., 1998; Braunger et al., 2014; Buss et al., 2006; Frade and Barde, 1999). The goals and the mechanisms of this form of regulated developmental plasticity remain obscure. The second phase provides opportunities for homeostatic compensation as each layer of the retina undergoes some amount of programmed cell death

coincident with synaptogenesis and retinal circuit refinement (Kerschensteiner, 2020; Young, 1984). Balance in cell number and position is achieved through competition for neurotrophic support (Bovolenta et al., 1996; Cusato et al., 2002), pro-apoptotic over-crowding signals (Keeley et al., 2012; Resta et al., 2005), and homotypic repulsion cues (Fuerst et al., 2008, 2009; Huckfeldt et al., 2009; Kay et al., 2012), among other mechanisms (Kerschensteiner, 2020). Consequently, multiple developmental pathways converge to generate the characteristic mosaics of the retina with even, tiled cellular distributions (Lefebvre et al., 2015; Reese, 2012; Sanes and Masland, 2015; Wässle and Boycott, 1991a). These mosaics can be preserved despite dramatic reductions in cell density (Lin et al., 2004) and are recapitulated for each of the more than 40 retinal ganglion cell types (Baden et al., 2016; Bae et al., 2018; Goetz et al., 2022; Helmstaedter et al., 2013; Rheaume et al., 2018; Tran et al., 2019), posing numerous homeostatic challenges to balance cell number, distribution, and connectivity across the retina. Developmental changes in the density of specific cell populations can engage multiple compensation mechanisms in diverse circuits (Johnson et al., 2017; Keeley et al., 2014a; Lee et al., 2011; Strettoi and Volpini, 2002), even when the cell density of specific types drops to or near zero (Okawa et al., 2014; Shen et al., 2020; Strettoi et al., 2004; Tien et al., 2017; Yoshimatsu et al., 2014). Developing cells face challenges as their own numbers change (Johnson et al., 2017; Lee et al., 2011; Okawa et al., 2014; Shen et al., 2020; Strettoi and Volpini, 2002) or as their synaptic partners change (Keeley et al., 2014a; Okawa et al., 2014; Strettoi et al., 2004; Yoshimatsu et al., 2014). Thus, the retina must homeostatically navigate a complex developmental landscape to give rise to the typical complement of cell types with normal numbers and positions and create stable and dynamic circuits in maturity.

2.2.2. *Disease-related triggers*

The culminating stage of many retinal diseases is neurodegeneration (Pfeiffer et al., 2020b). Dysfunction and death of photoreceptors can trigger similar compensation in downstream retinal circuits, but photoreceptor death often provokes more extensive changes. Inherited retinal degenerations are classified by the photoreceptor receptor type lost first: In retinitis pigmentosa and other rod-cone dystrophies, rods are lost first, and cones follow (Hamel, 2006), while in cone-rod dystrophies, the reverse is true (Hamel, 2007). A tremendous variety of mutations can lead to similar endpoints of photoreceptor death, and the nature and timing of the photoreceptor disruption shape the maladaptive or homeostatic responses of the downstream circuits (Lee et al., 2021). This is partly due to differences in the progression through the phases of retinal remodeling (Pfeiffer et al., 2020b). As retinal degenerations progress, microglia begin to phagocytose apoptotic photoreceptors, kill still-healthy neighboring cells, and create a pro-inflammatory environment (Gupta et al., 2003; Karlstetter et al., 2015; Neher et al., 2011; Zeng et al., 2005). Müller glia de-differentiate and undergo reactive gliosis (Bringmann et al., 2009; Jones et al., 2003; Roesch et al., 2012). The challenges posed by this inflammatory milieu reflect genetic programming geared to repress regeneration in both the mammalian retina and the central nervous system more broadly (Blackshaw, 2022; Hoang et al., 2020; Todd and Reh, 2022). Some vertebrates can escape this fate and have robust neuroregenerative responses to disease-related triggers, but the mammalian capacity is substantially limited (Todd and Reh, 2022). However, homeostatic plasticity can still respond to cell loss in mammals, albeit with a limited toolkit. As cells die, the remaining cells of that type and their former synaptic partners must form new connections with existing cells or strengthen existing connections (Cuenca et al., 2005; Leinonen et al., 2020; Peng et al., 2000, 2003) to promote homeostatic compensation. Without regeneration, it remains difficult to stave off the inevitable threat of progressive photoreceptor degeneration, and more studies are needed to understand how cell loss can be mitigated or restored to preserve vision (Blackshaw and Sanes, 2021).

2.2.3. *Experimental triggers*

By controlling the timing, nature, and extent of cell death, experiments can elicit and evaluate homeostatic plasticity in defined settings. The types of experimental manipulations most frequently used to cause cell death can be divided into direct injury models (e.g., laser photocoagulation) and conditional genetic ablation systems (e.g., diphtheria toxin receptor system). Laser-guided photocoagulation has been utilized to perturb horizontal cells (Huckfeldt et al., 2009) and photoreceptors (Akiba et al., 2022; Beier et al., 2017; Sher et al., 2013) with various size lesions from a few to several hundred micrometers. Selective control over the laser can also injure cones in a cell-type-specific manner (Beier et al., 2018). By inducing the injury during development (Huckfeldt et al., 2009) or in maturity (Akiba et al., 2022; Sher et al., 2013), plasticity during different periods can be easily observed. Laser ablation creates a nonspecific injury zone with potential immune modulatory interactions (Brown et al., 2007; Lam et al., 1993; Nonaka et al., 2002; Qiao et al., 2009), leading to a complex environment in which to study homeostatic changes. In contrast, inducible diphtheria toxin receptor systems (Buch et al., 2005) provide clean and targeted cell death. Unlike primates, the mouse is not susceptible to diphtheria toxin toxicity since it does not express the simian diphtheria toxin receptor (i.e., heparin-binding epidermal growth factor-like growth factor) (Naglich et al., 1992; Pappenheimer et al., 1982). The simian diphtheria toxin receptor can be selectively expressed in mice, usually via Cre-recombinase-based systems, with specificity defined largely by the specificity of the Cre system (Buch et al., 2005; Ruedl and Jung, 2018). Using cell-type specific Cre drivers, experiments can easily target rods (Care et al., 2020) or cones (Care et al., 2019; Lee et al., 2022; Shen et al., 2020). The diphtheria toxin receptor itself has little effect and requires diphtheria toxin injection to mediate cell ablation. By changing the timing of injection, cells can be targeted for deletion during development (Shen et al., 2020) or in maturity (Care et al., 2019, 2020; Shen et al., 2020). Developmental time points can be additionally targeted by directly inducing the expression of an attenuated form of diphtheria toxin within the cytosol of affected cells, bypassing the receptor and ablating them directly (Johnson et al., 2017; Okawa et al., 2014; Soucy et al., 1998; Tien et al., 2017). Thus, controlled loss of retinal cells at different time points with varying interventions can provide critical insight into the mechanisms mediating homeostatic change. Given that the retinal responses to photoreceptor loss vary tremendously across the numerous mutations linked to disease (Lee et al., 2021), it is important to study the triggers, mechanisms, and set points of homeostatic plasticity in diverse contexts.

3. Mechanisms of homeostatic plasticity

The diverse triggers of homeostatic plasticity engage an equally diverse set of compensatory mechanisms, which cooperate to stabilize neuronal activity and circuit function. The mechanisms of homeostatic plasticity range from adjustments to intrinsic excitability, the scaling of existing synapses, the formation and elimination of synapses with existing and new partner types, changes in axon and dendrite arborizations, to the generation of new neurons (Fig. 4).

3.1. *Homeostatic plasticity of intrinsic excitability*

Intrinsic excitability determines a neuron's input-output relationship (Hille, 2001). Neuronal excitability is shaped by the membrane properties and morphology of dendrites and axons (i.e., passive component) and the ion channel conductances within (i.e., active component).

In the retina, passive and active components of intrinsic excitability make critical contributions to visual processing. For example, membrane properties and neurite morphologies shape the integration and propagation of dim-light signals in the rod bipolar pathway (Hartveit et al., 2022; Oltedal et al., 2009), contribute to the centrifugal motion preferences of starburst amacrine cells (Hausselt et al., 2007; Poznanski,

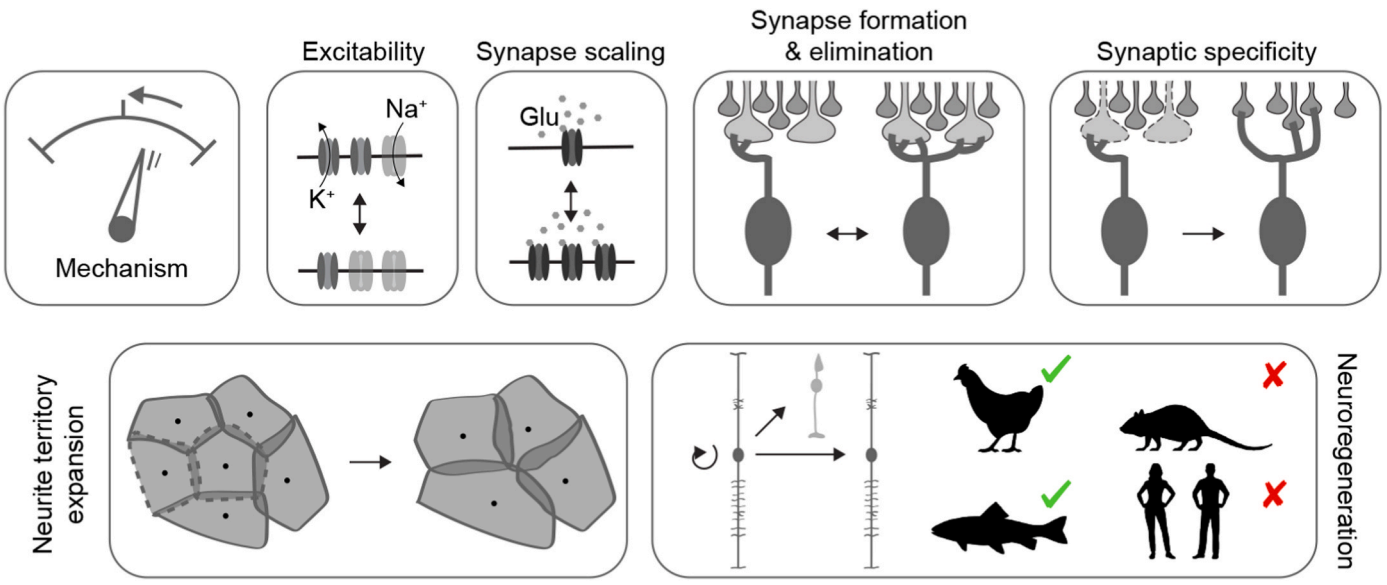

Fig. 4. Mechanisms of retinal homeostatic plasticity. A diverse set of mechanisms cooperates to return the retina to its set points following perturbations. Retinal neurons vary widely in their intrinsic excitability. Although homeostatic plasticity of intrinsic excitability remains to be explored in the retina, it is known to abound in other parts of the nervous system (panel: excitability). Retinal circuits frequently achieve response homeostasis through changes in synaptic connectivity. Thus, reduced activity can cause compensatory up-scaling of glutamatergic synapses (panel: synapse scaling). In addition, partial silencing or loss of input partners can elicit the formation and elimination of synapses with existing partners to restore the balance between excitation and inhibition (panel: synapse formation & elimination). When all preferred input partners are lost or silenced, retinal neurons can switch their synaptic allegiances (panel: synaptic specificity). Homeostatic rewiring appears to preserve the response properties of the respective neurons optimally. Changes in the density of neuronal populations or differential silencing of same-type neighbors can elicit homeostatic adjustments of dendritic and axonal territories, which maintain functional retinal coverage (panel: neurite territory expansion). Retinal neuron loss triggers homeostatic neuroregeneration in some non-mammalian species (e.g., chicken and zebrafish). In these species, Müller glia re-enter the cell cycle and undergo asymmetric divisions, giving rise to one neuron and one Müller glia. Although Müller glia can re-enter the cell cycle in mammals (e.g., mice and humans), they fail to regenerate neurons.

1992; Tukker et al., 2004; Wei, 2018), and parallelize the gain control exerted by A17 amacrine cells (Grimes et al., 2010). Heteromeric voltage-gated Kv2.1/Kv8.2 potassium channels mediate currents in the inner segments of rods that set their resting membrane potential and shape their light responses (Beech and Barnes, 1989; Gayet-Primo et al., 2018; Yan and Matthews, 1992). Mutations in KCNV2 (i.e., the gene encoding Kv8.2) cause supernormal rod responses and cone dystrophy in humans (Gouras et al., 1983; Wissinger et al., 2008; Wu et al., 2006). Melanopsin-driven closure of potassium channels increases the contrast sensitivity of sustained ON alpha (sONα) ganglion cells in a light-dependent manner (Sonoda et al., 2018b); and delayed rectifier potassium channels contribute to contrast adaptation in transient OFFα (tOFFα) ganglion cells (Weick and Demb, 2011). Differences in voltage-gated sodium channel types, abundances, and lengths of the axon initial segments housing them generate opposite spike responses (impressed vs. suppressed) to similar synaptic inputs at light decrements in sOFFα and bursty Suppressed-by-Contrast ganglion cells (Wienbar and Schwartz, 2022). Finally, extreme variation in the passive and active excitability of M1 intrinsically photosensitive ganglion cells helps distribute light intensity encoding across the population of these cells (Emanuel et al., 2017; Milner and Do, 2017). Thus, cell-type-specific properties of intrinsic excitability shape and diversify the visual functions of retinal circuits, suggesting that homeostatic plasticity of intrinsic excitability may stabilize those functions.

Neurite remodeling during homeostatic rewiring is expected to change the passive excitability of retinal neurons (Huckfeldt et al., 2009; Johnson et al., 2017; Soto et al., 2022). However, neither passive nor active components of intrinsic excitability have been studied during homeostatic plasticity in the retina. Given their importance to normal retinal function and frequent homeostatic regulation in other systems, this is an important area for future studies.

Elsewhere in the nervous system, homeostatic interactions between synaptic inputs and voltage-gated ion channels stabilize activity across development and in response to experimental perturbations (Baines et al., 2001; Morgan et al., 2019; Pratt and Aizenman, 2007; Tien and Kerschensteiner, 2018; Turrigiano, 2011). Different potassium channels are homeostatically balanced to maintain excitability (Bergquist et al., 2010; Kim et al., 2017; Turrigiano et al., 1995), sodium and potassium channels are co-regulated to compensate for input manipulations (Desai et al., 1999), and axon initial segment position and length shift to adjust spike thresholds in response to input changes (Grubb and Burrone, 2010; Kuba et al., 2010; Wefelmeyer et al., 2015, 2016). Whether, where, and how such homeostatic plasticity of intrinsic excitability occurs in the retina remains to be identified.

3.2. *Homeostatic plasticity of synaptic connectivity*

Most neuronal activity is driven by synaptic inputs, and activity perturbations are often compensated by homeostatic changes in synapses. Neurons can be connected by chemical and electrical synapses (i.e., gap junctions). Both chemical and electrical synapses are critical for visual processing in the retina, and both exhibit plasticity (Demb and Singer, 2015; O'Brien and Bloomfield, 2018). Yet, the literature on homeostatic plasticity (and our review of it) is skewed toward chemical synapses. This likely reflects the greater difficulty of studying electrical connections more than a limited involvement of gap junctions in homeostatic plasticity. Thus, greater resolution is needed to ultrastructurally identify electrical synapses (Sigulinsky et al., 2020), and paired rather than single-neuron recordings are needed to measure the strength of gap-junctional connections (Hartveit and Veruki, 2010). Future studies that explore changes in electrical synapses are needed to more comprehensively understand network homeostasis in the retina and elsewhere (Pfeiffer et al., 2020a).

Chemical synapses can be excitatory or inhibitory. In the retina, glutamate and acetylcholine transmit excitatory signals, whereas GABA and glycine mediate inhibition (Demb and Singer, 2015; Diamond,

2017). Neuronal activity depends on the ratio of excitation and inhibition, and both are targets of homeostatic plasticity (Isaacson and Scanziani, 2011; Tien and Kerschensteiner, 2018; Turrigiano, 2011).

Homeostatic changes in synaptic connectivity can be accomplished by adjustments to the strength of existing synapses (i.e., homeostatic synapse scaling), by the formation and elimination of synapses with existing partners or cells of the same types (i.e., homeostatic synapse formation and elimination), and by the recruitment of new synaptic partner types (i.e., homeostatic plasticity of synaptic specificity).

3.2.1. Homeostatic synapse scaling

Homeostatic plasticity was discovered as synapse scaling in cultured neocortical neurons (Turrigiano et al., 1998). Throughout the nervous system, synapses are scaled up and down by the insertion and removal, respectively, of neurotransmitter receptors in the postsynaptic membrane (Turrigiano, 2008), sometimes accompanied by presynaptic changes (Vitureira et al., 2012).

The glutamatergic synapses between bipolar and ganglion cells in the inner retina transmit signals through AMPA and NMDA receptors (Chen and Diamond, 2002; Diamond and Copenhagen, 1993; Lukasiewicz et al., 1997). Xia et al. (2006) found that AMPA receptor cycling (i.e., the turnover of synaptic receptors through removal and insertion) in ON-responsive ganglion cells depends on activity. In light (i.e., high activity), AMPA receptors cycle quickly, whereas, in darkness (i.e., low activity), AMPA receptors are exchanged slowly. AMPA receptors are heteromeric tetramers of four subunits (GluA1-GluA4). Xia et al. (2007) realized that the different cycling speeds reflect different AMPA receptor pools. The fast-cycling AMPA receptors contain GluA2 subunits and are calcium impermeable, whereas the slow-cycling AMPA receptors lack GluA2 subunits and are calcium permeable. Thus, increased activity in the light is associated with a switch toward GluA2-containing calcium-impermeable AMPA receptors. Jones et al. (2012) subsequently showed this switch depends on NMDA receptor signaling and lowers the sensitivity of ON-responsive ganglion cells to light through mechanisms that remain to be identified. Thus, the light-dependent switch in AMPA receptor composition is predicted to stabilize activity (Jones et al., 2012).

Inherited retinal degenerations are a common cause of visual impairment, including blindness (prevalence 1:2000) (Sohocki et al., 2001). An amino acid substitution (P23H) in rhodopsin, the light-sensing G-protein-coupled receptor of rod photoreceptors, accounts for 4.8% of inherited retinal degeneration cases in the USA (Daiger et al., 2019; Dryja et al., 1990; Sohocki et al., 2001; Van Soest et al., 1999). In patients and animal models with this mutation, rods progressively degenerate (e.g., rod loss in mice: 20% at 1 month, 60% at 3 months, 73% at 5 months) (Aleman et al., 2008; Bonilha et al., 2015; Leinonen et al., 2020; Machida et al., 2000; Ross et al., 2012; Sakami et al., 2011; Steinberg et al., 1996). Cones are initially spared but degenerate secondarily when most rods are gone, and cones lose their trophic support (Aït-Ali et al., 2015; Leinonen et al., 2020; Léveillard et al., 2004; Sakami et al., 2011). Electroretinographic (ERG) studies in rhodopsin P23H transgenic rats revealed that rod bipolar cell responses (i.e., dark-adapted b-waves) initially remain stable as rods degenerate and their population responses (i.e., dark-adapted a-waves) decrease (Aleman et al., 2001; Machida et al., 2000). The elevated ERG b-wave/a-wave ratio suggests enhanced signal transmission from the remaining rods to rod bipolar cells in rhodopsin P23H transgenic rats. Leinonen et al. (2020) made similar observations in rhodopsin P23H knockin mice (Sakami et al., 2011) and showed that synapse loss in the outer plexiform layer parallels rod degeneration, indicating that signal transmission is enhanced on a per-synapse basis. Leinonen et al. (2020) ruled out contributions of synaptic inhibition to response preservation. Together these findings suggest that synapses in the outer retina are homeostatically scaled up in animal models of an autosomally dominant retinitis pigmentosa to stabilize activity and preserve dim-light vision.

The synapses between rods and rod bipolar cells exist in multiple configurations (Johnson et al., 2017; Tsukamoto and Omi, 2013). In mice, each rod has a single presynaptic ribbon release site that is opposed by one to three rod bipolar cell postsynapses (Johnson et al., 2017; Tsukamoto and Omi, 2013). Each rod bipolar cell forms no, one (i.e., singlet), or two (i.e., doublet) postsynaptic densities with each rod in its dendritic territory (Johnson et al., 2017; Tsukamoto and Omi, 2013). When rod bipolar cell numbers are reduced during development by programmed cell death or experimental manipulation, the dendritic territories of the remaining rod bipolar cells expand to maintain rod coverage (Johnson et al., 2017; Keeley et al., 2014a). Dendritic territory expansion increases the number of rods contacted by each rod bipolar cell. Johnson et al. (2017) discovered that as rod bipolar cell dendrites expand, they gradually shift from doublet to singlet synapses (Fig. 5). Assuming that the strength of rod-rod bipolar cell connections is proportional to the number of postsynapses, this shift in synapse configurations could maintain input homeostasis. Consistent with this idea, the function of the rod bipolar pathway is preserved at the level of the retinal output when approximately half of the rod bipolar cells are removed, and the dendrites of the remaining cells expand (Johnson et al., 2017).

Mirroring the postsynaptic shift in synapse configurations, transgenic expression of the tetanus toxin light chain, a bacterial protease that cleaves vesicle-associated membrane protein 2 (Schiavo et al., 1992), to suppress neurotransmitter release in bipolar cells, promotes the formation of bipolar-to-ganglion cell synapses with multiple presynaptic ribbons in the boutons of the bipolar cells' terminal arborizations (Kerschensteiner et al., 2009). In wild-type mice, multi-ribbon configurations are found exclusively at the en-passant synapses between axon shafts of ON bipolar cells (predominantly type 6) and the dendrites of M1 intrinsically photosensitive ganglion cells (Kim et al., 2012; Sabbah et al., 2018). Thus, presynaptic configurations shift toward increased release when signal transmission is challenged by experimental perturbation or limited contact opportunities. Consistent with the notion that ribbon configurations are plastic within existing synapses, developmental studies found that ribbons appear in the inner retina after synapses have started to form and function and that synapses and synaptic transmission persist in the absence of ribbons (Fisher, 1979; Morgan et al., 2008; Okawa et al., 2019; Olney, 1968). Shifts in presynaptic and postsynaptic configurations may be unique scaling mechanisms of ribbon synapses and have so far only been observed in the retina.

3.2.2. Homeostatic synapse formation and elimination

In a variety of circumstances, retinal circuits can preserve or recover their function through the formation or elimination of synapses between existing cell-type partners. Sher et al. (2013) found that focal (200-μm diameter) ablation of photoreceptors and the retinal pigment epithelium with a laser (i.e., selective photocoagulation) in adult rabbits burns blind spots into the receptive fields of the underlying ganglion cells. Remarkably, over time, these blind spots fill in, and ganglion cell function is restored (Sher et al., 2013). A subsequent study revealed that bipolar cell rewiring recovers ganglion cell function; deafferented bipolar cells beneath the lesion extend dendrites that contact photoreceptors outside the lesion zone (Beier et al., 2017). Rod bipolar cells exhibit greater capacity for remodeling than at least one cone bipolar cell type in this model (Beier et al., 2017).

When half of the cone photoreceptors are removed by cell-type-specific expression of the diphtheria toxin receptor and injection of diphtheria toxin in mice, bipolar cells that lose partners form new synapses with the remaining cones (Care et al., 2019; Shen et al., 2020). Interestingly, the rewiring strategies differ between cone bipolar cell types. Type 6 and 7 bipolar cells, which normally contact (nearly) all cones within reach (Behrens et al., 2016), expand their dendritic territories to contact new partners (Care et al., 2019; Shen et al., 2020). By contrast, type 5 and X bipolar cells, which normally contact a subset of cones within reach (Behrens et al., 2016), recruit new partners within

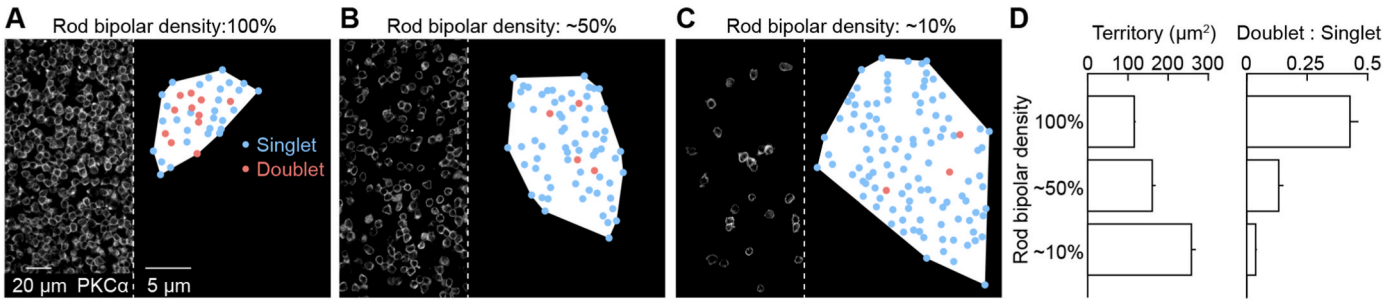

Fig. 5. Coordinated plasticity of rod bipolar cell dendrite territories and synapse configurations. **(A–C)** Representative images of retinal whole mounts stained for the rod bipolar cell marker PKCα from wild-type **(A)**, Pcp2-DTA **(B)**, and Pax6-DTA **(C)** on the left. Compared to wild-type, rod bipolar cell density is reduced to 50% and 10% in Pcp2-DTA and Pax6-DTA retinas, respectively. On the right, dendritic territories of individual rod bipolar cells and the distribution of singlet (one postsynaptic density for one presynaptic ribbon) and doublet (two postsynaptic densities for one presynaptic ribbon) in wild-type **(A)**, Pcp2-DTA **(B)**, and Pax6-DTA **(C)** retinas are depicted. **(D)** Summary data (mean ± SEM) showing the coordinated expansion of dendrite territories and shift toward singlet synapses with decreasing rod bipolar cell numbers. The data in this figure are published in (Johnson et al., 2017).

stable dendritic territories (Shen et al., 2020). The strategic differences between bipolar cell types could be explained by a shared goal of wiring length optimization (Chen et al., 2006). Each cone axon terminal (i.e., pedicle) contains multiple release sites and forms multiple synapses with bipolar cells (Haverkamp et al., 2000). Shen et al. (2020) found that the four bipolar cell types examined (i.e., types 5, 6, 7, and X), in addition to recruiting new cones, form more synapses with each cone. Together the recruitment of new cones and increased synapse number per cone precisely restore the input synapse numbers when cones are removed in young mice (Shen et al., 2020). This, in turn, preserves bipolar cell light responses and visual behaviors (Shen et al., 2020).

An important question is whether homeostatic rewiring preserves the cell-type specificity (i.e., synaptic specificity) of retinal circuits. Rod bipolar cells retain their preferences for rods over cones in rewiring after selective photocoagulation (Beier et al., 2017), and cone bipolar cells recruit new inputs preferentially from the thinned cone population after diphtheria toxin receptor/diphtheria toxin-mediated ablations (Care et al., 2019; Shen et al., 2020). Beier et al. (2018) conducted a more stringent test of synaptic specificity in bipolar cell rewiring using ground squirrels. In the cone-dominated ground squirrel retina, short-wavelength-sensitive (S-) cones connect one-to-one (occasionally, two-to-one) with S-cone bipolar cells, generating a dedicated chromatic channel (Li and DeVries, 2006; Puller et al., 2011). Beier et al. (2018) found that after selective photocoagulation, S-cone bipolar cells underneath the lesion extend new dendrites that selectively contact S-cones outside the lesion zone. These dendrites pass many middle-wavelength-sensitive (M-) cones before reaching their preferred partners (Beier et al., 2018).

Yoshimatsu et al. (2016) made similar observations for H3 horizontal cells in the zebrafish retina. Zebrafish have four cone types named for the spectral preferences of their opsins: UV, blue, green, and red (Baden and Osorio, 2019). H3 horizontal cells connect to UV and blue cones in a 5:1 ratio while avoiding green and red cones (Li et al., 2009; Yoshimatsu et al., 2014). Zebrafish can regenerate retinal neurons from resident Müller glia (Lenkowski and Raymond, 2014). Yoshimatsu et al. (2016) found that after selective UV cone ablation (via targeted expression of nitroreductase, which converts exogenously applied metronidazole into cytotoxins (Pisharath et al., 2007)), H3 horizontal cells retract their dendrites and then regrow them to contact regenerated UV cones selectively. Together, these findings suggest that, given the opportunity, homeostatic rewiring can preserve the synaptic specificity of retinal circuits.

When Care et al. (2020) deployed the diphtheria toxin receptor/-diphtheria toxin strategy to eliminate half of the rods in the adult mouse retina, they found no evidence of rewiring in the rod bipolar cell dendrites. Yet, the rod-mediated light responses of ganglion cells were preserved both in their excitatory bipolar cell input and their spike responses (Care et al., 2020). Indeed, the voltage responses of rod bipolar cells themselves were preserved because while rod bipolar cells lost half of the excitatory input to their dendrites, they also eliminated inhibition to their axons (Care et al., 2020). Thus, homeostatic synapse elimination can redress the balance of excitation and inhibition to restore neural activity and circuit function.

3.2.3. *Homeostatic plasticity of synaptic specificity*

In neural retina leucine zipper knock-out mice, where rods are unavailable, rod bipolar cell dendrites connect to cones (Strettoi et al., 2004). In retinitis pigmentosa models (e.g., rhodopsin P347L transgenic pigs, Royal College of Surgeons rats, and rd1 mice), rod bipolar cell dendrites switch their synaptic allegiances to cones as rods degenerate (Peng et al., 2000, 2003). Haverkamp et al. (2006) examined the motivation for and generalization of bipolar cells' photoreceptor switching in mice lacking the cyclic nucleotide-gated channel α3 subunit (CNGA3), rhodopsin, or both. In CNGA3 knock-out mice, cones do not respond to light; in rhodopsin knock-out mice, rods do not respond to light; and in CNGA3 rhodopsin double knock-out mice, neither cones nor rods respond to light (Biel et al., 1999; Jaissle et al., 2001). Haverkamp et al. (2006) found that rod bipolar cells switch to cones in rhodopsin knock-out mice and cone bipolar cells switch to rods in CNGA3 knock-out mice. However, neither rod nor cone bipolar cells switch their allegiances in CNGA3 rhodopsin double knock-out mice. Thus, synaptic specificity is not absolute in the retina, unlike in more austere places in the nervous system (Betley, 2009); both rod and cone bipolar cells can switch their photoreceptor partners but only do so to recover functional inputs.

Unlike the binary choices of bipolar cell dendrites between rods and cones in the outer retina, ganglion cell dendrites recruit convergent input from several bipolar and amacrine cell types in the inner retina (Dunn and Wong, 2014). The precise patterns of synaptic convergence in the inner retina generate the diverse feature representations that more than 40 ganglion cell types (in mice) send to the brain (Kerschensteiner, 2022). The sONα ganglion cells receive excitatory input from type 6, 7, 8, and rod bipolar cells (Della Santina et al., 2021; Morgan et al., 2011; Tien et al., 2017). Anatomically and functionally, type 6 bipolar cells dominate sONα excitation, accounting for approximately 70% of the respective synapses (Morgan et al., 2011; Schwartz et al., 2012; Tien et al., 2017). Tien et al. (2017) generated mice in which type 6 bipolar cells are selectively removed during development by transgenic expression of an attenuated diphtheria toxin. In these mice, sONα ganglion cells adjust their connectivity with the remaining bipolar cells in a cell-type-specific manner (Fig. 6). They recruit new partners (i.e., type X bipolar cells), increase their connectivity with some existing partners (i.e., type 7 and rod bipolar cells), and maintain constant input from others (i.e., type 8 bipolar cells) (Tien et al., 2017). These replacements

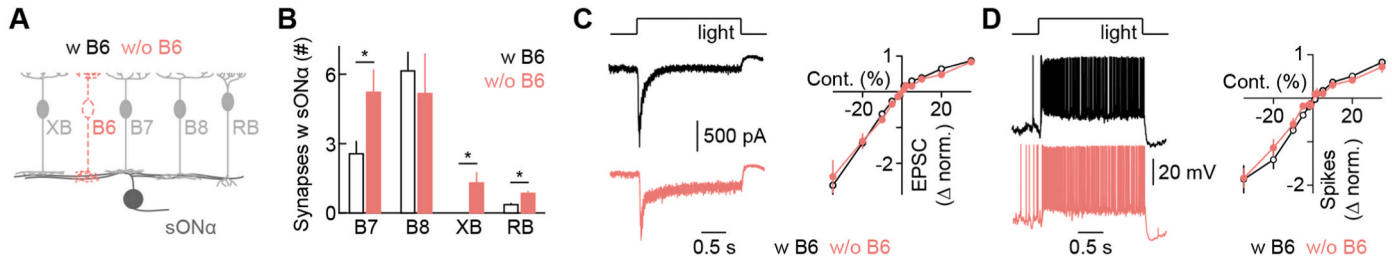

Fig. 6. Homeostatic plasticity of synaptic specificity preserves sONα ganglion cell function. **(A)** Schematic illustrating the selective removal of type 6 bipolar cells (B6) in B6-DTA mice. **(B)** Summary data (mean ± SEM) showing the cell-type-specific rewiring of sONα ganglion cells with other bipolar cell types. * indicates $p < 0.05$. **(C and D)** Representative traces (left) and population contrast-response functions (right, mean ± SEM) reveal that cell-type-specific rewiring preserves the high sensitivity and linear contrast encoding of sONα ganglion cells in their excitatory input **(C)** and spike output **(D)**. The data in this figure are published in (Tien et al., 2017).

preserve the hallmark features of the sONα ganglion cell light responses, including linear contrast-response functions, high contrast sensitivity, and the ability to encode high temporal stimulus frequencies (Fig. 6) (Tien et al., 2017). Interestingly, Okawa et al. (2014) showed that when more ON bipolar cell types are removed, sONα ganglion cell dendrites reach into the outer part of the inner plexiform layer to recruit OFF bipolar cell input.

During development, H3 horizontal cells contact UV, blue, red, and green cones in the Zebrafish retina (Yoshimatsu et al., 2014). They eventually eliminate contacts with red and green cones and maintain synapses with UV and blue cones in a 5:1 ratio (Li et al., 2009; Yoshimatsu et al., 2014). Yoshimatsu et al. (2014) reported that in mutants with fewer UV cones, H3 horizontal cells form more synapses with blue but not with red or green cones. H3 horizontal cells also form more synapses with each of the remaining UV cones (i.e., homeostatic synapse formation). A similar shift toward blue cones also occurs when synaptic transmission from UV cones is suppressed by expression of the tetanus toxin light chain, indicating that input activity drives rewiring (Yoshimatsu et al., 2014). However, H3 horizontal cells stay away from red and green cones when both UV and blue cones are silenced, suggesting limits to their synaptic flexibility (Yoshimatsu et al., 2014).

Together, these findings reveal homeostatic hierarchies in synaptic specificity that protect circuit function.

3.3. Homeostatic plasticity of neurite territories

Each retinal neuron type encodes visual space as a population. To ensure homogeneous representations of visual space, the dendrites and axons of each neuron type cover the retina evenly (Lefebvre et al., 2015; Wässle and Boycott, 1991b). Maintaining this coverage of visual space at a population level establishes an important set point for homeostatic plasticity distinct from single-cell set points for synapse scaling, formation, elimination, and specificity. Coverage varies widely between cell types. For example, bipolar cell axons tile the retina with few gaps and little overlap (i.e., coverage ~1), whereas starburst amacrine cell dendrites overlap extensively (i.e., coverage ~40) (Keeley et al., 2007; Wässle et al., 2009).

Homeostatic adjustments of neurite territories that stabilize population coverage have been observed for many retinal neurons in different contexts. The abundance of some neurons varies across the retina. In many species, ganglion cells are enriched in acute zones (e.g., the fovea in primates and the visual streak in rabbits) (Baden et al., 2020; Hughes, 1977). The ganglion cells' dendrite size scales inversely with their density to ensure constant coverage and produce smaller receptive fields and higher spatial resolution vision in the acute zones (Dacey and Petersen, 1992; Wässle and Boycott, 1991b). Mice lack a uniform ganglion cell acute zone. Yet, Bleckert et al. (2014) discovered that sONα and sOFFα ganglion cells are enriched, and their dendritic and receptive fields are smaller in the temporal retina, which views binocular visual space (spanning approximately 40° in azimuth).

In animals with steep density gradients in their ganglion cell populations (e.g., cats), homeostatic coverage setpoints produce asymmetric dendrite arbors whose center of mass is displaced from the soma in the direction of lower cell density (Schall and Leventhal, 1987). Such asymmetries can be accentuated or generated in species with shallower natural gradients (e.g., rats) by focal cell ablations through surgical interventions in the optic tract (Linden, 1993; Perry and Linden, 1982).

Homeostatic adjustments have also been identified in comparisons between mouse strains. Thus, bipolar cell dendrites and axons and horizontal cell dendrites scale inversely with strain-specific differences in cell density (Keeley et al., 2014b; Reese et al., 2005). Similarly, when programmed cell death is reduced or increased by genetic manipulations, bipolar cell dendrites and axons shrink and expand accordingly (Johnson et al., 2017; Lee et al., 2011).

Neurite territories can change rapidly and locally. Thus, developing horizontal cell dendrites in the mouse retina quickly fill in gaps left by laser ablation of neighbors (Huckfeldt et al., 2009). Together with growth-inhibiting interactions between dendrites of neighboring same-type ganglion cells observed during live imaging in the ferret retina (Lohmann and Wong, 2001), this highlights the action of homotypic repulsive cues that shape the space-filling arrangements of the neurite arbors in retinal cell populations (Lefebvre, 2021; Lefebvre et al., 2015; Prigge and Kay, 2018). Several cell-adhesion molecules that mediate homotypic repulsive interactions to establish even coverage have been identified (Fuerst et al., 2008, 2009; Lefebvre et al., 2012; Sun et al., 2013). Interestingly, arbor size and coverage set points appear to be defined by a separate set of cell adhesion molecules, including two of the three AMIGOs (Soto et al., 2019, 2022).

Within the molecularly defined space-filling and coverage factor of a retinal cell type population, activity can regulate the abor sizes of individual neurons. Johnson and Kerschensteiner (2014) generated mice in which transgenic expression of the tetanus toxin light chain suppresses glutamate release from different cone bipolar cell sets. In these mice, the dendrites shrink and form synapses with fewer cones when silenced bipolar cells are surrounded by active neighbors (Johnson and Kerschensteiner, 2014). Dendrites expand and form synapses with more cones when active bipolar cells are surrounded by silenced neighbors, and dendrite territories and cone connectivity are indistinguishable when all bipolar cells are active or silenced (Johnson and Kerschensteiner, 2014). Thus, activity-dependent competition between same-type neighbors appears to stabilize signal relay by a neuron population across stages of a pathway.

3.4. Homeostatic regeneration of neurons

Homeostatic neuroregeneration in the retina is a reality for some species and a therapeutic ambition for others. Some non-mammalian vertebrates, including chicken and zebrafish, can restore retinal neuron populations lost to injury or disease through regeneration; the source of homeostatic regeneration are Müller glia, the resident glia of

the retina (Fischer and Reh, 2003; Lenkowski and Raymond, 2014). All retinal neurons and the Müller glia arise from a common pool of multipotent retinal progenitor cells (Holt et al., 1988; Turner et al., 1990; Turner and Cepko, 1987). Müller glia are the last cells to differentiate during retinal development (Jadhav et al., 2009; Livesey and Cepko, 2001; Young, 1985). After injury or neurodegeneration, Müller glia in regenerating species can dedifferentiate, re-enter the cell cycle, and undergo self-renewing asymmetric divisions in which one daughter replaces the original Müller glia and the other gives rise to a neuron (Fischer and Reh, 2003; Lenkowski and Raymond, 2014; Nagashima et al., 2013).

Regeneration can be triggered by indiscriminate retinal injuries and cell-type-specific degenerations (D'Orazi et al., 2020; Fausett and Goldman, 2006; Fischer and Reh, 2001; Lombardo, 1968; Morris et al., 2011; Sullivan et al., 1997). For cell-type-specific degenerations, regeneration can produce neurons that were not lost in the original degeneration (Powell et al., 2016; Yoshimatsu et al., 2016), but its outcomes are biased toward cell-type replacement (D'Orazi et al., 2020; Fischer and Reh, 2002; Morris et al., 2005). D'Orazi et al. (2020) genetically ablated all cones, only the red cones, or only the UV cones in the zebrafish retina. Cones regenerated in approximately their normal proportions after pan-cone ablation, whereas regeneration was biased toward the lost cell type after selective red-cone and UV-cone ablations (D'Orazi et al., 2020). The ability to replace neurons in approximately the right proportions needed to restore function identifies regeneration as a homeostatic mechanism.

In mammals, Müller glia in the injured or degenerating retina also dedifferentiate and proliferate. However, this proliferation fails to produce neurons and instead results in gliosis and glial scarring (Bringmann et al., 2009; Jones et al., 2003; Pfeiffer et al., 2020b). How and why mammalian Müller glia lost their regenerative capacity remains uncertain (Blackshaw, 2022; Hoang et al., 2020; Todd and Reh, 2022). Efforts to restore it are ongoing (Jorstad et al., 2017; Mahato et al., 2020; Yao et al., 2018), but considerable challenges remain, particularly in regenerating photoreceptors and ganglion cells, which are the most common targets of retinal degenerations (Blackshaw and Sanes, 2021).

3.5. Choice and coordination of homeostatic plasticity mechanisms

The remarkable diversity of homeostatic plasticity mechanisms raises two questions. (1) How do neurons and circuits choose which mechanisms to use? (2) How do they coordinate multiple mechanisms to accomplish homeostatic goals?

The evidence so far suggests that in many circumstances, the retina chooses the available homeostatic mechanisms that least disrupt the functional circuit organization. Consider the homeostatic plasticity triggered by the degeneration of input partners. Species that can, regenerate the lost neurons and restore connections without changes in circuit organization (Yoshimatsu et al., 2016). If input partners cannot be regenerated and degeneration is partial, neurons increase their connectivity with the remaining partners (Beier et al., 2017, 2018; Care et al., 2019; Okawa et al., 2014; Shen et al., 2020). For bipolar cells responding to partial cone loss in mice, cells that can increase the fraction of cones contacted within their dendritic territories do so and avoid changes in coverage, whereas cells that already contact all cones within reach expand their dendritic territories and increase coverage (Care et al., 2019; Shen et al., 2020). If all the preferred input partners are lost or silenced, neurons switch their synaptic allegiances (Haverkamp et al., 2006; Okawa et al., 2014; Tien et al., 2017; Yoshimatsu et al., 2014). This rewiring follows a hierarchy. Thus, when sONα ganglion cells lose type 6 bipolar cells (i.e., their dominant input), they form synapses with other ON bipolar cell types to preserve their function (Tien et al., 2017). However, when more ON bipolar cell types are removed, sONα ganglion cells recruit input from OFF bipolar cells, which alters their contrast response functions (Okawa et al., 2014).

Also, the nature and timing of the perturbation appear to matter in some circumstances (Lee et al., 2021). Thus, rod bipolar cells respond to input loss from selective photocoagulation by dendritic rewiring (Beier et al., 2017), whereas dendrites remain stable after diphtheria toxin receptor/diphtheria toxin-mediated rod ablation, and rod bipolar cells achieve functional homeostasis by eliminating inhibition to their axons (Care et al., 2020).

In homeostasis, the goals of individual neurons can clash with those of neuronal populations. For example, when the rod bipolar cell density is decreased, the population goal of restoring coverage demands that individual neurons expand their dendrite territories and contact more rods. Because the sensitivity of rod bipolar cells depends on the convergence of rods, territory expansion risks response saturation (Dunn et al., 2006; Field et al., 2005). Johnson et al. (2017) found that as rod bipolar cells expand their dendrite territories and contact more rods, they shift synapse configurations to reduce the input from each rod (Fig. 5). Similarly, when individual cone bipolar cells are unable to pass on information, reducing the number of cones allocated to them would limit the blind spot in the population but risks the quiescence of the individual neurons. Johnson et al. (2014) found that the dendritic territories of silenced cone bipolar cells surrounded by active neighbors shrink while the number of synapses they form with their remaining cone partners increases. Thus, different plasticity mechanisms can cooperate to reconcile the homeostatic goals of individual neurons and neuronal populations.

4. Set points and outcomes of homeostatic plasticity

Central to homeostasis is the idea of set points from which deviations are measured and to which the system is trying to return (Cannon, 1940; Carroll, 2016). What the set points are and how deviations from them are measured is not well understood for homeostatic plasticity in the retina or elsewhere in the nervous system.

Homeostatic plasticity stabilizes neural function across different levels of organization, from synapses and synaptic neighborhoods to neurons and circuits to behavior (Turrigiano, 2012). Several set points are likely monitored to maintain stability throughout, with the possibility that some high-level stability emerges from lower-level homeostatic controls without additional set points.

Individual cortical neurons in culture monitor their average firing rates to control homeostatic synaptic scaling (Ibata et al., 2008). This control loop involves a series of calcium-dependent sensors that regulate the transcription, trafficking, and membrane insertion of postsynaptic receptors (Cingolani et al., 2008; Gainey et al., 2009; Goold and Nicoll, 2010; Ibata et al., 2008; Shepherd et al., 2006). In addition, to cell-autonomous controls, two secreted factors, BDNF (secreted by neurons) and TNFα (secreted by glia), have been suggested to read out network activity to control synaptic scaling (Beattie et al., 2002; Rutherford et al., 1997, 1998; Stellwagen et al., 2005; Stellwagen and Malenka, 2006). Whether similar pathways govern synaptic scaling in the retina and what set points control other forms of homeostatic plasticity remains unclear. Here, we discuss the outcomes of homeostatic plasticity in the retina across different levels of organization, which may guide the search for set points (Fig. 7).

4.1. Homeostatic plasticity for individual neurons

In several instances, retinal neurons that have lost presynaptic partners have been shown to stabilize their activity. Cone bipolar cells employ cell-type-specific dendritic rewiring strategies to preserve their light responses in vivo after half of the cones are lost (Shen et al., 2020). Similarly, rod bipolar cells maintain their light sensitivity and response amplitudes when a subset of rods are removed (Care et al., 2020; Leinonen et al., 2020). Leinonen et al. (2020) found that rod degeneration in rhodopsin P23H knockin mice triggers homeostatic up-scaling of dendritic synapses to preserve rod bipolar cell responses. By contrast, Care et al. (2020) showed that after diphtheria toxin

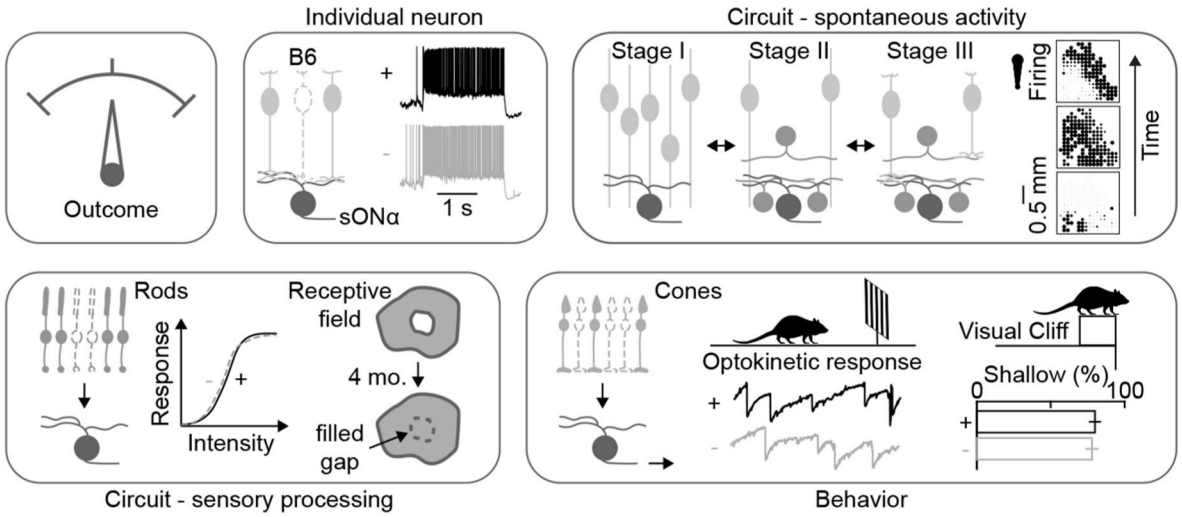

Fig. 7. Outcomes of retinal homeostatic plasticity. Homeostatic plasticity of the retina preserves visual function across different levels of organization. The rewiring of neurons that have lost a subset of their input partners preserves their average firing rates and light responses (panel: individual neuron). At a circuit level, homeostatic plasticity stabilizes the spontaneous waves of activity generated by the developing retina. For example, if stage II waves are genetically abolished or pharmacologically blocked, stage I waves persist or reappear until premature stage III waves take over (panel: circuit - spontaneous activity). In mature circuits, homeostatic plasticity preserves the input-output transformation (i.e., light to ganglion cell spike trains). Thus, after partial rod loss, ganglion cells maintain their intensity-response functions, and retinal circuits fill in gaps in the ganglion cells' spatial receptive fields after selective photocoagulation of photoreceptors (panel: circuit - sensory processing). Finally, retinal homeostatic plasticity stabilizes visual behaviors after partial cone loss, including the gaze-stabilizing optokinetic responses and depth perception (panel: behavior).

receptor/diphtheria toxin-mediated rod removal (approximately 50%), rod bipolar cells stabilize their light responses by eliminating synaptic inhibition to their axons. Thus, bipolar cells can achieve response homeostasis by a variety of mechanisms. Whether intracellular calcium functions as a set point in these non-spiking neurons and why different deviations engage different compensatory mechanisms remains to be explored.

The sONα ganglion cells are able to restore their spontaneous activity and characteristic light response properties after losing their main source of synaptic excitation (i.e., type 6 bipolar cells) (Tien et al., 2017). They accomplish this by switching their synaptic specificity and rewiring with bipolar cells in type-specific ratios (Tien et al., 2017). The sONα ganglion cells' activity homeostasis does not involve synapse scaling (Tien et al., 2017). Instead, homeostatic changes in synaptic specificity restore the tonic excitation to sONα ganglion cells, which contributes to their high baseline firing rates and high contrast sensitivity (Grimes et al., 2014; Murphy and Rieke, 2006; Pang et al., 2003; Tien et al., 2017). When ON bipolar cells are eliminated more broadly, sONα ganglion cells recruit OFF bipolar cell inputs, stabilizing their average firing rate at the expense of their visual function (Okawa et al., 2014). This suggests that the respective set point relates to the time-averaged sONα ganglion cell activity rather than their visual function. We speculate that the accurate preservation of light response properties observed by Tien et al. (2017) reflects the cooperation between a lower-level set point and a molecularly defined homeostatic hierarchy of synaptic partners.

4.2. *Homeostatic plasticity for circuits*

Homeostatic plasticity stabilizes the patterned spontaneous activity of the developing retina and the visual processing of mature circuits.

4.2.1. *Homeostatic plasticity for the spontaneous activity of developing circuits*

Before vision, the retina generates waves of spontaneous activity (i.e., retinal waves) that propagate through the early visual system and help pattern its connections (Ackman and Crair, 2014; Kerschensteiner, 2014; Kirkby et al., 2013; Wong, 1999). Across many species, retinal waves mature in three stereotypic stages (I-III), in which different circuit mechanisms generate unique activity patterns that serve specific functions in visual system refinement. Stage I waves (embryonic day 16 to postnatal day 0 in mice) are mediated by gap junctions and cholinergic transmission (Bansal et al., 2000; Catsicas et al., 1998; Syed et al., 2004); stage II waves (postnatal day 1 to postnatal day 9 in mice) are mediated by cholinergic transmission from starburst amacrine cells (Ackman et al., 2012; Bansal et al., 2000; Burbridge et al., 2014; Feller et al., 1996; McLaughlin et al., 2003; Zheng et al., 2006); and stage III waves (postnatal day 10 to eye-opening around postnatal day 14) rely on glutamatergic transmission from and gap-junctional coupling of bipolar cells (Akrouh and Kerschensteiner, 2013; Blankenship et al., 2009; Gribizis et al., 2019; Kerschensteiner and Wong, 2008; Wong et al., 2000).

The function of stage I waves remains obscure. Stage II waves correlate the activity of ganglion cells in the same eye in a distance-dependent manner and instruct the eye-specific segregation and topographic refinement of ganglion cell axons in the brain (Burbridge et al., 2014; McLaughlin et al., 2003; Xu et al., 2015; Zhang et al., 2011). Stage III waves retain distance-dependent correlations and desynchronize the activity of neighboring ON and OFF ganglion cells in each passing wavefront (Akrouh and Kerschensteiner, 2013; Demas et al., 2003; Gribizis et al., 2019; Kerschensteiner and Wong, 2008). Stage III waves maintain eye-specific segregation (Demas et al., 2006; Xu et al., 2016; Zhang et al., 2011). They may also separate ON and OFF ganglion cell inputs to neurons in the dorsolateral geniculate nucleus (dLGN) of the thalamus and shape orientation selectivity in primary visual cortex (Kerschensteiner, 2016; Kerschensteiner and Wong, 2008). In mice, late stage II and early stage III waves propagate preferentially from the temporal to the nasal retina, mimicking optic flow patterns experienced when the animal is moving forward (Ackman et al., 2012; Elstrott and Feller, 2010; Ge et al., 2021; Stafford et al., 2009). Waves during this period and maybe their propagation bias are required for the emergence of horizontal-motion-preferring directions-selective responses of ganglion cells and neurons in the superior colliculus (Ge et al., 2021; Tiriac et al., 2022; Tiriac and Feller, 2022).

The activity patterns of retinal waves and the transitions between wave stages are under homeostatic control. Thus, stage II wave patterns

remain relatively stable as GABAergic signaling in the inner retina switches from excitatory to inhibitory (around postnatal day 6 in mice) (Barkis et al., 2010; Maccione et al., 2014; Zhang et al., 2006); and stage III waves are robust to the germline removal of connexin subunits even though acute pharmacological gap junction blockade silences them (Akrouh and Kerschensteiner, 2013; Blankenship et al., 2011). When stage II waves are disrupted by genetic deletion or pharmacological blockade of β2 nicotinic acetylcholine receptors or genetic deletion of choline acetyltransferase, stage I waves reappear and persist until premature stage III waves take over (Bansal et al., 2000; Stacy et al., 2005; Stafford et al., 2009; Sun et al., 2008). Similarly, in vesicular glutamate transporter 1 knock-out mice, in which stage III waves are eliminated, stage II waves persist until eye opening (Blankenship et al., 2009). Finally, the end of waves is linked to the maturation of photoreceptor synapses with bipolar cells (Demas et al., 2003, 2006). Waves and light responses co-exist late during stage III (Kerschensteiner and Wong, 2008; Tiriac et al., 2018b), and if signal transmission from photoreceptors to bipolar cells fails, waves can persist (Demas et al., 2006).

4.2.2. Homeostatic plasticity for the sensory processing of mature circuits

In addition to stabilizing the activity of neurons directly responding to triggers (see 4.1.), homeostatic plasticity can preserve the input-output transformation of the retina across multiple stages of processing.

The dendritic rewiring of rod bipolar cells after selective photocoagulation fills in the receptive field scotomas of ganglion cells to restore homogeneous representations of visual space in the retinal output (Sher et al., 2013). Similarly, the elimination of synaptic inhibition onto rod bipolar cell axons after partial rod loss maintains the ganglion cells' sensitivity to dim light (Care et al., 2020). Ganglion cell receptive fields broaden in time and widen their spatial surround after partial cone loss (Care et al., 2019). Wider spatial surrounds are predicted to support efficient coding under reduced signal-to-noise, which is a consequence of partial cone loss (Atick and Redlich, 1990; Care et al., 2019). Ganglion cells also retain much of their information about visual scenes as photoreceptors degenerate in CNGB1 knock-out mice (Scalabrino et al., 2022). Finally, Johnson et al. (2017) found that the countervailing adjustments of dendritic territories and synaptic configurations of rod bipolar cells precisely preserve dim-light and contrast sensitivity in the retinal output when half of rod bipolar cells are removed.

Together these findings indicate that whether through specific set points or emerging from lower-level set points in the cells responding to triggers, homeostatic plasticity can preserve the sensory information encoded in the retinal output (i.e., the spike trains of ganglion cells).

4.3. Homeostatic plasticity for behavior

The retina generates diverse feature representations of the visual world and sends them to the brain to support perception and guide behavior (Gollisch and Meister, 2010; Kerschensteiner, 2022). In a few instances, causal relationships between retinal feature representations and visual behaviors have been established (Chen et al., 2011; Güler et al., 2008; Johnson et al., 2021; Kim et al., 2020; Wang et al., 2021; Yonehara et al., 2016). To understand the evolutionary purpose and gauge the therapeutic potential of homeostatic plasticity in the retina, we need to track its impact on behavior. Shen et al. (2020) demonstrated that the extent of bipolar cell dendritic rewiring after partial cone loss predicts the preservation of gaze-stabilizing eye movements and depth perception in mice. Correlations of human psychophysics and retinal imaging suggest that visual sensitivity and acuity are only appreciably reduced when more than half the cones are lost, indicating that homeostatic plasticity may preserve the function of cone pathways in humans as well (Foote et al., 2018; Geller et al., 1992; Ratnam et al., 2013). Leinonen et al. (2020) found that the up-scaling of the synapses between rods and rod bipolar cells protects dim-light sensitivity measured by the optomotor response. An important open question is whether non-image-forming visual functions (e.g., circadian photoentrainment, pupillary light responses, effects of light on mood and learning), which rely on measurements of ambient illumination, can be preserved by homeostatic plasticity in the retina (Do, 2019; Lazzerini Ospri et al., 2017).

4.4. Limits of homeostatic plasticity

In many cases, homeostatic plasticity successfully restores neuron and circuit functions to their set points. However, some perturbations overwhelm the homeostatic capacity of the retina. Transgenic expression of tetanus toxin in bipolar cells is an example of this. Although bipolar cells add ribbons to their presynaptic terminals (Kerschensteiner et al., 2009), this cannot compensate for the loss of VAMP2. Nonetheless, tetanus toxin expression unmasks a homeostatic mechanism expected to recover transmitter release from milder insults. Furthermore, homeostatic rewiring preserves function at a circuit level when tetanus toxin is expressed sparsely in the bipolar cell population (Johnson and Kerschensteiner, 2014). Homeostatic rewiring also compensates for the partial loss of photoreceptors in small photocoagulation patches (Beier et al., 2017; Sher et al., 2013) or distributed loss across the retina (Care et al., 2019, 2020; Lee et al., 2022; Leinonen et al., 2020; Shen et al., 2020). However, without regeneration, rewiring is doomed to fail if photoreceptor degeneration progresses to completion. Although plasticity can balance the homeostatic goals of individual neurons and circuits, in some instances, it is forced to choose one over the other. For example, the selective loss type 6 bipolar cell input to sONα ganglion cells results in homeostatic rewiring that restores cellular activity (i.e., time-averaged firing rate) and circuit function (Tien et al., 2017). However, more severe loss of ON bipolar cells preserves ganglion cell activity at the expense of visual function, as sONα ganglion cells recruit OFF bipolar cell inputs (Okawa et al., 2014). Finally, in retinal degenerations changes in the retinal milieu and progressive degeneration can prevent and overwhelm homeostatic plasticity and lead to maladaptive remodeling (Jones et al., 2016; Lee et al., 2021; Marc and Jones, 2003; Pfeiffer et al., 2020b; Telias et al., 2020). Through a better understanding of how and when homeostatic mechanisms fail, or why they give way to maladaptive remodeling, we hope that future studies can identify therapeutic opportunities for homeostatic plasticity in the retina.

5. Control of homeostatic plasticity

The neuronal and glial responses to triggers for homeostatic plasticity can vary dramatically by cell type, age, and species.

5.1. Cell-type specificity of homeostatic plasticity

In response to activity suppression, cortical neurons scale up synapses with excitatory partners and scale down synapses with inhibitory partners (Kilman et al., 2002; Turrigiano et al., 1998). Similarly, rod bipolar cells can stabilize their activity after partial input loss by forming new or scaling up existing glutamatergic synapses from rods on their dendrites or eliminating GABAergic synapses from amacrine cells on their axons (Beier et al., 2017; Care et al., 2020; Leinonen et al., 2020). The sONα ganglion cells further differentiate their rewiring with closely related excitatory input partners (i.e., type 7, 8, X, and rod bipolar cells) after losing their dominant source of excitation (i.e., type 6 bipolar cells) to stabilize their responses (Tien et al., 2017).

Beyond cell-type specificity in the homeostatic rewiring with different input partners, the extent of homeostatic plasticity varies between cell types. Whereas excitatory cortical neurons scale up their excitatory inputs in response to activity suppression, inhibitory cortical neurons do not (Rutherford et al., 1998; Turrigiano et al., 1998). This differential plasticity is critical for network homeostasis (Maffei and Fontanini, 2009). In the mouse retina, related bipolar cell types differ in the extent of their dendritic rewiring after partial cone loss (type X >

type 5i/o = type 6 > type 7) (Fig. 8) (Shen et al., 2020). Similar differences appear to exist in the homeostatic plasticity of rabbit bipolar cells (Beier et al., 2017). The purpose of these differences remains to be uncovered.

5.2. Age dependence of homeostatic plasticity

As circuits mature, neuronal plasticity decreases (Burke and Barnes, 2006; Hensch, 2005; Oberman and Pascual-Leone, 2013; Takesian and Hensch, 2013). This decrease in plasticity is thought to make the adult nervous system vulnerable to neuron loss and limit recovery from neurodegeneration and injury (Hübener and Bonhoeffer, 2014; Veenstra--VanderWeele and Warren, 2015). In the retina, homeostatic plasticity has been observed during development and at maturity (Beier et al., 2017; Care et al., 2019; Johnson et al., 2017; Leinonen et al., 2020; Tien et al., 2017). Shen et al. (2020) compared how bipolar cells in the developing (postnatal day 10) and mature (postnatal day 30) mouse retina respond to the removal of half of the cones (Fig. 8). When cones were deleted in the developing retina, three of four bipolar cell types (i.e., types X, 5i/o, and 6) precisely restored their input synapse numbers through dendritic rewiring (Shen et al., 2020). By contrast, only one of four bipolar cell types (i.e., type X) accomplished synaptic homeostasis in the mature retina. The steep maturational decline in bipolar cell plasticity was associated with the emergence of functional deficits (Fig. 8). Whereas ERG b-waves, reflecting bipolar cell responses, were preserved after cone ablation in the developing retina, they were reduced after cone ablation in the mature retina (Shen et al., 2020). Similarly, gaze-stabilizing eye movements and depth perception were intact when cones were removed in the developing retina but impaired when they were deleted at maturity (Shen et al., 2020). Thus, whether cone degeneration results in visual impairments or not depends on the bipolar cells' homeostatic plasticity. The effect of homeostatic plasticity on functional outcomes identifies it as a promising therapeutic target for retinal and other neurodegenerative diseases.

Recent studies have revealed that rather than losing plasticity passively, maturing circuits actively suppress plasticity to stabilize connectivity and function (Kobayashi et al., 2015; Morishita et al., 2010; Sommeijer et al., 2017; Sugiyama et al., 2008; Takesian et al., 2018; Toyoizumi et al., 2013). Yet, we know little about the mechanisms regulating the maturational plasticity decline. Insights into these mechanisms are fundamental to understanding how the retina establishes and maintains its circuits. In addition, such insights may lead to novel therapies for degenerative diseases, in which the low plasticity of mature circuits limits the preservation and recovery of function.

5.3. Species differences in homeostatic plasticity

Homeostatic plasticity has been observed in a wide range of species from fruit flies to humans (Davis, 2006; Davis and Goodman, 1998; Karabanov et al., 2015; Ramocki and Zoghbi, 2008). The homeostatic capacity and plasticity mechanisms of the retina differ between species. For example, whereas some non-mammalian vertebrate retinas (e.g., zebrafish and chicken retinas) can undergo homeostatic neuroregeneration, mammalian retinas cannot (Bringmann et al., 2009; Fischer and Reh, 2003; Lenkowski and Raymond, 2014). With the increasing availability of and decreasing price for generating genome and transcriptome information from different animals, species-specific differences provide an opportunity to uncover the molecular mechanisms that control homeostatic plasticity (Hoang et al., 2020). Species-specific differences in the molecular landscape and plasticity from model organisms to humans (Peng et al., 2019; Yan et al., 2020b) also underscore the importance of studying homeostatic plasticity in the human or non-human primate retina (Akiba et al., 2022).

6. Future directions and conclusions

We were motivated to summarize our understanding of homeostatic plasticity in the retina in part because we believe its therapeutic

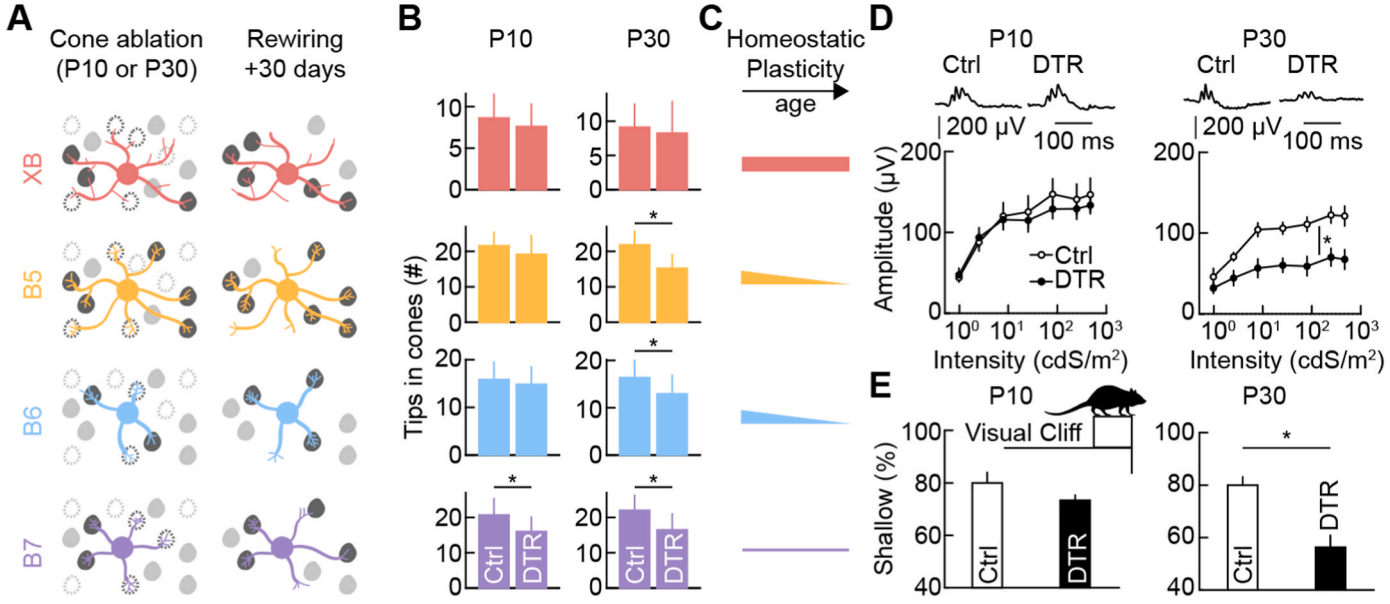

Fig. 8. Maturational decline in homeostatic plasticity causes functional deficits after photoreceptor degeneration. **(A)** Schematic illustrating the cell-type-specific rewiring strategies of type X (XB), 5i/o (B5), 6 (B6), and 7 (B7) bipolar cells after removal of half the cones through a diphtheria toxin receptor/diphtheria toxin-mediated approach. **(B)** 30 days after cone ablation at postnatal day 10 (P10, i.e., during development), three of four bipolar cell types (type X, 5i/o, and 6) restore input synapse numbers to normal levels. By contrast, 30 days after cone ablation at P30 (i.e., at maturity), only type X bipolar cells restore input synapse numbers to normal levels. **(C)** Schematic illustrating maturational dependence of homeostatic plasticity. Bar width denotes capacity for homeostatic plasticity as a function of age. While type X recovers lost cone inputs in young and mature mice (i.e., from P10 to P30), type 5i/o and 6 are highly plastic at P10 but fail to recover synapses at P30. Type 7 bipolar cells exhibit little homeostatic rewiring at either time point. **(D and E)** The decline in homeostatic rewiring is accompanied by the emergence of functional deficits in the ERG b-waves (**D**, i.e., bipolar cell light responses) and behavioral performance in a visual cliff test **(E)**. * indicates $p < 0.05$. The data in this figure are published in (Shen et al., 2020).

potential for retinal neurodegenerations (e.g., inherited retinal degenerations, age-related macular degeneration, glaucoma) is high and somewhat underappreciated. Several studies have shown that homeostatic plasticity can preserve retinal circuit function and visual behaviors in the face of extensive cell loss (e.g., half of the cones, half of the rods, half of the rod bipolar cells, all type 6 bipolar cells) (Care et al., 2019, 2020; Johnson et al., 2017; Leinonen et al., 2020; Shen et al., 2020; Tien et al., 2017). In addition to its potency, an appealing feature of homeostatic plasticity is its precision. Through built-in set points, homeostatic plasticity restores retinal function to its intended operating range (Care et al., 2019, 2020; Johnson et al., 2017; Shen et al., 2020; Tien et al., 2017). Finally, homeostatic plasticity is orthogonal to and expected to synergize with therapeutic approaches aimed at reducing neuron loss or replacing lost cells (Ludwig and Gamm, 2021; Roska and Sahel, 2018; Sahel et al., 2019; Van Gelder et al., 2022). Thus, homeostatic adjustments could optimize the circuit integration and functional impact of salvaged and newly introduced neurons. Encouraging observations in this context indicate that homeostatic plasticity preserves the synaptic specificity of retinal circuits when possible (Beier et al., 2018; Care et al., 2019; Shen et al., 2020; Yoshimatsu et al., 2016) and otherwise changes it to optimally preserve circuit function (Tien et al., 2017; Yoshimatsu et al., 2014).

Major challenges to unlocking the therapeutic potential of homeostatic plasticity relate to the neuronal and glial responses. First, not all neurons are equally inclined to homeostasis. Thus, bipolar cell types respond differently to photoreceptor degeneration, some restore input connectivity, but others do not (Beier et al., 2017; Shen et al., 2020). In addition, to cell-type-specific differences, homeostatic plasticity declines with age. This was tested explicitly by Shen et al. (2020), who found that in young mice with high homeostatic plasticity, cone degeneration (50%) is compensated by bipolar cell rewiring, whereas the same degeneration in mature mice with lower homeostatic plasticity causes circuit dysfunction and impaired vision. This both highlights the therapeutic potential of homeostatic plasticity and the challenge posed by its age-dependent decline. The identification of cell-type-specific differences and the age-dependent decline provides an opportunity to identify molecular breaks that limit plasticity and develop strategies that release them when it would be therapeutically beneficial.

Whereas in some non-mammalian vertebrates, Müller glia are the source of homeostatic neuroregeneration (Fischer and Reh, 2003; Lenkowski and Raymond, 2014), in mammals Müller glia proliferation, hypertrophy (i.e., gliosis), and eventual scarring disrupt the retinal organization and limit homeostatic neuronal plasticity (Bringmann et al., 2009; Jones et al., 2003; Pfeiffer et al., 2020b). Efforts are underway to uncover the molecular mechanisms underlying the species-specific differences in the Müller glias' responses to limit their disruptive and promote their homeostatic capacity in mammals (Blackshaw and Sanes, 2021).

CRediT authorship contribution statement

Michael J. Fitzpatrick: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Daniel Kerschensteiner:** Conceptualization, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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