Annual Review of Vision Science

Retinal Connectomics: A Review

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Annu. Rev. Vis. Sci. 2024. 10:263–91

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

https://doi.org/10.1146/annurev-vision-102122-110414

Keywords

retinal connectomics, retina, synapses, visual processing, electron microscopy, connectomics

Abstract

The retina is an ideal model for understanding the fundamental rules for how neural networks are constructed. The compact neural networks of the retina perform all of the initial processing of visual information before transmission to higher visual centers in the brain. The field of retinal connectomics uses high-resolution electron microscopy datasets to map the intricate organization of these networks and further our understanding of how these computations are performed by revealing the fundamental topologies and allowable networks behind retinal computations. In this article, we review some of the notable advances that retinal connectomics has provided in our understanding of the specific cells and the organization of their connectivities within the retina, as well as how these are shaped in development and break down in disease. Using these anatomical maps to inform modeling has been, and will continue to be, instrumental in understanding how the retina processes visual signals.

INTRODUCTION

Topology: a description of the spatial and relational organization of constituent parts and their connections

Class: a set of cells sharing certain attributes that separate them from others and that (ideally) cannot be further separated

The retina is an excellent tool with which to understand how neural principles are established and function. The neuronal networks of the retina are organized into a multilaminar, highly structured tissue (Wassle 2004) lining the back of the eye, responsible not only for sensing light, but also for the initial processing of this visual information. The remarkable advantage of the retina for studying the network basis for neural computations is its compact representation of a complex network, completely contained within a few hundred microns. To obtain the same network topology representation in the brain, you need substantially larger volumes and all of the technical limitations that they bring.

Many of us in retinal science have become accustomed to various diagrams illustrating the major retinal populations, showing their approximate positions and the areas where neural processes contact one another (**Figure 1**). These schematics simplify our understanding but also obscure the incredible complexity that underlies the actual organization of the networks, or topologies, in the retina. Even a conservative estimate of the number of cell classes in a typical mammalian retina reveals anywhere from 120–240 distinct kinds of neurons and glia, if one takes into account all of the distinct populations of glial, horizontal, photoreceptor, amacrine, bipolar, and ganglion cells. We are learning that each one of these cell classes also has its own distribution pattern across the retina, or retinal mosaic, as well as a unique relationship with the broader retinal networks associated with it, including the type, frequency, size, and spatial organization of connections. Despite

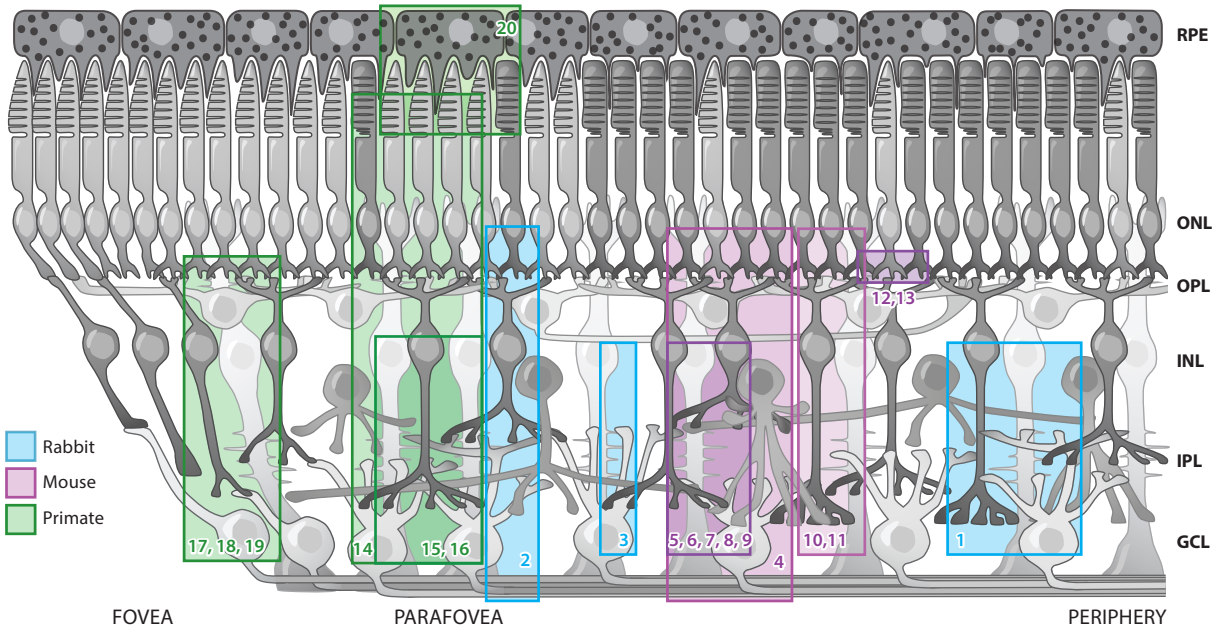

Figure 1

Diagram of the retina illustrating the general regional layout, laminar organization, and cell classes. The diagrams are overly simplistic and do not illustrate the real network topology of the retina. Boxes indicate the approximate regional localization and laminar extent of described retinal connectomes from rabbits (*blue*), mice (*purple*), and primates (*green*). Note that sizes and regional positions are relative and not true to scale. Numbers refer to retinal connectome descriptions and references detailed in **Table 1**, which are restricted to those with available linked databases. Not all retinal connectomes are illustrated due to insufficient volume information. Abbreviations: GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; ONL, outer nuclear layer; OPL, outer plexiform layer; RPE, retinal pigment epithelium.

150 years of neuroanatomical and electrophysiological research, we still lack a complete wiring diagram of these networks. For example, if one were to hypothetically inject current from a rod photoreceptor into a retina at a single synapse, we do not know the comprehensive list of the locations where that current would ultimately end up.

In essence, retinal connectomics is the study of how retinal cells are connected (Anderson et al. 2009, 2011; Briggman & Bock 2012; Briggman et al. 2011; Helmstaedter et al. 2013). Practically, however, by working at synaptic resolution, retinal connectomics provides not only connections between neurons, but also the morphology of cells and detailed synaptic properties, including location, number, type, size, and specific partnerships, as well as associations with the glia and vasculature. Combined, these components generate accurate maps of more complete network topologies. This provides the ideal framework upon which to hang all of the genetics, expression, electrophysiology, and even psychophysics data to define how current flows through these networks. Ultimately, the combination of data from all of these fields is essential to our understanding of how visual information is encoded and the precise sequence of functions, or algorithms, that ultimately generates vision. These computations are what define the emergent phenomena that we can observe, e.g., luminance, color, velocity, vector, orientation selectivity, circadian encoding, adaptation, sensitization, texture, and more.

Understanding the complexity of neural pathways in healthy and diseased states is critical to intervention in blinding diseases and trauma that impact the vision of millions globally (Jones & Marc 2020). All retinal degenerations, inherited or acquired, cause remodeling, a form of negative plasticity, of the neural circuitry, glia, and vasculature (Jones et al. 2003, 2005, 2016a). Neuronal aspects of remodeling include receptor reprogramming, neurite sprouting and panretinal ectopic synaptogenesis, and ultimately neuronal cell death, while glial aspects include hypertrophy, metabolic malfunction (Pfeiffer et al. 2016), outer retinal seal formation, and microglial activation and migration (Jones & Marc 2005; Jones et al. 2003, 2011, 2012, 2016a,b; Marc et al. 2003). These remodeling events, combined with the progressive neuronal degeneration of the later stages of retinal degeneration (Pfeiffer et al. 2020b), create barriers to therapeutic interventions (Jacobson et al. 2015a,b; Jones et al. 2003, 2016a; Marc et al. 2013b). Knowing the topologies of the rewired retina throughout the progression of remodeling is essential to vetting treatments for all conditions threatening vision. Thus, the natural extension of retinal connectomics to retinal pathoconnectomics (Pfeiffer et al. 2019, 2020a) offers us an understanding of how retinal degenerative diseases alter these network topologies, allowing us to identify how they fail in disease states and break vision.

This article aims to serve as an overview of retinal connectomics and its history in advancing our understanding of retinal networks. More detailed summaries of what retinal connectomics approaches and strategies are available exist elsewhere (Jones & Marc 2020). The intention of this review is to provide a guide for further reading or exploration of some of the most notable recent efforts using volumetric ultrastructural approaches in retinal network reconstruction that have furthered our understanding of how retinas are wired and function.

HISTORY OF RETINAL CONNECTOMICS

Retinal connectomics as a discipline stands on the shoulders of a broad history of 3D reconstructions of tissues originating in light microscopy, before being applied in electron microscopy (EM) (Ware 1975). The question of what is a connectome is a reasonable one that has many answers, which will likely depend upon who you ask. Some consider a connectome as simply a volume of registered ultrastructural images that subtend some distance in a neural tissue. However, in its most exact sense, a connectome is the complete connectivity graph of a network. While typically

Canonical connectome: a ground-truth network model containing a complete topological description of the constituent parts and interactions

considered in the context of neural tissue, it need not be exclusive to it, as it could also be used to describe electrical and metabolic networks in organs such as the heart and liver that are created by small molecule diffusion through gap junctions. A more sophisticated, idealized description of a connectome is that it is a set of registered ultrastructural images with linked annotations and a database describing the complete catalog of structures in the image volume and their locations, features, and relationships that together define the network topologies (Marc 2008, Marc et al. 2013b).

For as long as people have been able to image ultrastructure, they have been looking for ways to go bigger and to tell more of the story than they are able to see within the glowing chamber of the electron microscope or the individual pictures that can be taken. Retinal connectomics could reasonably be seen as encompassing several scales with the aim of exploring, through volumetric ultrastructural approaches, the connections of neurons and glia within the retina. Given this somewhat loose definition, the history of retinal connectomics could date back to the 1950s, when Sjöstrand (1958) first published 3D reconstructions of rod synapse ultrastructure interpreted from serial section electron micrographs of the guinea pig retina. These early attempts at volumetric reconstruction of retinal tissue were heroic, especially considering that the early initiatives were limited to capturing transmission electron microscopy (TEM) data on film negatives that were then reassembled by hand and manually annotated. Thus, early efforts focused on discrete, often small-arbored cells such as photoreceptors; bipolar cells; certain narrow-field amacrine cells; and small ganglion cell types, like the midget ganglion cells of the primate retina (Famiglietti & Kolb 1975, Kolb 1970, Kolb & Dekorver 1991, Kolb & Famiglietti 1974, Stevens et al. 1980). These taught us a lot about the structure and synaptic patterns and relationships of these retinal neurons, which together defined the basic wiring of the primary rod and cone pathways. As questions arose regarding the variability and diversity of the major neuronal populations and retinal networks as a whole, reconstruction of more cells in larger volumes was required. These questions resulted in herculean efforts to demonstrate the existence of discrete populations among cone bipolar cells that differ beyond simple variation in individual animals or retinal location (Cohen & Sterling 1990; McGuire et al. 1984; Tsukamoto & Omi 2014, 2015, 2016, 2017).

Capturing full networks at high enough resolution to visualize all cell–cell contacts, including synapses and gap junctions, is crucial to defining the complete network topologies, which are in turn key to understanding retinal function and how these topologies and functions change in disease. Fragmentary or incomplete models of any network are of limited value (Marc 2008, Marc et al. 2012) and remain major barriers to understanding the networks that underlie visual processing (Marc et al. 2013a,b, 2015), understanding remodeling in retinal disease (Jones et al. 2011, 2016a,b), testing prosthetics (Loizos et al. 2014), validating therapeutic schemas, or developing computational models (Kosta et al. 2021; Loizos et al. 2014, 2016a,b).

Consequently, the goal of the field became collecting complete neuronal and glial topologies that encompass entire networks important for the calculation of all of the primitives associated with vision. Technological advances have propelled retinal connectomics toward the realization of such canonical connectomes by generating larger and more comprehensive volumes containing complete retinal network topologies with multiple representatives of all components. Earlier connectivity studies (Boycott & Kolb 1973, Calkins et al. 1998, Famiglietti & Kolb 1975, Tsukamoto et al. 2001) lack metadata, access to raw data, and queryable databases that allow one to extract the precise relationships and build the statistics necessary to establish physiological relevance.

Thus, the modern era of retinal connectomics started with publications centered around the theoretical and practical implementations of approaches designed to create the logistical or technological infrastructure permitting larger, more comprehensive connectomes (Anderson

et al. 2009, Briggman & Bock 2012, Lichtman et al. 2008). The development of serial block-face scanning electron microscopy (SBF-SEM) has helped capture larger volumes faster and with less postprocessing effort in mosaicking and alignment of serial sections, albeit often at a cost in resolution. TEM remains a powerful tool for high-resolution connectomes, including the visualization of gap junctions. Modern computational infrastructure allows for the evaluation of connectomes from both imaging modalities to be done with far greater scales than were possible even a decade ago, as the price and framework costs of computational storage have plummeted. Critically, these efforts paved the way for the database strategies necessary for investigating the interactions of the complex networks in these larger-scale datasets. It is this ability to define the complete network topologies that has defined the modern era of retinal connectomics.

These larger, more comprehensive volumes and associated databases (**Table 1**, **Figure 1**) are teaching us about general principles of network connectivity in retinal circuits. We now know that the retina harbors networks so complex that prior approaches could neither discover nor map them (Lauritzen et al. 2019; Marc et al. 2012, 2014, 2015), and the high precision of retinal connections (Lauritzen et al. 2019, Marc et al. 2013a, Sigulinsky et al. 2020) makes it essential to discover which networks are resistant and which are vulnerable to negative plasticity in retinal degenerations (Pfeiffer et al. 2020a).

This approach of defining complete neural network maps is one of the audacious challenges (see Becker et al. 2021) in neuroscience, and efforts in the retina are informing larger efforts elsewhere in the brain. Incorporating artificial intelligence/machine learning (AI/ML) technologies to autosegment and identify connectivity is pushing us into the future of retinal connectomics, toward the realization of a truly canonical connectome detailing complete retinal networks. Then, one can ask questions of the additional kinds of data that are contained within these comprehensive connectomes, depending on how tissues are processed and the available resolution of the dataset. Indeed, the ability to identify all sorts of features, including synapses and gap junctions, glial associations, organelles, and cytoskeletal features, all while encoding their sizes, locations, and relationships both within and between cells, gives us, for the first time in history, the ability to go back and forth among ultrastructural image data, morphology, and connectivity, as well as running statistical inquiries and queries on all of this interactively. While going bigger is valuable, there remains substantial benefit to creating smaller, more targeted connectomes that reveal specific relationships among known structures, identified cell classes, and cells that have been physiologically recorded prior to volume construction. Moreover, while recent efforts have effectively been limited to studies in mouse, rabbit, and nonhuman primate, additional retinal connectomes for other species are forthcoming. Such efforts into alternative model systems have much to teach us about biology in normal and pathological states.

WHAT HAS RETINAL CONNECTOMICS TAUGHT US IN RECENT YEARS?

Although the retina is a remarkably compact representation of neural circuit topology, almost unrivaled in the nervous system, it is nonetheless a large, complex neural network performing an exceedingly broad range of computations in diverse conditions. The entirety of these computations and underlying components is outside the scope of this review, and much of the current knowledge in the field was beautifully articulated in a recent book (Schwartz 2021). In this section, our primary goal is to examine recent contributions of retinal connectomics–based studies to our understanding of retinal network topology and, where possible, explain the role of these networks in computations underlying vision.

Table 1 Retinal connectomes reported in the literature

Name	Species	Age	Sex	Genetics; strain	Retinal region	Retinal layers	Method	Resolution (nm^3)	Dimensions (μm^3)	Reference(s)	Annotation platform	Figure 1[a]
RC1	Rabbit	13 months	F	WT; DB	MPer	GCL-INL	TEM	2.18 × 2.18 × 70	250 dia × 26	Anderson et al. 2011; Bordt et al. 2019; Lauritzen et al. 2013a,b, 2019; Marc et al. 2014, 2018; Pfeiffer et al. 2020a; Sigulinsky et al. 2020; Yu et al. 2023	Viking	1
RPC1	Rabbit	10 months	M	Tg P347L; NZW	PeriVS	NFL-ONL	TEM	2.18 × 2.18 × 70	70 dia × 66	Pfeiffer et al. 2019, 2020a	Viking	2
e1088	Rabbit	6 weeks	NA	NA	NA	GCL-INL	SBF-SEM	22 × 22 × 30	45 × 39 × 60	Helmstaedter et al. 2011	Knossos	3
RC2	Mouse	5 months	F	WT; C57BL/6J	NA	NFL-ONL	TEM	2.18 × 2.18 × 70	250 dia × 100	PC	Viking	4
e2006	Mouse	P30	NA	WT; C57BL/6	NA	GCL-ONL	SBF-SEM	16.5 × 16.5 × 25	80 × 117 × 135	Behrens et al. 2016; Briggmann et al. 2011; Helmstaedter et al. 2011, 2013; Ishibashi et al. 2022; Stabio et al. 2018	Knossos	5
K0563	Mouse	P30	NA	WT; C57BL/6	NA	GCL-INL	SBF-SEM	12 × 12 × 25	50 × 65 × 145	Briggman et al. 2011, Helmstaedter et al. 2011, Hogarth et al. 2015, Jain et al. 2022	Knossos	6
e2198	Mouse	P29	NA	NA	NA	GCL-INL	SBF-SEM	16.5 × 16.5 × 23	60 × 350 × 300	Briggman et al. 2011, Kim et al. 2014, Greene et al. 2016	Knossos	7
K0731	Mouse	9–12 weeks	NA	C57BL/6	MPer[b]	GCL-INL	SBF-SEM	12 × 12 × 25	73.2 × 27.6 × 57.6	Grimes et al. 2021, Pallotto et al. 2015	Knossos	8
k0725	Mouse	P30	NA	WT; C57BL/6	NA	GCL-INL	SBF-SEM	13.2 × 13.2 × 26	50 × 210 × 260	Bleckert et al. 2018; Ding et al. 2016; Graydon et al. 2018; Grimes et al. 2021, 2022; Hanson et al. 2023; Huang et al. 2019; Jain et al. 2022; Mani et al. 2023; Matsumoto et al. 2019; Park et al. 2020; Sawant et al. 2021; Stabio et al. 2018; Yu et al. 2023	Knossos	9
Singer eel001	Mouse	NA	NA	NA	NA	GCL-ONL	SBF-SEM	7 × 7 × 40	57.34 × 114.68 × 65.96	Ishibashi et al. 2022	Knossos	10

(*Continued*)

Table 1 (*Continued*)

Name	Species	Age	Sex	Genetics; strain	Retinal region	Retinal layers	Method	Resolution (nm^3)	Dimensions (μm^3)	Reference(s)	Annotation platform	Figure 1[a]
NA	Mouse	2 months	NA	Tg (Gjd2-EGFP) JM16Gsat	NA	GCL-ONL	SBF-SEM	5 × 5 × 50	125 × 160 × 48	Yu et al. 2023	TrakEM2	11
NA	Mouse	NA	NA	Tg (Dact2-GFP)	NA	NA	SBF-SEM	6–8 × 6–8 × 70–80	NA	Grimes et al. 2021	TrackEM	NA
NA	Mouse	P60	M	C57BL/6	Per	INL-OPL	SBF-SEM	5 × 5 × 50	NA	Saha et al. 2023	TrakEM2	NA
NA	Mouse	P11	NA	C57BL/6	NA	NA	SBF-SEM	5 × 5 × 50	NA	Gamlin et al. 2020	TrakEM2	NA
NA	Mouse	P24	NA	WT	NA	NA	SBF-SEM	5 × 5 × 50	NA	Bleckert et al. 2018, Gamlin et al. 2020, Sinha et al. 2020	TrakEM2	NA
NA	Mouse	P24	NA	VIAAT KO	NA	NA	SBF-SEM	5 × 5 × 50	NA	Bleckert et al. 2018, Sinha et al. 2020	TrakEM2	NA
NA	Mouse	Adult	NA	LRRTM4 KO	NA	NA	SBF-SEM	? × ? × 50	NA	Sinha et al. 2020	TrakEM2	NA
NA	Mouse	P12	NA	WT	NA	NA	SBF-SEM	? × ? × 50	NA	Sinha et al. 2020, 2021	TrakEM2	NA
NA	Mouse	P12	NA	LRRTM4 KO	NA	NA	SBF-SEM	? × ? × 50	NA	Sinha et al. 2020	TrakEM2	NA
NA	Mouse	NA	NA	$GABA_A$ α3 KO	NA	NA	SBF-SEM	? × ? × 50	NA	Sinha et al. 2021	TrakEM2	NA
NA	Mouse	P30	NA	Grm6-tdtomato	NA	NA	SBF-SEM	5 × 5 × 50	NA	Wisner et al. 2023	TrakEM2	NA
NA	Mouse	NA	NA	Thy1-YFP	NA	NA	SBF-SEM	? × ? × 50	NA	Sawant et al. 2021	TrakEM2	NA
FIB-SEM 1	Mouse	NA	NA	NA	NA	OPL	FIB-SEM	4 × 4 × 4	25 × 25 × 4.6	Ishibashi et al. 2022	NA	12
FIB-SEM 2	Mouse	NA	NA	NA	NA	OPL	FIB-SEM	4 × 4 × 4	25 × 25 × 4.6	Ishibashi et al. 2022	NA	13
Inferior monkey	Macaque	NA	M	NA	PF	GCL-PR OS	SBF-SEM	7.5 × 7.5 × 95	240 × 230 × 174	Bordt et al. 2022; Patterson et al. 2019, 2020b,c, 2022	Viking	14
Nasal monkey	Macaque	NA	M	NA	PF	GCL-INL	SBF-SEM	5 × 5 × 50	170 × 180 × 117.7	Bordt et al. 2022, Patterson et al. 2022	Viking	15
Temporal monkey	Macaque	Adult	M	NA	PF	GCL-INL	SBF-SEM	7.5 × 7.5 × 70	220 × 200 × 65.6	Bordt et al. 2021, 2022; Patterson et al. 2020a	Viking	16
NA	Macaque	Adult	M	NA	Fo	HFL-GCL	SBF-SEM	5 × 5 × 80	200 × 200 × 33	Kim et al. 2023, Wool et al. 2019	TrakEM2	17
NA	Macaque	Adult (2–7 years)	M	NA	Fo	INL-OPL	SBF-SEM	5 × 5 × 50	NA	Saha et al. 2023	TrakEM2	NA

(*Continued*)

Table 1 (*Continued*)

Name	Species	Age	Sex	Genetics; strain	Retinal region	Retinal layers	Method	Resolution (nm^3)	Dimensions (μm^3)	Reference(s)	Annotation platform	Figure 1[a]
NA	Macaque	Adult (2–7 years)	M	NA	PF	INL-OPL	SBF-SEM	5 × 5 × 50	NA	Saha et al. 2023	TrakEM2	NA
NA	Macaque	Adult (2–7 years)	M	NA	MPer	INL-OPL	SBF-SEM	5 × 5 × 50	NA	Saha et al. 2023	TrakEM2	NA
NA	Macaque	Adult (2–7 years)	M	NA	Per	INL-OPL	SBF-SEM	5 × 5 × 50	NA	Saha et al. 2023	TrakEM2	NA
NA	Macaque	NA	NA	NA	NA	NA	SBF-SEM	5 × 5 × 50	NA	Kim et al. 2022	TrakEM2	NA
NA	Macaque	NA	NA	NA	NA	NA	SBF-SEM	5 × 5 × 50	NA	Kim et al. 2022	TrakEM2	NA
NA	Marmoset	6 years	M	NA	Fo	HFL-GCL	SBF-SEM	5 × 5 × 50	200 × 200 × 61	Kim et al. 2023	TrakEM2	18
NA	Marmoset	7 years	F	NA	MPer	INL-OPL	SBF-SEM	6 × 6 × 50	NA	Saha et al. 2023	TrakEM2	NA
NA	Human	52 years	M	NA	Fo	HFL-GCL	SBF-SEM	5 × 5 × 50	200 × 200 × 95	Kim et al. 2023	TrakEM2	19
NA	Human	21 years	M	NA	Fo	GCL-ONL	SBF-SEM	5 × 5 × 50	NA	Kim et al. 2023, Zhang et al. 2020	TrakEM2	NA
Fwk 14	Human	Fd 101	NA	NA	Fo	GCL-ONL	SBF-SEM	6 × 6 × 60	NA	Zhang et al. 2020	TrakEM2	NA
Fwk 18	Human	Fd 127	NA	NA	Fo	GCL-ONL	SBF-SEM	6 × 6 × 60	NA	Zhang et al. 2020	TrakEM2	NA
Fwk 21	Human	Fd 145	NA	NA	Fo	OPL-INL	SBF-SEM	5 × 5 × 50	NA	Zhang et al. 2020	TrakEM2	NA
NA	Human	21 years	M	NA	PF	RPE[c]	SBF-SEM	5 × 5 × 50	30 × 30 × 40	Lindell et al. 2023	TrakEM2	20
NA	Zebrafish	Adult	NA	WT	NA	NA	SBF-SEM	7 × 7 × 70	NA	Hellevik et al. 2023	TrakEM2	NA

[a]Numerical reference for illustration in **Figure 1**.
[b]Tissue acquired from halfway between the optic disc and periphery.
[c]RPE volume spans the photoreceptor inner–outer segment junction to the Bruch's membrane.
This table is restricted to retinal connectomes with linked databases. Abbreviations: DB, Dutch Belted; dia, diameter; Fd, fetal day; FIB-SEM, focused ion beam scanning electron microscopy; Fo, foveal; Fwk, fetal week; GCL, ganglion cell layer; HFL, Henle fiber layer; INL, inner nuclear layer; KO, knockout; MPer, midperipheral; NA, not available; NFL, neural fiber layer; NZW, New Zealand White; ONL, outer nuclear layer; OPL, outer plexiform layer; P, postnatal day; PC, personal communication; Per, peripheral; PF, parafoveal; PR OS, photoreceptor outer segment; RPE, retinal pigment epithelium; SBF-SEM, serial block-face scanning electron microscopy; VS, visual streak.

Retinal Pigment Epithelium

The retinal pigment epithelium (RPE) is a monolayer of cells and might seem to be a simple tissue for which volume EM approaches may appear of limited value. However, there are many things that can be learned from an ultrastructural exploration of this monolayer, including the density and distribution of organelles, cytoskeletal organization, and membrane specializations of the RPE cells, and their relationships with photoreceptors or other RPE cells. In fact, early EM evaluation proved integral to our understanding of RPE phagocytosis of cone outer segments (Anderson et al. 1978). Very recently, deep learning techniques and SBF-SEM were used to reconstruct a human RPE cell with attached retina, demonstrating that photoreceptor outer segments are surrounded by multiple apical processes rather than ensheathed by a single process, at least in the parafoveal human retina, and provided much needed quantification of the cell and tissue volume portioning and membrane surface area for understanding molecular exchange within the subretinal space and at basolateral infoldings (Lindell et al. 2023). Furthermore, this reconstruction revealed opposing polarization of pigment granules and mitochondria and a striking linear array of nuclear pore complexes that are closely associated with the underlying euchromatin (Lindell et al. 2023). Expanded connectomics in the future will be important for understanding the diversity and complexity of cells within the RPE and potentially how the RPE changes its associations in disease.

Pedicles: output synapses to dendrites of bipolar and horizontal cells from a cone photoreceptor

Photoreceptors

In photoreceptors, prior even to the first synapse of the visual system, recent connectomics efforts have resolved our understanding of the direct contacts between photoreceptors, in the form of gap junction–mediated coupling. Using a combination of SBF-SEM and high-resolution, focused ion beam scanning electron microscopy (FIB-SEM) volumes, the exclusivity of rod–cone photoreceptor coupling was confirmed in the mouse (Ishibashi et al. 2022). Such rod–cone coupling via gap junctions provides alternative routes for rod and cone signals that may increase cone sensitivity and optimize rod signaling by prioritizing noise reduction (Jin et al. 2020). Additionally, by combining physiological data with the quantitative measurements of the frequency and size of these gap junctions provided by the connectomics evaluations, the researchers were able to calculate the potential contribution of these connections, and their plasticity, in retinal networks through the gating of the secondary rod pathway (Ishibashi et al. 2022).

In primates, however, rod–cone coupling is further supplemented by cone–cone coupling in the fovea. Cone–cone coupling among LM-cones is thought to enhance signal saliency with little detriment to chromatic processing. Numerous connectomic reconstructions in nonhuman primates suggest that S-cones do not participate in this robust L-cone–M-cone coupling (Klug et al. 2003, Wool et al. 2019). This network topology maintains the purity of the S-cone signal utilized for blue–yellow color opponency. These findings are in contrast to early reconstructions showing gap junctions in the peripheral human retina between S-cone pedicles and either L-cone or M-cone telodendria (Kolb et al. 1997). A recent comparative connectomics effort resolves this debate, demonstrating cone–cone coupling between S- and LM-cones in the fovea of humans but not macaques or marmosets, suggesting that there are fundamental differences in the processing of color opponency between human and nonhuman primates (Kim et al. 2023). While preservation of a pure S-cone signal makes sense for blue–yellow color opponency networks, direct cross talk between S- and LM-cones in the human fovea suggests that complex noncardinal opponency may begin in the S-cone through imbalances in LM weighting in S-cone center-surround fields (Kim et al. 2023). In sum, retinal connectomics efforts have helped resolve many of the gap junctional coupling patterns among photoreceptors and their differential employment among species that may hint at evolutionary specialization of visual networks (Cangiano & Asteriti 2021).

The First Synapse

Spherules: output synapses to dendrites of bipolar and horizontal cells from a rod photoreceptor

Moving down in the retina, the first synapse, between the rod and cone photoreceptor terminals (termed spherules and pedicles, respectively) and the dendrites of bipolar and horizontal cells, was the first to be reconstructed in the retina (Sjöstrand 1958). Indeed, the Sjöstrand study might be the first serial section EM reconstruction in any tissue. This and subsequent efforts defined stereotyped topologies, including the segregation of rod and cone signals to rod bipolar and cone bipolar cells, respectively, and the distinct structural anatomy of contacts with ON versus OFF bipolar cells and horizontal cells at photoreceptor terminals. However, as larger and more complete sets of bipolar cells have been reconstructed through more comprehensive retinal connectomics efforts, these classical views have proven too simplistic.

The lack of pure segregation of rod and cone output to downstream bipolar cells was first demonstrated by Tsukamoto and colleagues (2001) using a high-resolution mouse TEM dataset, where they identified several OFF cone bipolar cells receiving both cone and rod inputs and thereby identified a third rod pathway. Later work from these investigators documented similar mixed rod and cone input to OFF cone bipolar cells in the macaque retina, as well as a possible population of ON cone bipolar cells in mice (Tsukamoto & Omi 2014, Tsukamoto et al. 2007). A comprehensive analysis of photoreceptor–bipolar cell connectivity in another extensively mined mouse retinal connectome confirmed direct rod input to three OFF cone bipolar cell classes and quantified the relative contribution of these rod inputs to their cone input, but in contrast to the previous work, no direct rod input was identified for any ON cone bipolar cells in this mouse dataset (Behrens et al. 2016). Importantly, this reconstruction also extended the breakdown in rod–cone segregation by showing reciprocal direct cone input to rod bipolar cells. Together, these findings indicate that rod and cone signals are often mixed in the downstream networks, perhaps extending the sensitivity of the network across luminosities or facilitating temporal processing. In fact, it has been suggested that the single-step connections from rods to OFF cone bipolar cells may facilitate a faster OFF response than the three steps of the primary pathway from rods to rod bipolar cells to Aii amacrine cells, which may underlie electrophysiological and psychophysical findings of an achromatic fast rod signal (Tsukamoto & Omi 2014).

The structural anatomy of bipolar cell connectivity to photoreceptor terminals has classically been thought to diverge based on functional class, with ON bipolar cells forming invaginating contacts where the bipolar cell tips extend into the terminal and OFF bipolar cells forming flat, or basal, contacts where the bipolar cell tips terminate in contact with the base of the terminal. However, more comprehensive reconstructions have revealed that not all ON cone bipolar cell contacts with cone pedicles are of the invaginating type, and one class (exhibiting other classical ON cone bipolar cell features and physiology) appears to prefer this atypical basal contact anatomy (Behrens et al. 2016). Detailed reconstruction of OFF cone bipolar cell contacts with cone pedicles suggests that further delineation of these basal contacts is important, as class-specific biases exist in the position of these contacts relative to the ribbon zone, at least in the nonfoveal macaque retina (Tsukamoto & Omi 2015). These positional differences have been proposed to influence access to glutamate spillover, possibly shaping the spatial and temporal response of bipolar cells.

Horizontal cell dendrites occupy the lateral invaginating position at all photoreceptor terminals. In primates, the two horizontal cell classes exhibit distinct connectivity with the different cone photoreceptors. Patterson and colleagues (2019) recently provided the first full connectomics reconstruction of the H1 and H2 horizontal cell classes in the primate fovea, further detailing the connectivity of both H1 and H2 cells with M- and L-cones and H2 cells with S-cones. This is consistent with a role for H2 cells carrying both S- and ML-cone signals, which is important for initiating color and spatial opponency at the first synapse by conferring mixed surround

inhibition to both cones and bipolar cells. At rod spherules, invaginating horizontal cell processes also occupy the lateral position but arise from horizontal cell axons, rather than from dendrites. Recent connectomics reconstructions of the invaginating rod bipolar and horizontal cell processes in both mouse and primate reveal that, while the organization of these components within the spherule is highly stereotyped, the configurations outside the spherule can be diverse and quite complex, with fasciculation often resulting in helical and hook configurations (Tsukamoto et al. 2021). The importance of these external configurations to the establishment or maintenance of bipolar–horizontal cell topologies or signal modulation within the rod spherule is unclear.

Together, these observations of the first synapse generated through retinal connectomics approaches demonstrate a greater complexity in outer plexiform networks than was previously appreciated (Rogerson et al. 2017). This complexity has implications for network function, including expanding the sensitivity range of pathways and initial spatiotemporal processing of light signals.

Bipolar Cell Networks

Retinal connectomics has greatly advanced our understanding of the bipolar cell populations and their respective synaptic patterns and partnerships. Studies using Golgi staining and immunohistochemical methods have revealed multiple classes of ON and OFF cone bipolar cells. However, these methods are often limited in resolving costratifying or coexpressing classes and risk missing or misclassifying rare classes. Retinal connectomics in large, comprehensive datasets overcomes these limitations by providing the ability to assess the morphology and connectivity of all bipolar cells in a region and with multiple examples of each, leading to the creation of a complete parts list of bipolar cells in mouse and macaque and of ON cone bipolar cells in rabbit (Helmstaedter et al. 2013; Sigulinsky et al. 2020; Tsukamoto & Omi 2014, 2015, 2016, 2017).

Further exploration of the connectivity across bipolar cell classes revealed class-specific topologies. This is particularly evident in their connectivity with the Aii amacrine cell, which was thought to universally distinguish OFF from ON cone bipolar cells. Surprisingly, not all OFF cone bipolar cell classes form chemical synapses, and not all ON cone bipolar cell classes form gap junctions, with the Aii amacrine cell. Among those that do, each exhibits a unique but stereotyped frequency and, at least in the case of gap junctions mediating coupling, sizing of these contacts (Cohen & Sterling 1990, Graydon et al. 2018, Sigulinsky et al. 2020, Tsukamoto & Omi 2017). These studies also revealed class-specific patterns of gap junction–mediated homocellular coupling both within and between bipolar cell classes that, together with their heterocellular Aii coupling patterns, are useful as powerful class identifiers (Cohen & Sterling 1990, Sigulinsky et al. 2020, Tsukamoto & Omi 2017). While within-class coupling may aid signal saliency, cross-class coupling provides a mechanism for dynamic mixing across bipolar channels and therefore has substantial implications for how signals are processed, possibly to either smooth transitions in spatial computing (Lauritzen et al. 2013b) or to rapidly create current spread for essential reflex signals like the looming response. Recently, further dissection of the diversity in the structural organization of the excitatory output synapses formed by cone bipolar cells has also shown stereotyped class-specific patterns in both the presynaptic architectures (single ribbon, multiribbon, ribbonless) and postsynaptic structural configurations (monads, dyads, triads) (Yu et al. 2023). Conservation across species and evidence of partner-specific biases toward these structural motifs further suggest that these topologies may contribute to shaping network function by diversifying bipolar cell output to different retinal networks (Yu et al. 2023).

The collection of signals from photoreceptors by bipolar cells and their subsequent transmission to inner retinal cells involve stereotyped but varying degrees of divergence and convergence

at each interface across bipolar classes and influence the sensitivity and spatial resolution in the network. The extreme of this is the midget pathway in the primate fovea, where the midget bipolar cell creates a private line of communication critical for the high spatial acuity for which the fovea is known. Reconstruction of cone bipolar cells at varying eccentricity from the primate fovea showed increasing convergence of cone input to ganglion cell output with eccentricity but with notable differences between ON and OFF pathways (Kolb & Marshak 2003). Detailed mapping of cone input also reveals class-specific differences in cone sampling among OFF cone bipolar cells in primates that largely reflect differences in dendritic field size (Tsukamoto & Omi 2015). In contrast, several ON cone bipolar cell classes in mouse exhibit lower-than-expected cone sampling based on dendritic field size that was not noted among the OFF cone bipolar cell classes (Behrens et al. 2016). Whether this reflects differences in ON versus OFF pathway networks or species-specific differences remains unclear. Reconstruction of the inner retinal networks downstream of primate OFF cone bipolar cells revealed that classes with vastly different cone sampling converged on the same midget ganglion cells but with different connection frequencies, perhaps conferring a wider receptive field to the midget ganglion cell while preserving spatial acuity (Tsukamoto & Omi 2015).

Differences in the divergence and convergence properties have also been described for rod bipolar cells in the primary rod pathway. Detailed connectomics reconstructions revealed that the bifurcation of rod signals and subsequent reunification in downstream Aii amacrine cells in the mouse retina balance the noise reduction afforded by Aii/Aii coupling with little loss of spatial resolution (Tsukamoto & Omi 2013). Revisiting this, Tsukamoto & Omi (2022) demonstrated that the initial divergence of rod signals in primates is much greater than in mice. Morphological differences in the rod-to-rod bipolar cell synapse may counter this divergence by enhancing the strength or efficiency of individual synapses in the primate (Tsukamoto & Omi 2022). However, reconstruction of rod synapses at varying eccentricities from the primate fovea reveal region-specific convergence patterns that are driven by rod density and likely influence the sensitivity of the primary rod pathway across the visual field (Saha et al. 2023). Whether synaptic morphology or signaling strength follows an inverse pattern remains unassessed but will be crucial in understanding how sensitivity and spatial acuity regionally vary across the retina.

Amacrine Cell Networks

Amacrine cells make up a diverse population of retinal interneurons participating in a host of network topologies with bipolar, ganglion, and often other amacrine cells. Although they predominantly provide inhibition through release of the inhibitory neurotransmitters GABA or glycine at chemical synapses, amacrine cells may also release a second neurotransmitter that can be excitatory. Some participate in coupling through gap junctions that provide a means of lateral inhibition or excitation. These interactions can take many forms, including feedforward and feedback motifs, as well as nested versions of these, where a network is embedded within another neural network, forming a hierarchical structure. One example of this is serial inhibition, where layers of amacrine cell inhibition are stacked within a network. These complex relationships can be counterintuitive and often require extensive efforts to map their topologies. Nonetheless, progress is being made, in part through connectomics efforts.

Perhaps one of the most notable, albeit unexpected, amacrine cell networks is that of the Aii amacrine cell, first identified by early volumetric reconstructions in the 1970s (Famiglietti & Kolb 1975, Kolb & Famiglietti 1974). This mammal-specific amacrine cell collects rod-derived signals from rod bipolar cells and transmits them indirectly to ganglion cells via cone bipolar cells. Despite extensive study, our understanding of the complexity of this network was largely incomplete

until fairly recently, when detailed reconstructions of all inputs and outputs of the Aii amacrine cell revealed specific connectivity with at least 28 different partner cell classes, earning the Aii the reputation as the most complex neuronal interaction repertoire yet documented (Marc et al. 2014). Furthermore, the selective, weighted distribution of rod signals by the Aii amacrine cell to the various cone bipolar cell classes, which was expanded upon by later retinal connectomics efforts (Graydon et al. 2018, Sigulinsky et al. 2020, Tsukamoto & Omi 2017), explains the lack of scotopic sensitivity observed for some ganglion cell classes. Despite their relatively narrow-field arborizations, recent reconstructions in larger datasets demonstrated that the synaptic topologies of Aii amacrine cells, once believed to be stereotyped, could be altered, as shown by direct Aii amacrine cell inputs to the soma, rather than the dendrites, of OFF alpha ganglion cells for those Aii amacrine cells positioned above the somas of this ganglion cell class (Grimes et al. 2022). Other recent advances in our understanding of Aii amacrine cell circuits from retinal connectomics include the identification of the NOS-1 amacrine cell as a candidate wide-field amacrine cell mediating surround inhibition of the Aii amacrine cell (Park et al. 2020). Interestingly, new connectomics efforts mapping the retinal networks involving rod-dominant bipolar cells in the zebrafish retina have identified amacrine cells with synaptic connectivity suggestive of the evolutionary origin of the Aii and A17 amacrine cells (Hellevik et al. 2023), as was previously predicted (Marc et al. 2014).

Amacrine cells play important roles in crossover inhibition, in which activity in one pathway suppresses another pathway and vice versa. Retinal connectomics has identified the topologies of some of these networks. In the rabbit retina, accessory ON input to OFF layers provided by axonal ribbons from ON cone bipolar cells targets OFF-driven glycinergic and GABAergic amacrine cells with diverse bipolar, amacrine, and ganglion cell targets that together underlie a variety of mechanisms for ON–OFF crossover inhibition (Lauritzen et al. 2013a). Although rod–cone crossover suppression was long predicted by psychophysics to be mediated by lateral inhibition in winner-take-all networks, the precise topologies underlying this remained elusive. Recent connectomics efforts identified at least 13 distinct topologies through which specific sets of amacrine cells mediate cone-driven suppression of rod bipolar cells or rod-driven suppression of cone bipolar cells (Lauritzen et al. 2019). Another unexpected mode of crossover inhibition was also revealed by connectomics efforts. Reconstruction of the gap junction patterns and partners of ganglion cells in the rabbit retina identified heterocellular coupling with sets of GABAergic amacrine cells (Marc et al. 2018). These amacrine cells, in turn, provide direct inhibition to neighboring ganglion cell processes of presumably different classes, providing a potential mechanism for crossover inhibition within disjointed ganglion cell populations that influences synchrony (Marc et al. 2018).

Adding to their complexity, amacrine cells are now known to exhibit dual transmitter release. Recent connectomics efforts identified a wide-field ON amacrine cell exhibiting presynaptic architectures consistent with dual transmitter release (in this case, GABA and glycine) from distinct vesicular pools at a shared contact site with ON sustained alpha ganglion cells, in support of immunohistochemical and physiological findings (Sawant et al. 2021). In contrast, while VGluT3 amacrine cells exhibit both excitatory glutamatergic and inhibitory glycinergic outputs, these appear to occur at separate sites and possibly with distinct targets (Mani et al. 2023).

Ganglion Cell Networks

Due to the large arbor sizes of many ganglion cell classes, much of the early volumetric reconstruction efforts were restricted to mapping their (sometimes partial) bipolar cell and amacrine cell input. As larger, more comprehensive datasets have become available, full connectivity maps of the upstream networks are providing insights into the modulation of signals that shape ganglion cell outputs.

Midget pathways for chromatic processing. This has led to recent advances even in the well-described midget pathways of the primate fovea, including the color network underlying blue–yellow color opponency. Serial TEM reconstructions initially confirmed the predicted wiring driving blue–yellow color opponency in the sparse, bistratified B-Y ganglion cell (Herr et al. 2003). Antagonism is set up through S-cone-driven ON input and ML-cone-driven OFF input (Calkins et al. 1998). Subsequent reconstructions demonstrated the existence of the S-cone OFF midget pathway, where a single S-OFF midget bipolar cell provides a private line from a single S-cone to a single S-OFF midget ganglion cell, at least in the macaque fovea (Klug et al. 2003, Patterson et al. 2019, Wool et al. 2019). Coupling connectomics-based reconstruction of this S-cone OFF midget pathway with single-cell electrophysiology has led to opposing theories for the role of the horizontal cell-driven center-surround: color perception (Wool et al. 2019) or edge detection (Patterson et al. 2019). Recent comparative connectomics efforts confirmed and extended these findings through careful evaluation in the human and nonhuman primate fovea, demonstrating species-specific absence of an OFF cone bipolar cell target of the foveal S-cone in marmosets (Kim et al. 2023). This study also showed that, in contrast to the macaque, where there is pure S-cone contact to ON and OFF cone bipolar cells, cone bipolar cells in the human fovea receive input from LM-cones as well, providing a novel mechanism in humans for deviations in spectral tuning reported by psychophysical studies.

The direction selectivity circuit. Our understanding of direction-selective circuits has exploded with recent retinal connectomics in these larger datasets. Direction-selective ganglion cells are motion detectors, responding maximally to images moving in a preferred direction and weakly to those moving in the opposing null direction due to GABAergic inhibition from starburst amacrine cells. Briggman et al. (2011) used a dataset in which the direction-selective ganglion cells were first functionally classified using two-photon calcium imaging to define their preferred direction; reconstruction of the inhibitory input of these cells confirmed the structural wiring asymmetry with starburst amacrine cells underlying this computation, as predicted by electrophysiology. Specifically, feedforward inhibition selectively arises from individual starburst amacrine cell processes oriented along the null axis of the direction-selective ganglion cell (Briggman et al. 2011).

Researchers then sought to understand the neural computation underlying the selective response of starburst amacrine cells to images moving outward from the soma. In this case, connectomics-based reconstruction of the bipolar cell inputs to both ON and OFF starburst amacrine cells revealed another structural wiring asymmetry, the space-time wiring specificity, whereby preferential input from a bipolar cell class with more sustained activity is positioned closer to the starburst amacrine cell soma, and input from a bipolar cell with more transient activity is positioned out toward the dendritic tips (Greene et al. 2016, Kim et al. 2014). Contemporaneous reconstructions revealed additional synaptic segregation: Excitatory bipolar inputs are positioned closer to the starburst amacrine cell soma, and synaptic outputs are closer to the dendritic tips (Ding et al. 2016). Physiological imaging and modeling show that this synaptic segregation enhances the direction selectivity of starburst amacrine cells (Ding et al. 2016). Furthermore, this analysis also identified species-specific differences in the localization of inhibitory inputs to the starburst dendritic field, a result that supports a proposed role for accommodating differences in eye size between species (Ding et al. 2016).

Recent connectomics efforts in the nonhuman primate retina have confirmed the underlying structural basis for the origin of direction selectivity in the starburst amacrine cell, suggesting that motion detection does indeed originate in the retina, as in other mammals (Kim et al. 2022, Patterson et al. 2022). This has led to the identification of primate homologs for an ON

direction-selective ganglion cell through connectomics-based reconstruction of the postsynaptic targets of starburst amacrine cells (Patterson et al. 2022) and an ON–OFF direction-selective ganglion cell through tracer labeling (Kim et al. 2022).

Numerous efforts have since extended our knowledge regarding the contributions of the complex networks of the inner retina to the contextual modulation of the direction-selective circuits (Huang et al. 2019). Retinal connectomics has been integral to this advancement through the identification of candidate cells and synaptic mechanisms underlying the encoding of features beyond direction selectivity in complex scenes. For example, reconstruction of the networks upstream of starburst amacrine cells revealed direct inhibition by wide-field amacrine cells at the terminals of their bipolar cell inputs (Hoggarth et al. 2015, Huang et al. 2019). The global inhibition provided by these predicted wide-field GABAergic amacrine cells has been suggested by physiological studies to contextualize object movement against background illumination, conferring spatial tuning that underlies size selectivity (Hoggarth et al. 2015) and continuity detection (Huang et al. 2019). One of these wide-field amacrine cells likely includes homologs to the polyaxonal, ON–OFF spiking, A1 amacrine cell from nonhuman primates, which has been shown through connectomics-based reconstruction to exhibit just such connectivity (Kim et al. 2022). Other connectomics efforts identified multiple classes of narrow-field amacrine cells with direct or indirect input to starburst amacrine cells that together are predicted to provide the glycinergic inhibition modulating the output gain of starburst amacrine cells, enabling direction selectivity even under sustained activity (Jain et al. 2022).

Connectomics reconstruction also confirmed that the physiologically detected spatiotemporal organization of glutamatergic excitation along the dendrites of ON direction-selective ganglion cells corresponds to wiring asymmetry among the classes of their bipolar cell inputs (Matsumoto et al. 2019). This excitatory space-time wiring specificity is proposed to enhance direction selectivity in the preferred direction, tuning these ON direction-selective cells to the slow speeds needed for mediating the optokinetic response, a reflex circuit for gaze stabilization (Matsumoto et al. 2019). However, extensive direct input from VGluT3 amacrine cells to these ON direction-selective ganglion cells, as revealed by recent reconstructions together with physiological manipulations, argues that this slow-speed tuning is driven more by VGluT3 glycinergic feedforward inhibition (Mani et al. 2023). Lastly, connectomics reconstruction has been used to identify a candidate wide-field amacrine cell and synaptic mechanism conferring orientation tuning to ON–OFF direction-selective ganglion cells via a single bipolar cell input class (Hanson et al. 2023).

Intrinsically photosensitive retinal ganglion cells and the melanopsin circuits. Other ganglion cell networks receiving significant advancement from connectomics efforts are the melanopsin circuits, which are mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) and are important for non-image-forming functions such as circadian rhythms and pupillary reflexes. In this case, connectomics efforts are detailing the upstream networks that utilize classical photoreceptor signals to modulate their intrinsic photosensitivity mediated by the photopigment melanopsin. In mice, the bipolar inputs to the least well-described ipRGCs, the M5 type, were reconstructed to define the origin of the physiological demonstration of color opponency from UV to green (Stabio et al. 2018). Mechanisms for chromatic sensitivity have also been defined for intrinsically photosensitive M1- and M2-type ganglion cells in the nonhuman primate retina (Patterson et al. 2020b,c). While reconstructions reveal that the M2 type receives direct excitatory S-ON bipolar input (Patterson et al. 2020c), the M1 type is indirectly inhibited by the same S-ON bipolar cells through their drive of an S-ON bipolar-selective amacrine cell (Patterson et al. 2020b). Subsequent efforts by this group detail the connectivity of displaced M1

cells, revealing exclusive OFF bipolar drive with substantial rod crossover inhibition (Bordt et al. 2022). Together, these findings contribute to our understanding of how chromatic and scotopic cues could influence circadian rhythm and/or pupillary reflex.

Other ganglion cell circuits. There are many different classes of ganglion cells in the retina, and connectomics efforts are systematically mapping their connectivity. Separate reconstructions of ON parasol ganglion cells in the macaque have defined the bipolar cell excitatory drive (Tsukamoto & Omi 2016) and inhibitory contribution from two classes of wide-field amacrine cells (Patterson et al. 2020a). Detailed reconstructions of the bipolar and amacrine cell input of the SB3 ganglion cell, a sparsely branched member of the Class IV cells, in the rabbit retina (Bordt et al. 2019) and the broad thorny ganglion cell in the macaque retina (Bordt et al. 2021) have also been reported. These studies defining the upstream connectivity of ganglion cells are beginning to elucidate the network topologies underlying the neural computations that drive their responses to stimuli.

Connectomics in Retinal Development

Researchers are beginning to use retinal connectomics to explore the developmental principles driving circuit formation, where it is particularly suited to addressing questions regarding the development of synaptic organization. Detailed reconstruction of the foveal midget pathways across human fetal development demonstrates that the private line connectivity conferring visual acuity emerges through significant, complex synaptic remodeling, rather than early, precise synaptic wiring (Zhang et al. 2020). Several principles of this remodeling have emerged, including general refinement of initially more diffuse connectivity, earlier refinement of connectivity in the outer than the inner plexiform layer, and maturation of OFF pathways prior to ON, although these principles are largely determined by maturation rates of the individual component populations (Zhang et al. 2020).

Even for a single neuron, differential strategies of synaptic remodeling may be engaged in a partner-specific manner, independently and in parallel, as has been demonstrated for the partner-specific changes in output connectivity of the Aii amacrine cell, which shape its characteristic biased synaptic divergence patterns (Gamlin et al. 2020). Combining retinal connectomics with powerful genetic dissection revealed that disruption of the GABA receptor switching associated with circuit maturation impairs the postsynaptic assembly of A17–Aii dyadic pairs at rod bipolar cell ribbon synapses (Sinha et al. 2020, 2021). Subsequently, EM reconstructions were used to show that visual deprivation did not impair the formation of inhibitory synapses onto rod bipolar cell terminals, despite immunohistochemical evidence of disruption in GABA receptor expression and switching (Wisner et al. 2023). However, visual deprivation was shown to alter ribbon morphology in rod bipolar terminals and the postsynaptic configurations in which they participate (Wisner et al. 2023).

Connectomics in Retinal Disease

The use of ultrastructural approaches has a long history in exploring the anatomy of retinal diseases. There have been investigations of retinal degenerative diseases like retinitis pigmentosa (Kolb & Gouras 1974); age-related macular degeneration (AMD) (Curcio et al. 2005, Knupp et al. 2002); and macular telangiectasia, commonly known as Mac Tel, a disease similar to AMD that results in the degeneration of central vision (Zucker et al. 2020). Recently, beautiful tomographic reconstructions of the rod photoreceptor synapse demonstrated synaptic morphological alterations, including abnormal ribbon morphology and retraction of rod bipolar cell processes, as a result of retinal detachment (Torten et al. 2023).

However, within the context of connectomics, the first retinal pathoconnectome, indeed the first pathoconnectome in any system, was recently constructed for a large-eye model of early stage autosomal dominant retinitis pigmentosa in rabbits (Pfeiffer et al. 2019, 2020a). Reconstructions in this volume demonstrated altered morphology and variability of metabolite and lipid content across the Müller cells, the major glia of the retina (Pfeiffer et al. 2019). Subsequent reconstructions showed that, despite the early stage of degeneration, wherein rod photoreceptors had not fully degenerated, rod bipolar cells began to receive input from both rod and cone photoreceptors or even solely cone photoreceptors (Pfeiffer et al. 2020a). In addition, all of the rod bipolar cells fully contained within the volume were found to participate in additional novel connectivity: aberrant gap junctions with Aii amacrine cells (Pfeiffer et al. 2020a). These findings clearly demonstrate that the classically established rod pathway is altered in disease. The incorporation of these specific changes to retinal networks into modeling efforts is already helping us to better understand the progression of retinal degeneration and identify therapeutic accessibility (Farzad et al. 2023, Kosta et al. 2021).

Retinal pathoconnectomics is still in its infancy and is likely to explode as more connectomes from various diseases are produced in the coming years. Retinal remodeling has already demonstrated that, in every evaluated retinal disease, there is a sequela of plasticity events that follows, including rewiring, reprogramming, metabolic divergence, and eventual neurodegeneration (Jones et al. 2003, 2011, 2016a; Marc & Jones 2003; Pfeiffer et al. 2020b). A clear avenue for evaluation of the rewiring component using retinal pathoconnectomics has been demonstrated (Pfeiffer et al. 2020a). This only scratches the surface of our understanding of the new network topologies that emerge in disease, yet our understanding of these topologies is essential to the development of robust therapeutic interventions capable of interfacing with the remodeled retina.

THE FUTURE OF RETINAL CONNECTOMICS

The future of retinal connectomics is likely not going to be rooted in the generation of large-scale volumes for the canonical connectomes, although many more will certainly be produced in various systems, several of which are already being produced and many more of which are in the planning stages. Instead, we expect an explosion of smaller, more targeted connectomes to be produced around very specific questions, such as looking at the impact of targeted gene defects or knockouts on the abilities of specific cell classes to perform trafficking, exploring synaptic changes under various protein expression manipulations, or investigating the response of the retina and its various components to different treatment and therapeutic interventions. Additionally, we expect advancements in the near future in a variety of other novel applications of existing connectomes, including those discussed in the following sections.

Organelles

Because of the very nature of large-scale connectomics data, there exists an incredible opportunity to ask new questions of structures that have long been known about or described. Recent studies have generated full volumetric reconstructions of cells or regions of neurons that enable complex analysis of the intracellular organization of their organelles, including mitochondrial organization, relationships between organelles and synapses, and internal synaptic structures (Lindell et al. 2023, Thomas et al. 2019, Tribble et al. 2019). These approaches generally have involved the creation of new small volumes falling within the volume EM field. However, existing retinal connectomics datasets are ripe for use in the evaluation of many of these questions and allow for a broader analysis, including relationships with network connectivity. Additionally, utilizing existing

connectomes allows exploration by groups without EM infrastructure and can be correlated with other methodologies (Molnar et al. 2016).

Glia and Vasculature

Similarly, the glia and vasculature of the retina are also natively found within ultrastructural connectomics datasets but are largely unevaluated. One study has explored the potential for Müller cell gap junctions with a specific population of amacrine cells (Grimes et al. 2021). Additionally, a volumetric analysis of Müller cells in the retina has begun, including defining how their structure and metabolic relationships change in retinal degenerative disease (Pfeiffer et al. 2019). As for the microglia, their normal physiological function largely remains undefined, but connectomics could lend valuable insights by detailing microglial contacts within the healthy and degenerate retina at ultrastructural resolutions.

The vasculature remains ripe for connectomics evaluation. Multiple cell classes exhibit complex interactions that are particularly amenable to ultrastructural assessment, including contact or connectivity with adjacent glia and neurons. Indeed, light microscopy efforts have demonstrated specific pericyte interactions and their disruptions in diabetes, including a loss of directionality (Kovacs-Oller et al. 2020).

Comparative Anatomy

Despite the critical dependence upon the mouse, rabbit, and nonhuman primate retinas for human-relevant disease research, the interspecies understanding of many elements of retinal network topologies, which serve as the foundation for entire therapeutic strategies, is limited. Although a long history of targeted genetic manipulations have made the mouse an invaluable tool, we know that its retina is dimensionally different than a human retina, and even nonhuman primate or rabbit retinas, but the functional implications of these differences are less clear. For example, mice only have one class of horizontal cells, compared to the two classes in rabbits (Pan & Massey 2007) and nonhuman and human primates (Chapot et al. 2017). Recent comparative retinal connectomics approaches have yielded a more complete picture of the differences in photoreceptor network topologies across even closely related species (Hellevik et al. 2023; Kim et al. 2023; Saha et al. 2023; Tsukamoto & Omi 2014, 2022). Other fundamental retinal networks critical to visual processing may also differ.

One network that has been heavily investigated through connectomics is the Aii amacrine cell network, which is present in all mammals. Aii amacrine cells bridge rod and cone pathways, allowing mammals to operate in low light and bright light environments and switch rapidly between them. Many homologies in the network topology of the Aii amacrine cell are shared across species, allowing for generalizations in retinal function and pathology. The rabbit retinal connectome generated by Anderson and colleagues (2009) and later expanded upon (Marc et al. 2014, Sigulinsky et al. 2020) provided a foundational analysis for comparisons with other species. Network reconstructions from the mouse retina (Briggman et al. 2011; Graydon et al. 2018; Park et al. 2020; Tsukamoto & Omi 2013, 2017) support extensive homology but also suggest differences, particularly in their connectivity through gap junctions and inhibitory input to lobular dendrites. Whether the former arises due to species-specific utilization of gap junctions or the resolution of the datasets remains to be addressed. Extending such comparisons to primates and hopefully other species in the future will shed light on how these networks and their processing of the visual signal can be tweaked to accommodate different ecological or behavioral needs.

In terms of color perception, the evolution of tandem red and green visual pigment genes (Sharpe et al. 1998) sets primate vision and anatomy apart from those of rodents. However,

rabbit and mouse cone bipolar cells are coupled into distinct yet extensive arrays (Sigulinsky et al. 2020, Tsukamoto & Omi 2017), challenging earlier models of mouse bipolar cell–horizontal cell parallel processing (Chapot et al. 2017). In-class and cross-class coupling motifs among bipolar cells have implications in signal-to-noise control and smoothing transitions across operating ranges, respectively. The existence of in- and cross-class coupling is also supported in the human retina by light microscopy analyses, including robust cross-class coupling by at least one OFF midget bipolar cell (Kantor et al. 2017). Furthermore, the giant bistratified ON–OFF bipolar cell of the blue cone pathway exhibits putative gap junction sites with this midget bipolar cell, in addition to at least two other diffuse types. Thus, it will be essential to determine the extent and selectivity of midget and diffuse bipolar cell coupling in primates. If such cross-class coupling is functional, this will change models of color coding in nonhuman primates and humans. Some interspecies similarities exist in color coding; for example, foveal amacrine cells appear to provide only broad spectral tuning in the primate retina (Haverkamp & Wassle 2000, Marc 2008, Reese 2008, Volland et al. 2015), so their key roles may be luminance feedback and feedforward and rod–cone crossover (Protti et al. 2005) in nonhuman primates, as is found in rabbits (Lauritzen et al. 2013a; Marc et al. 2013b, 2014; Wassle et al. 2009).

Additionally, functional ganglion cell networks are ripe for comparative analysis given the broad range of species that have been evaluated. For example, species-specific differences have been noted at multiple levels of the direction-selective circuits. At the level of the starburst amacrine cell, the distribution of inputs, particularly amacrine cell–derived inhibition, is proximally restricted in mice but not rabbits, which may be a compensatory mechanism to accommodate the smaller eye size of mice (Ding et al. 2016). Mice and rabbits also differ in their populations of direction-selective ganglion cells (Wei 2018). In rabbits, a class of transient ON direction-selective ganglion cells has been identified that exhibits characteristic coupling with a subset of amacrine cells (Ackert et al. 2006, 2009; Hoshi et al. 2011; Kanjhan & Sivyer 2010; Wei 2018). Connectomics-based reconstruction demonstrates that, even though the dendrites marginally overlap, this transient ON direction-selective ganglion cell in rabbits lacks starburst amacrine cell input, unlike all other ON direction-selective ganglion cell classes (Marc et al. 2018). It also selectively samples (>90%) from specific classes of bipolar cells that starburst amacrine cells largely avoid (Marc et al. 2018). A homologous transient ON direction-selective ganglion cell has not been reported in mice, but at least one ON and two OFF ganglion cells exhibit direction selectivity and lack overlap with starburst amacrine cells (Wei 2018). The mechanism by which direction selectivity is conferred to these classes and whether it is similar between rabbits and mice remain open questions. This is particularly important given the disparity of direction selectivity models in rabbits and mice (Briggman et al. 2011, Kim et al. 2014, Srivastava et al. 2022), as well as prior physiologic analysis (Barlow & Levick 1965), which is now cast as species differences (Ding et al. 2016). Many of these comparative studies are described above in the context of the individual networks, but many network topologies remain to be evaluated, compared, and contextualized.

As more datasets are constructed for mice, rabbits, nonhuman primates, teleosts, avians, humans, and others, the comparative anatomical approaches will teach us about how each ecological niche influences the construction of neural circuits and their components. Ideally, we will also gain new insight into how some organisms deal with environmental challenges that might have impact on the human condition and disease (Merriman et al. 2016).

Unanswered Retinal Circuitry Questions

Despite the numerous connectomes of various scales generated in recent years, there are still outstanding fundamental questions regarding how retinal networks are wired, which have

implications for how retinas process information. Of particular note, the resolution of these retinal connectomics databases will influence our ability to understand form and function. For example, gap junctions are formed by every major retinal cell class and play important roles in many retinal computations. To date, datasets with sufficient resolution for the visualization of gap junctions are limited in their coverage of amacrine and ganglion cells with large arbors or sparse coverage patterns. Ultimately, we will need to hybridize retinal connectomics efforts across resolutions to assess all aspects of retinal connectivity.

Many basic questions of retinal signal processing underlie the production of connectomics datasets, including questions of color processing (Wool et al. 2019) and directional selectivity (Briggman et al. 2011, Ding et al. 2016, Huang et al. 2019, Marc et al. 2018). However, we still have a lot to learn about many of these networks, particularly across species. This view is supported by recent advances demonstrating that many aspects of our prior understanding of Aii networks were wrong (Anderson et al. 2011, Field et al. 2009, Kolb et al. 2002, Marc & Liu 1985, Marc et al. 2011, Protti et al. 2005). For example, rabbit A17 and Aii amacrine cells are both directly driven via sparse ribbon synapses from a specific subset of ON cone bipolar cells (Marc et al. 2014, Sigulinsky et al. 2020). This feedback excitation is in contrast to all other published models of the primary rod pathway. Additionally, Aii amacrine cell synaptic output and its control by inhibitory circuitry both matches (Beaudoin et al. 2008, Field et al. 2009) and conflicts with (Bloomfield & Dacheux 2001, Bloomfield et al. 1997, Xin & Bloomfield 1999) physiological interpretations.

Furthermore, despite our significant advances in color networks, numerous questions remain. For example, multiple connectomes have detailed the paths of blue cone signals (Calkins et al. 1998, Dacey 2000, Famiglietti 2008, Field et al. 2009, Kim et al. 2023, Klug et al. 2003, Kouyama & Marshak 1992, Lee 2008, Liu & Chiao 2007, Patterson et al. 2019, Wool et al. 2019), yet the primary path for blue or blue–yellow perception remains uncertain. The horizontal cell surround is believed to dominate at low spatiotemporal frequencies (Davenport et al. 2008, Field et al. 2009), but bistratified ganglion cells clearly receive both OFF-L and ON-S drive (Crook et al. 2010). Do the differential blue loadings of nonhuman primate and human H1 versus H2 horizontal cells (Dacey et al. 1996, Kolb et al. 1994, Perlman et al. 2004) impact yellow OFF pathways? What are the roles for the many amacrine cells converging on blue ON and OFF channels (Patterson et al. 2020b)? Is red–green connectivity selective? Anatomic (Calkins & Sterling 1996, Kolb & Dekorver 1991, Kolb & Marshak 2003), physiologic (Gauthier et al. 2009; Reid & Shapley 1992, 2002; Sun et al. 2006), and modeling (Lebedev & Marshak 2007) studies have yet to give a decisive answer.

In summary, retinal connectomics is constantly reshaping our understanding of the networks underlying visual processing. From networks considered solved decades ago, like photoreceptor to bipolar cell connectivity at the first synapse and the Aii amacrine cells, to previously understudied networks like color processing, retinal connectomics facilitates our understanding of what computations are possible. These comprehensive maps further expose questions of how circuits underlie structure and function and provide a basis for targeted analysis across technical approaches.

Functional Connectomics and Modeling

Ultimately, the creation of canonical connectomes will enable modeling based on the biophysical properties of the individual neurons and synapses. These biologically informed models facilitate a more precise understanding of neural network processing by taking into account both Euclidean and non-Euclidean distances, which will be important, as we know that neurons are not isoelectric and that local processing occurs (Euler et al. 2002). Additionally, the specificity of the locations and types of synapses and other potential modes of cell–cell communication play important roles in specific retinal networks that define precise topologies (Marc et al. 2014). These biologically

informed models are in contrast to some of the excellent work in ordinary or partial differential equations and stochastic models that have been so useful in tissues (Roberts et al. 2016) but ultimately fall short of recapitulating the processing of visual inputs achieved by the retina. There is some existing work in this area already that hybridizes structure and function, including the evaluation of fundamental network topologies (Dunn & Wong 2014) and providing the basis for new approaches to modeling structure and functional receptive field properties (Nath et al. 2023). Additionally, collaborative efforts have begun to directly utilize connectomics-derived biological features to better inform modeling of current flow in the healthy and degenerate retina (Farzad et al. 2023, Kosta et al. 2021, Loizos et al. 2016b). These initial attempts have increased the compartmentalization of modeling, but future efforts seek to take true Euclidean and non-Euclidean morphology into account.

CONCLUSION

Retinal connectomics promises to provide anatomical frameworks of the precise topology of retinal networks, which are critical to our understanding of the algorithms underlying how the retina processes light input and ultimately conveys visual information. Early approaches to volume EM revolutionized our understanding of retinal structure and function, but newer technologies and approaches promise to deliver a more complete picture through the creation of large, complex databases that will serve as hypothesis-generating machines. These databases are tremendously rich and, combined with their associated electron microscopic imagery, contain a myriad of additional data about structures from organelles to non-neuronal components. Furthermore, as a broad subfield of the much larger volume EM and neural communities, advances in retinal connectomics promise to enhance our fundamental understanding of the neuroscience principles by which neuronal systems operate and fail in degenerative disease. Additionally, more abstract benefits may derive from work in this field that informs general biologically inspired computing principles that may be applied to in silico–based systems.

SUMMARY POINTS

1. Complete network mapping is required to understand function and pathology.
2. Retinal connectomics has played a pivotal role in defining the organization of retinal networks, often revealing that they are more complex than was originally anticipated.
3. Retinal networks likely are multiplexed with respect to the kinds of information that they carry, and only precise network mapping followed by modeling will reveal these functions.
4. Using complete network mapping is critical to understanding how the networks fail in retinal disease.
5. Neurons are only part of the rich tapestry of data types that can be elucidated from retinal connectomes. Vascular and glial components are a rich area of growth.
6. Common solutions to image processing problems likely arose several times through evolution, and a comparative anatomy approach will likely reveal multiple evolutionary solutions.
7. Modeling of networks is still underinformed by data describing the properties of those networks, including cell class associations and biophysical constraints.

FUTURE ISSUES

1. Even in well-studied networks, much of the amacrine cell connectivity has yet to be explored. Retinal connectomics can shed light on the identities of these amacrine cells and the topologies of their connections but will require hybridization with electrophysiology to define their activity.
2. Although many retinal networks appear largely conserved among vertebrates, differences in their organization exist. Further comparative connectomics approaches will be required to identify these differences, which are critical for understanding the evolutionary adaptations in visual processing and model selection for disease and therapeutic evaluation.
3. Retinal connectomics and pathoconnectomics promise to provide a detailed anatomical framework for the computations performed in healthy and diseased retinal networks. Future modeling efforts will need to better incorporate these features.
4. Glial networks are crucial to understanding normal retinal function, including neurotransmitter cycling, and maintenance of both excitatory and inhibitory synapses.
5. Vascular and neurogliovascular approaches to connectomics promise new advances, as retinal vasculature is strongly affected by degenerative pathologies and, in turn, may also contribute to their progression. However, much of what we understand about the normal, healthy interaction among neurons, glia, and blood vessels at the ultrastructural level is limited to single-section electron microscopy. Connectomics approaches promise to change that.

DISCLOSURE STATEMENT

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

AUTHOR CONTRIBUTIONS

All authors contributed equally to this review.

ACKNOWLEDGMENTS

We thank Marla Feller from the University of California, Berkeley for helpful comments on the manuscript. The lab has been supported by National Institutes of Health R01 Grant EY028927 (to B.W.J.) and P30 Grant EY014800 (to the Moran Eye Center Core); National Science Foundation Grant 2014862; an Unrestricted Research Grant from Research to Prevent Blindness, New York, NY to the Department of Ophthalmology & Visual Sciences, University of Utah; and an Unrestricted Research Grant from Gabe Newell (to B.W.J.).

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