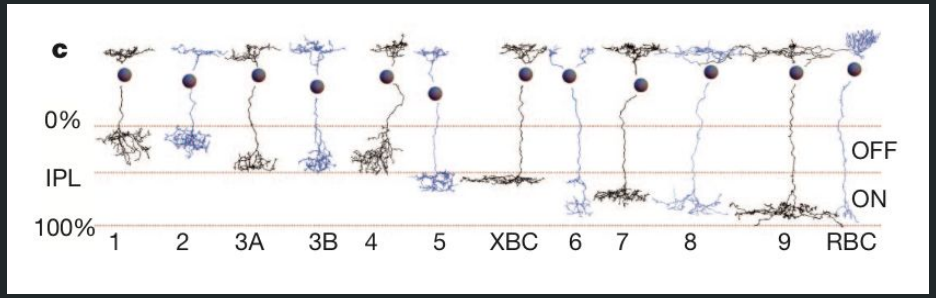


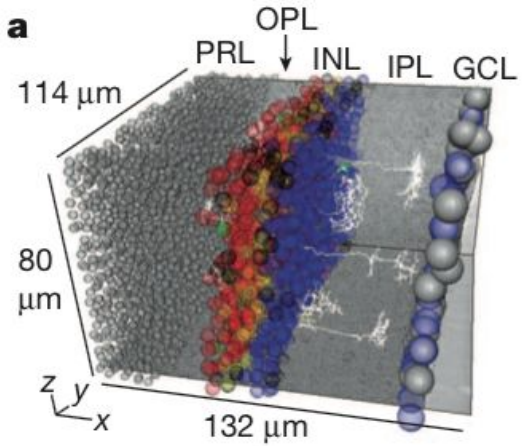
Connectomic reconstruction of the inner plexiform layer in the mouse retina

Moritz Helmstaedter, Kevin L. Briggman, Srinivas C. Turaga, Viren Jain, H. Sebastian Seung, & Winfried Denk

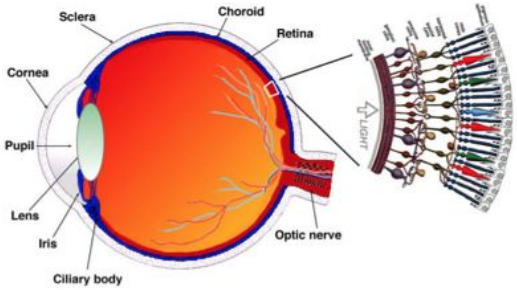
Presented by Katie Link
January 19th, 2016

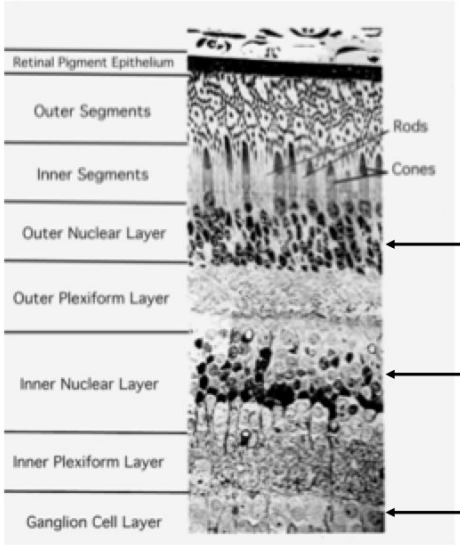
Summary

- Dense **reconstruction of 950 neurons** and their mutual contacts from **electron microscopy** data
- Achieved using **crowd-sourced manual annotation** and **machine-learning-based volume segmentation**
- Characterized **new type** of retinal bipolar cell
- Tested ability to classify based on **connectivity**
- Explored **functional implications** of connectivity
- *What can we really find out using connectomics?*



Neuroscience review…



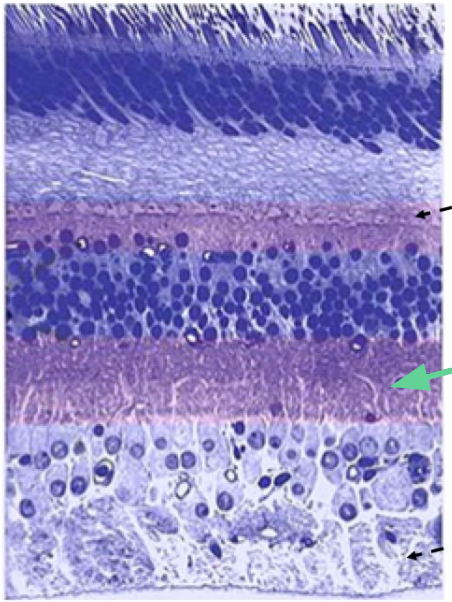


Layers of Cell Bodies

Outer nuclear layer = cell bodies of rods & cones

Inner nuclear layer = cell bodies of bipolar cells, horizontal cells & amacrine cells.

Ganglion cell layer = cell bodies of ganglion cells.



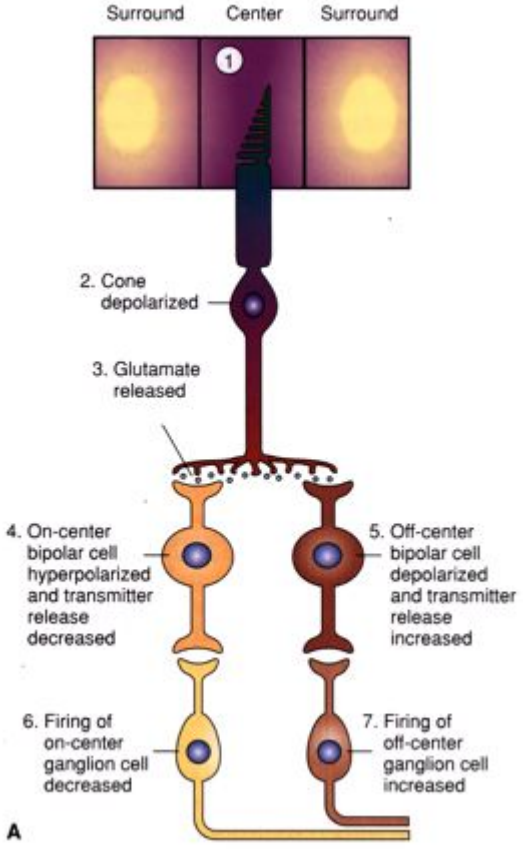
Layers of Synapses

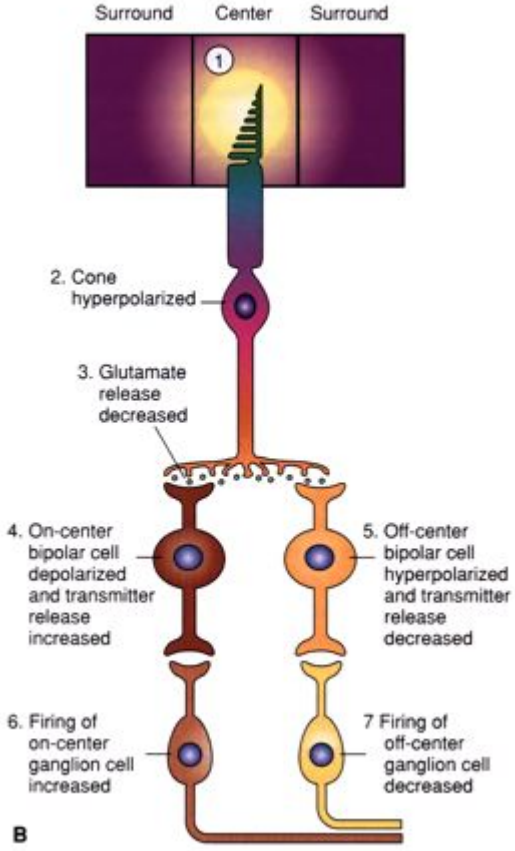
Outer plexiform layer = synapses formed by photoreceptor axon terminals

Inner plexiform layer = synapses between bipolar cells and ganglion cells.

This is not a layer of synapses – is it the **optic nerve layer**; it contains all the axons that will form the optic nerve of that eye.

Source: Dr. Hendry's Nervous System I slides

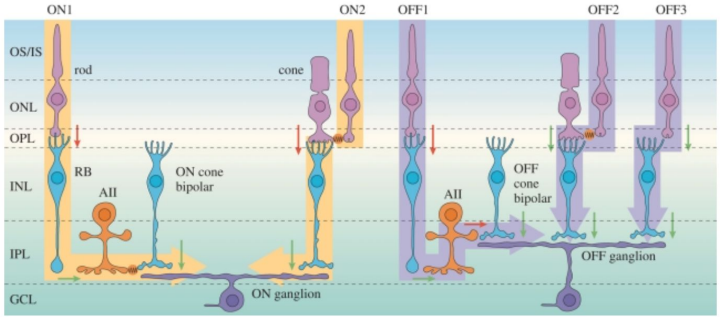


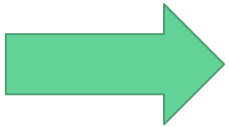


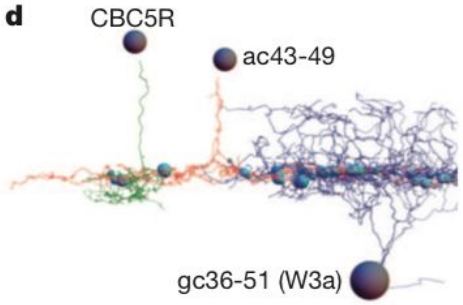
Source: Dr. Hendry's Nervous System I slides

Opportunity

- **Retina**: one of the best studied parts of the central nervous system
  - But few plausible explanations of underlying neural computation exist
- Neuronal wiring information: **how computation is performed** by neural circuits
- Unlike light microscopy, **electron microscopy** data can follow **thin neurites** and can detect whether **two cells touch** and over what area

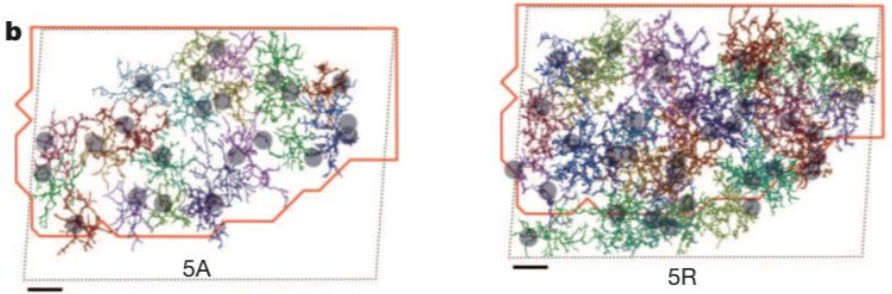






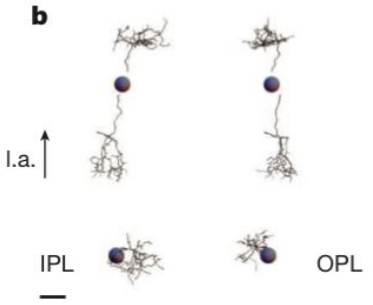
Challenge

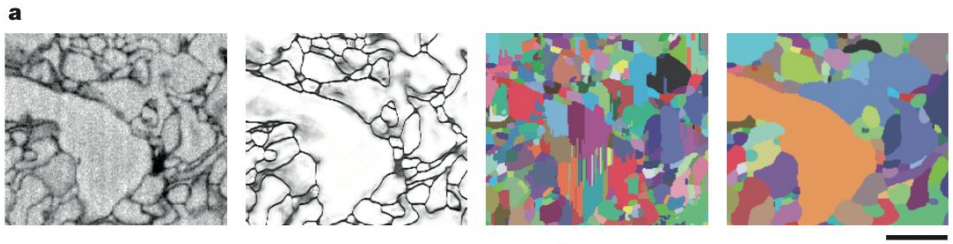
- Nervous system requires **high resolution** and **large spatial extent**
  - Challenges data acquisition and analysis capabilities
- **Peter's Rule** (mingling neurites connect) frequently violated
  - Connectivity must be **explicitly tested**
- Labeling such a large volume (1 million micrometers cubed) by hand would be prohibitively **expensive** ($10 million)
- Automatic pipeline **fragments cells** into many pieces

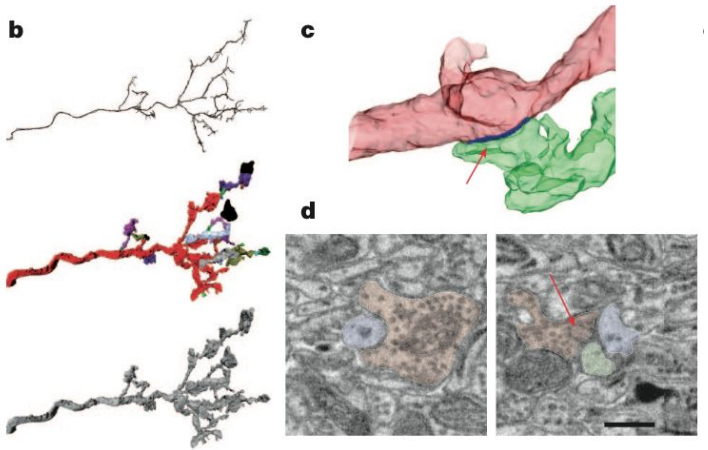


Action

- Serial block-face electron microscopy (SBEM)
- Crowd-sourced manual annotation
  - Skeletonization: KNOSSOS program
- Automated volume segmentation and contact detection
- Classification by:
  - Visual inspection
  - Contact and connectivity

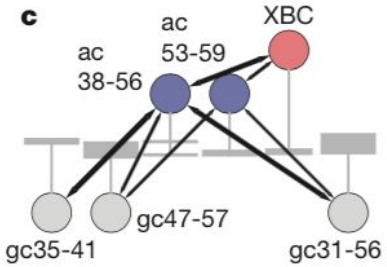


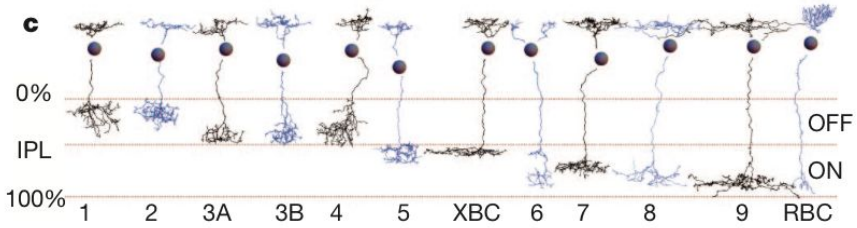


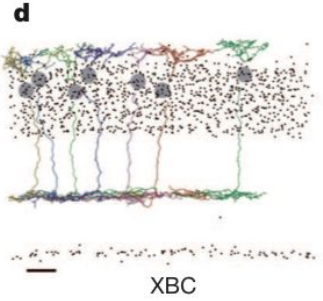


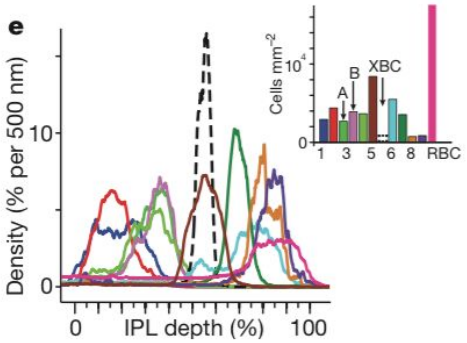
Resolution

- Successful reconstruction of all bipolar cells and many amacrine and ganglion cells in the volume
  - Prevalence of different types can be determined precisely
- Classification of novel retinal bipolar cell type, XBC
  - Visual inspection: distinct morphology
  - Absence of similar BC on OFF side
  - Functional role unclear, possibly luminance pathway



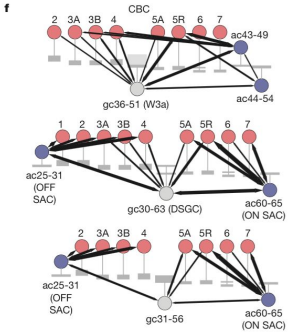


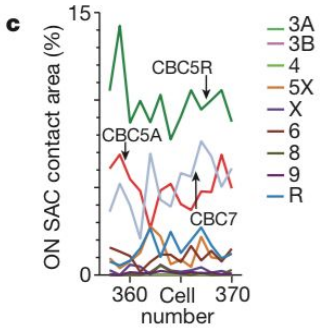


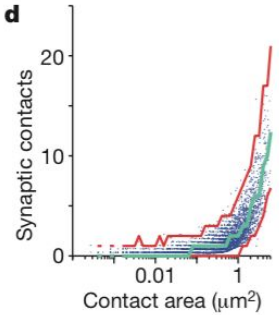


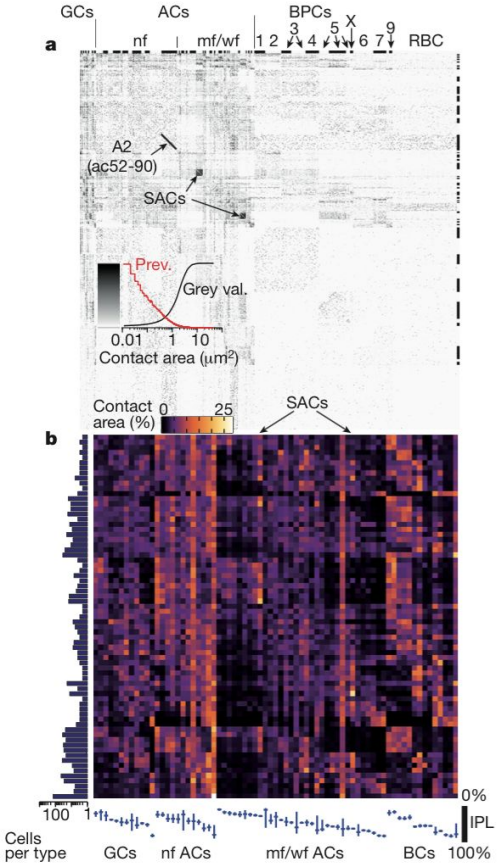
Resolution (cont.)

- Connectivity-based classification
  - e.g. similar connectivity to XBC indicate ac38-56 and ac37-52 could be the same type of amacrine cell
- Connectivity-indicated functional roles
  - Direction-sensitive ganglion cells (e.g. W3)
- Peter's Rule violated
  - e.g. absence of contacts between XBC and gc35-41









Future

- Larger volume might be able to complete tracings of **more amacrine and ganglion cells**
  - Functional implications of more comprehensive connectivity diagrams in retina
  - Contact information may become sufficient for classification
- Further classification of XBC and other circuitry systems
- Use **geometric parameters describing contact shape** to identify contact area
- Reconstruction of human retina?

Discussion

Pros

- Successfully implemented efficient pipeline
- Confirmed as well as revealed existence of bipolar cell types
- Revealed new functionality of certain circuits based on connectivity
- Showed promise of connectomics

Cons

- Took a long time (>20,000 hours) with many people (224+) helping
- Not a perfect pipeline
- Not complete classification of amacrine and ganglion cells
    - Limited by volume