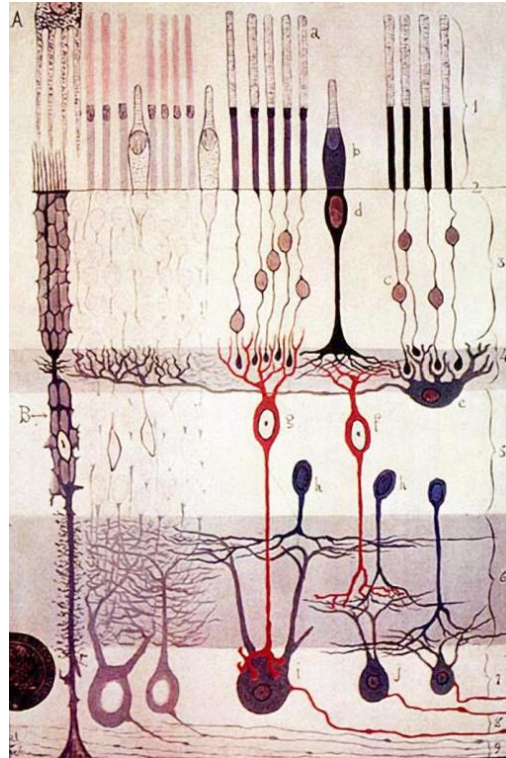


Retina basics



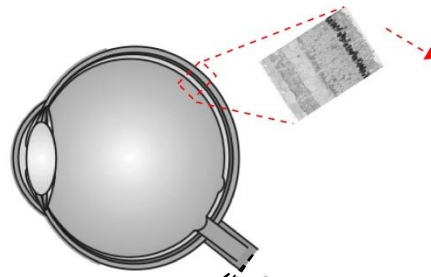
Santiago Ramon y Cajal

Florentyna Debinski, Ryan Arlinghaus | AG Franke/Euler

Bernstein Center for Computational Neuroscience

Institute for Ophthalmic Research

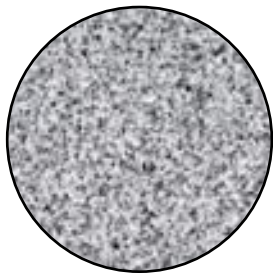
The retina is a sophisticated image processor



~3.5 mm / 1.3 million fibers



Bottle neck!!!



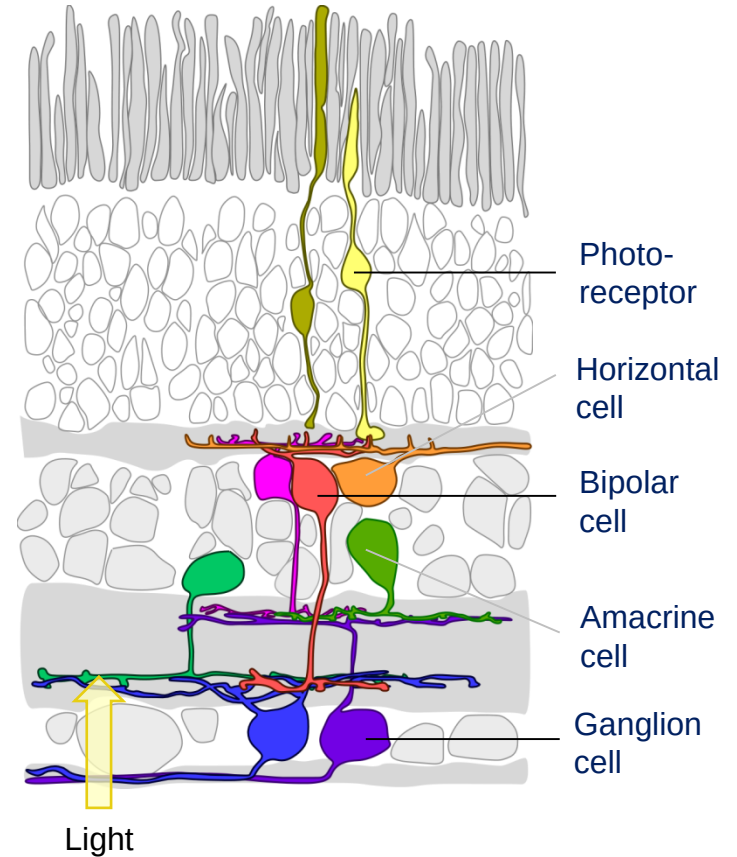
~35 mm / 130 million fibers



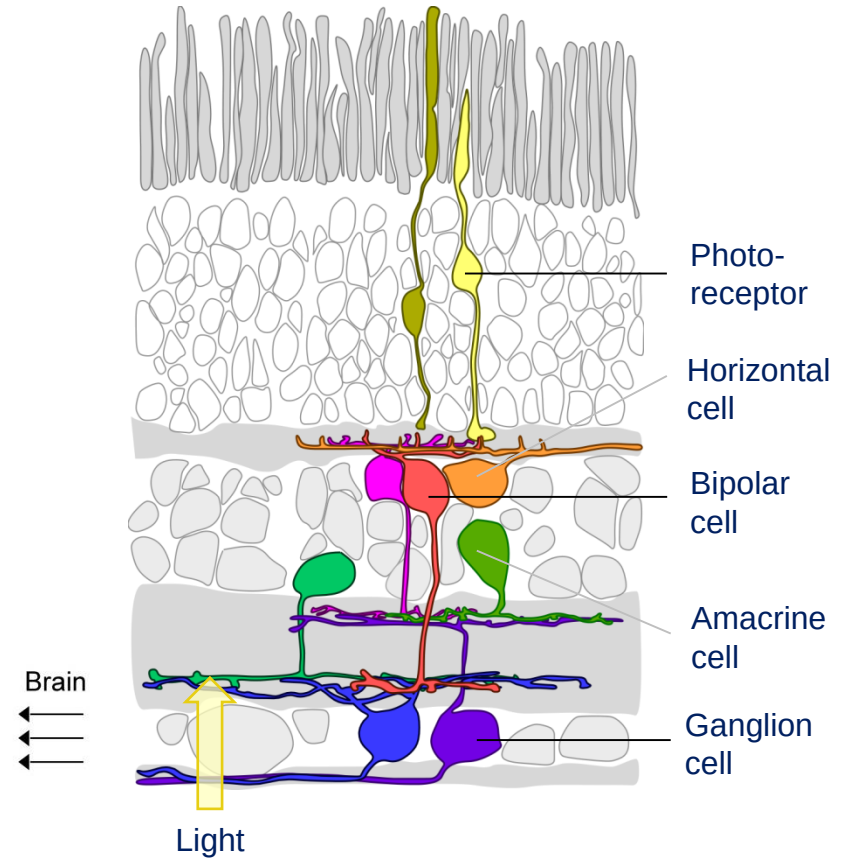
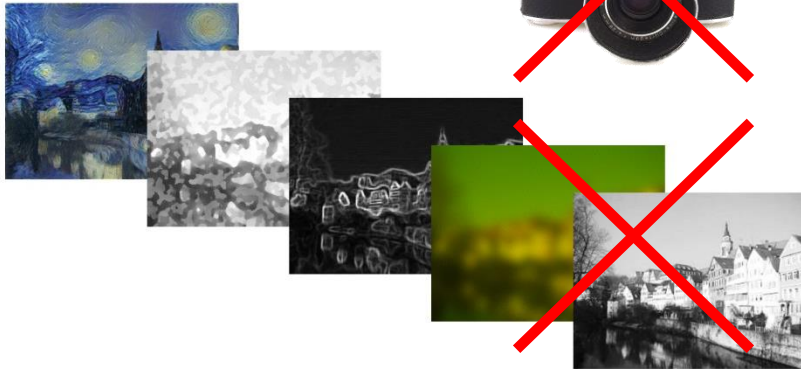
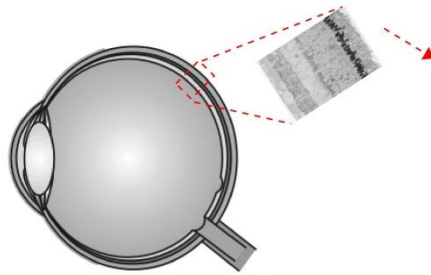
**Transduction,
Adaptation**

**Convergence
and extensive
processing of
the visual input**

**Spike trains to
the optic nerve**



The retina is NOT a simple camera





Diversity of cell types in the retina



Photoreceptors

3..4

Horizontal cells

2..3

Bipolar cells

10..14

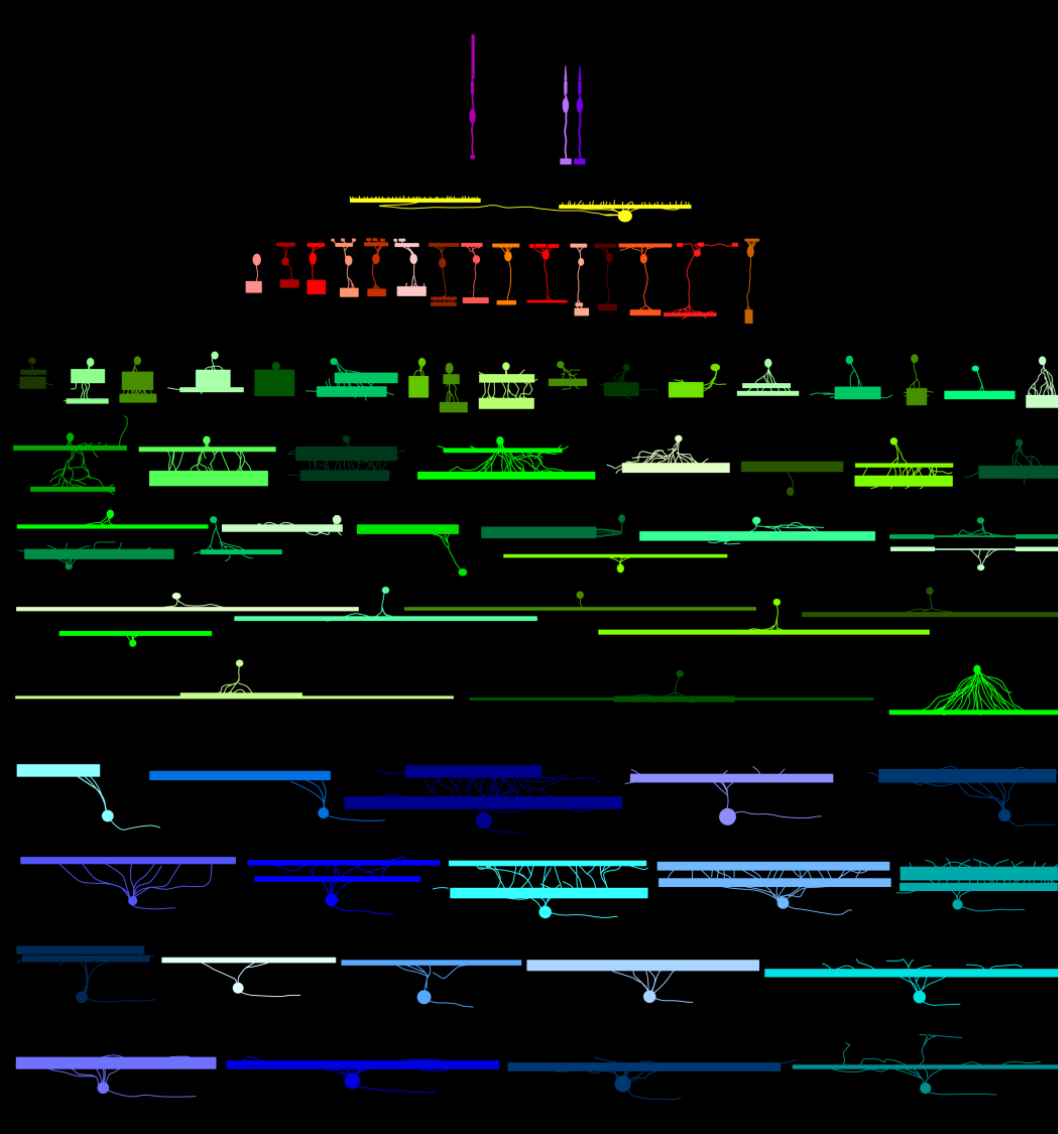
Amacrine cells

30..40

Ganglion cells

30..40

75..100



Retinal cell classes – Photoreceptors



- 1 type of rod + 1-3 types of cones
(primates: S-, M-, L-cones, most other mammals S- and M-cones, a few only S- or M-cones)
- Classified by opsin type and morphology/function
- Peak sensitivities (primates):
S (“blue”, ~437 nm), M (“green”, ~ 533 nm)
L (“red”, ~ 564nm)
- Graded, glutamatergic neurons; glutamate release is increased by darkness and decreased by light

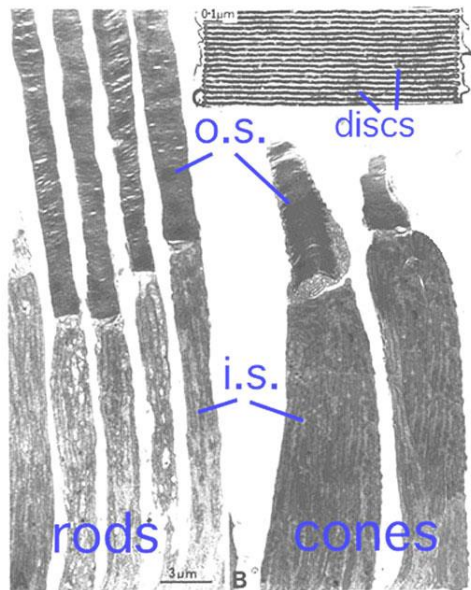
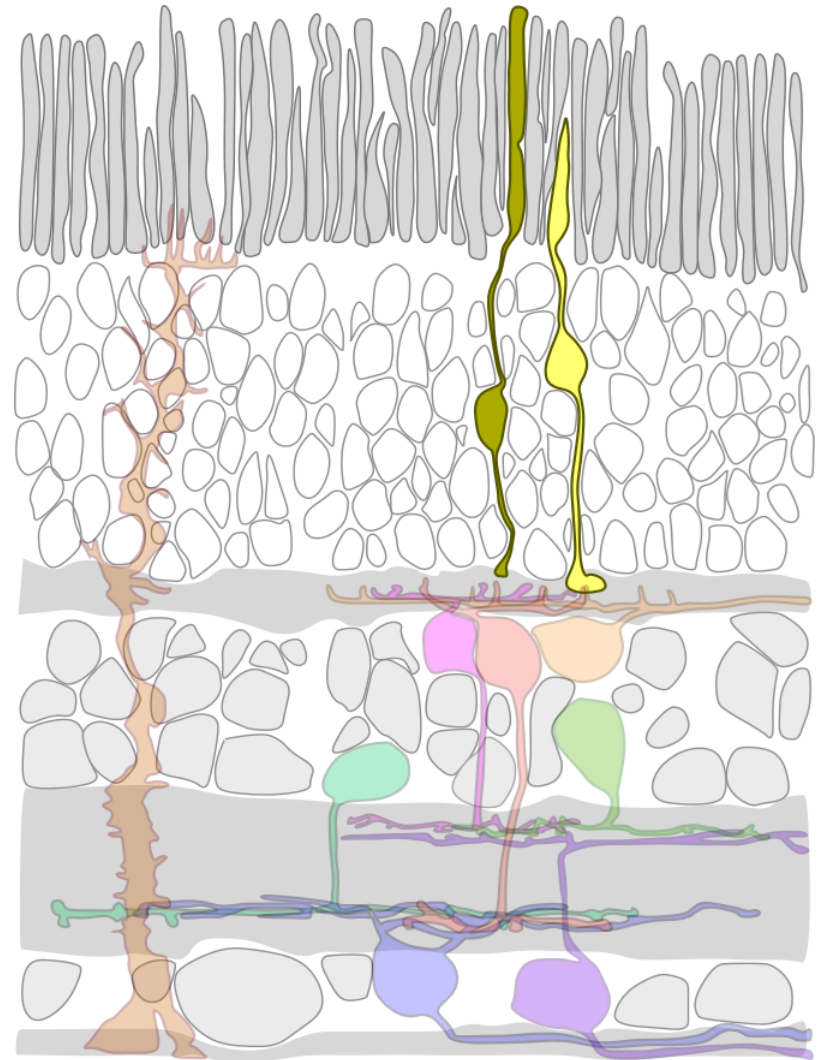


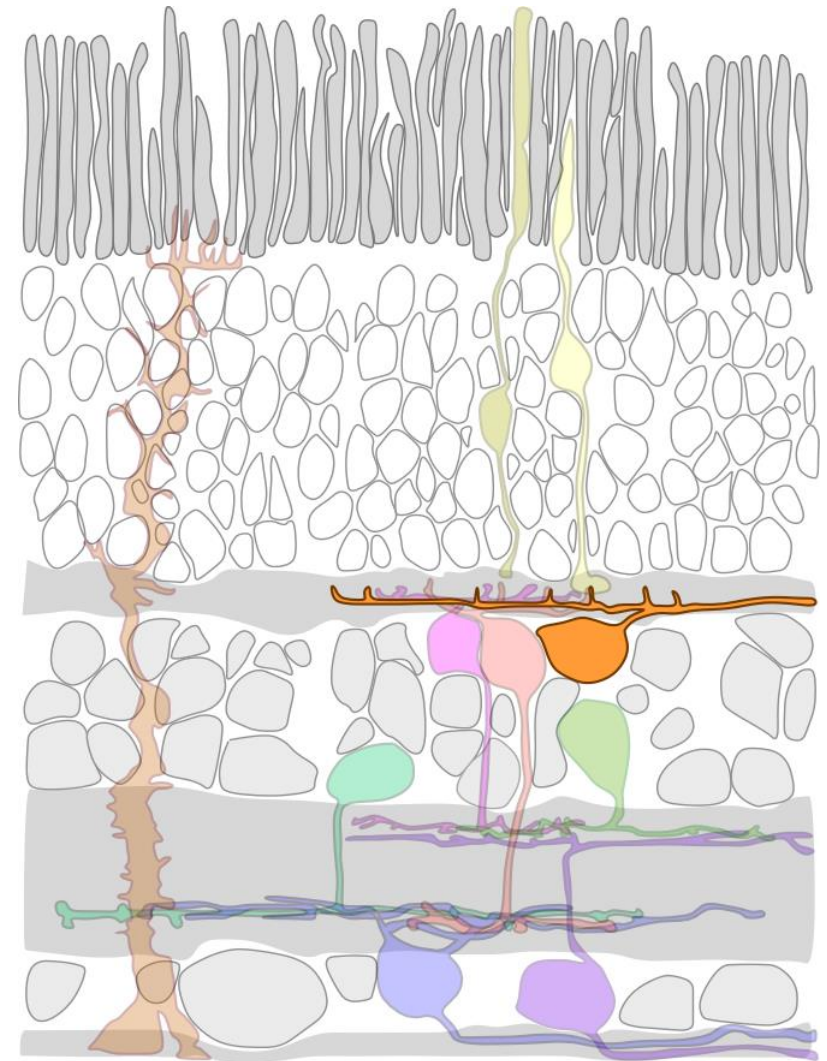
Fig 2. Low magnification EM image of monkey rods and cones with an enlargement of the outer segment discs.



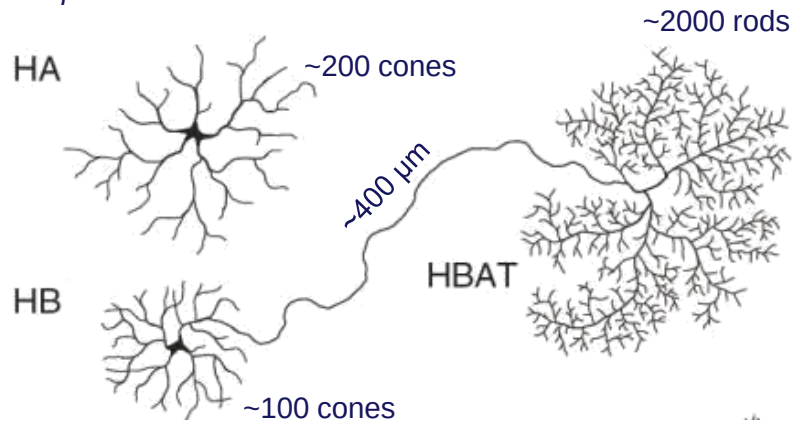
Retinal cell classes – Horizontal cells



- Two types in most retina (but e.g. 1 in mouse, 3 in horses)
- **a-type** (= axon-lacking): sparse, larger, contacts only cones (cat: ~200),
- **b-type** (= axon bearing): denser, smaller, contacts cones with “dendrites” (cat: ~100) and rods with “axon terminal” (cat: ~2000)
- OFF cells, GABAergic, graded neurons
- feed-back to photoreceptors
three different feed-back mechanism suggested:
1) ephaptic, 2) pH-mediated, 3) GABA



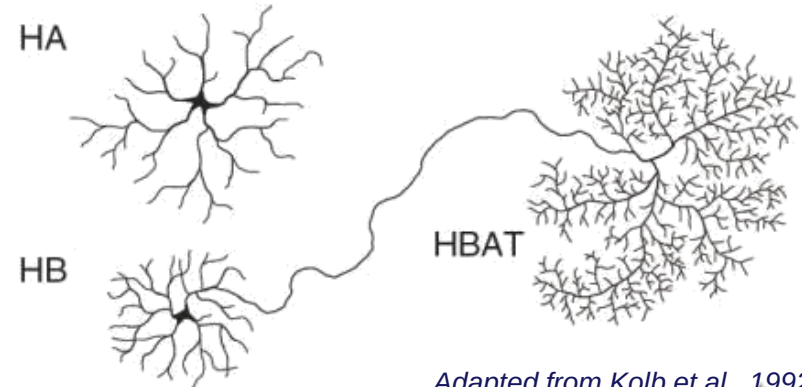
Examples from cat:



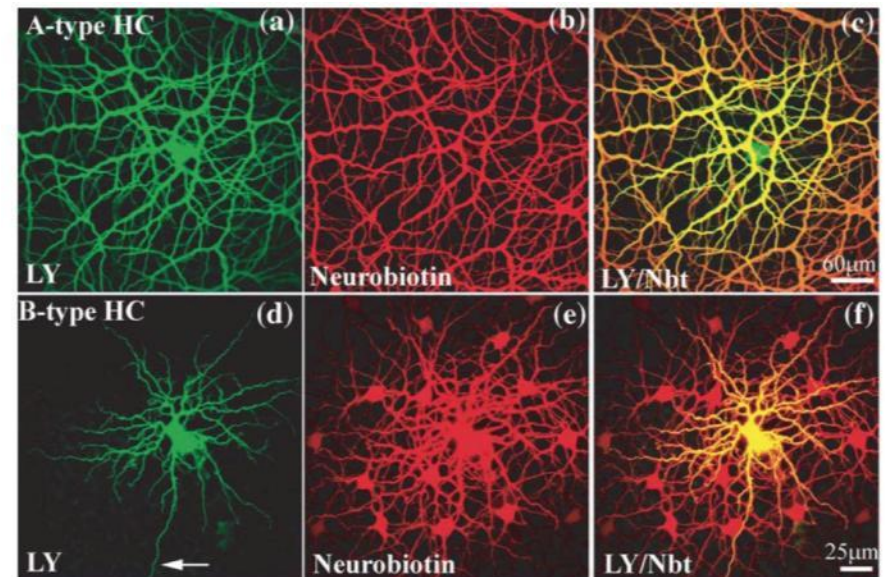
Retinal cell classes – Horizontal cells



- Two types in most retina (but e.g. 1 in mouse, 3 in horses)
- **a-type** (= axon-lacking): sparse, larger, contacts only cones (cat: ~200),
b-type (= axon bearing): denser, smaller, contacts cones with “dendrites” (cat: ~100) and rods with “axon terminal” (cat: ~2000)
- OFF cells, GABAergic, graded neurons
- feed-back to photoreceptors
three different feed-back mechanism suggested:
1) ephaptic, 2) pH-mediated, 3) GABA
- each type is coupled via gap-junctions (controlled by dopamine)
- involved in: gain control, adjustment of photoreceptor integration time, generation of receptive fields



Adapted from Kolb et al., 1992

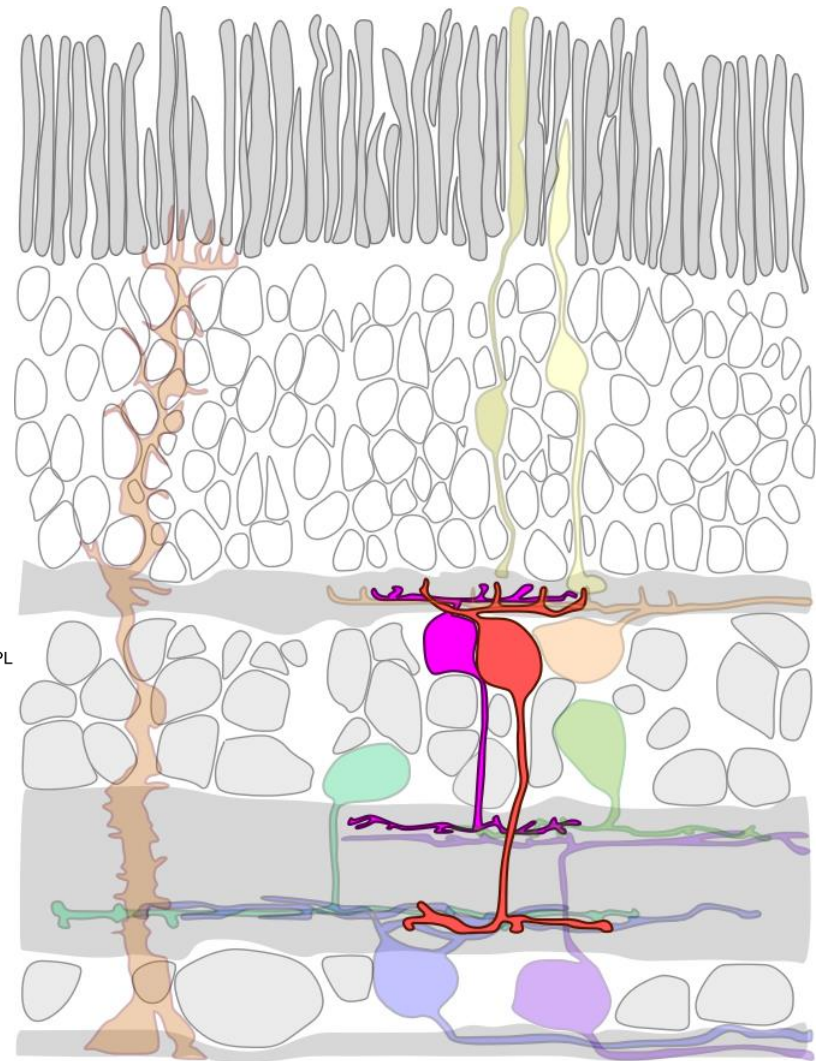
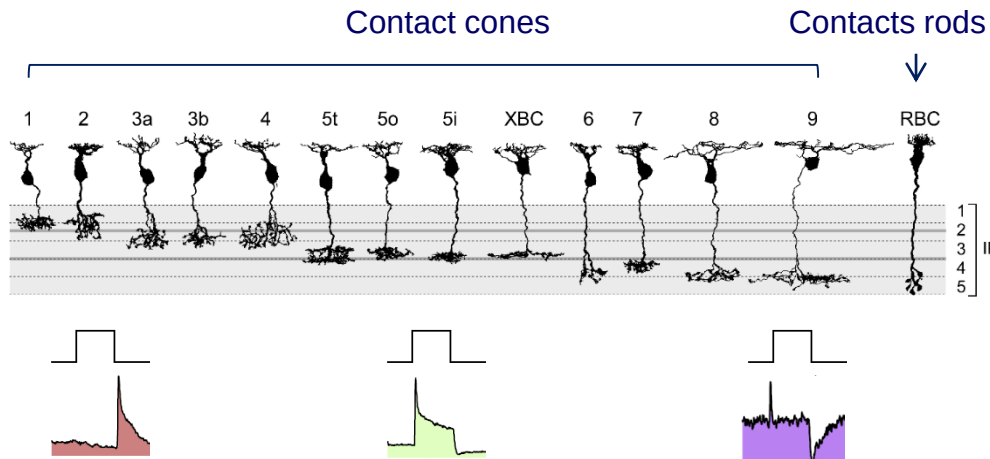


O'Brien et al., 2006

Retinal cell classes – Bipolar cells



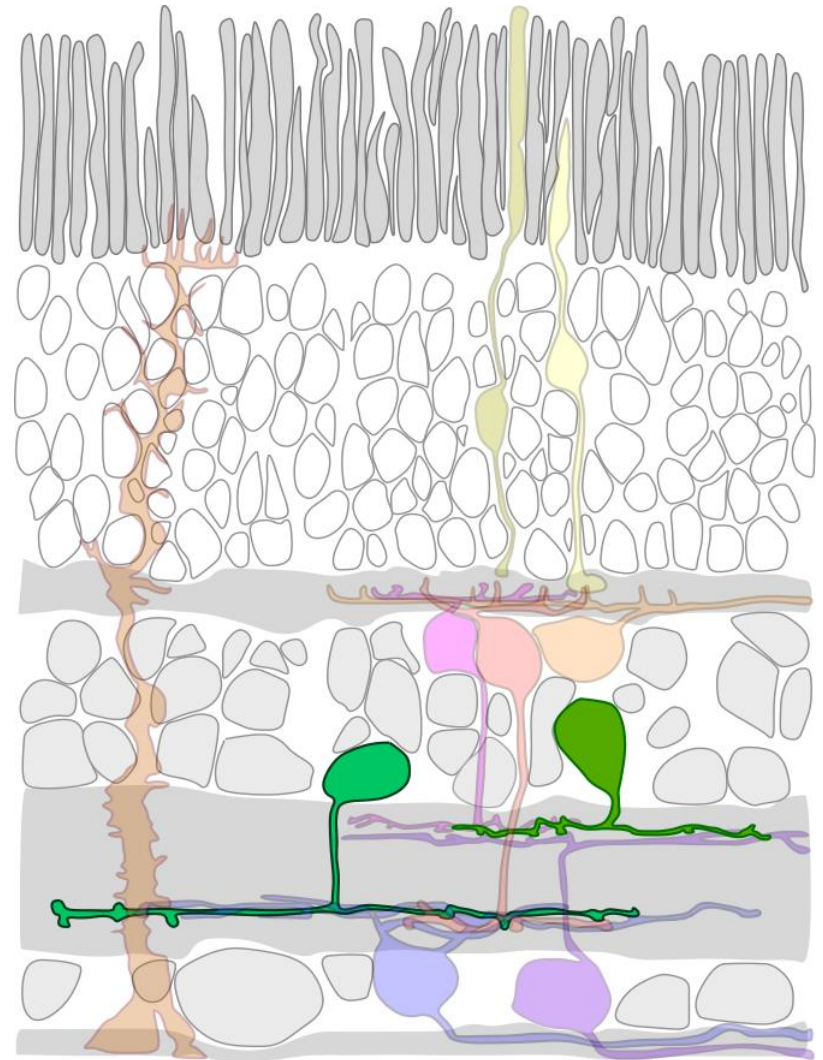
- 10-14 types, stratifying at different levels of the inner plexiform layer (IPL)
- relaying photoreceptor signals to the circuits in the inner retina (parallel signal pathways)
- Graded, glutamatergic neurons
- rough classification: On vs. Off, transient vs. sustained, rod vs. cone, etc.



Retinal cell classes – Amacrine cells



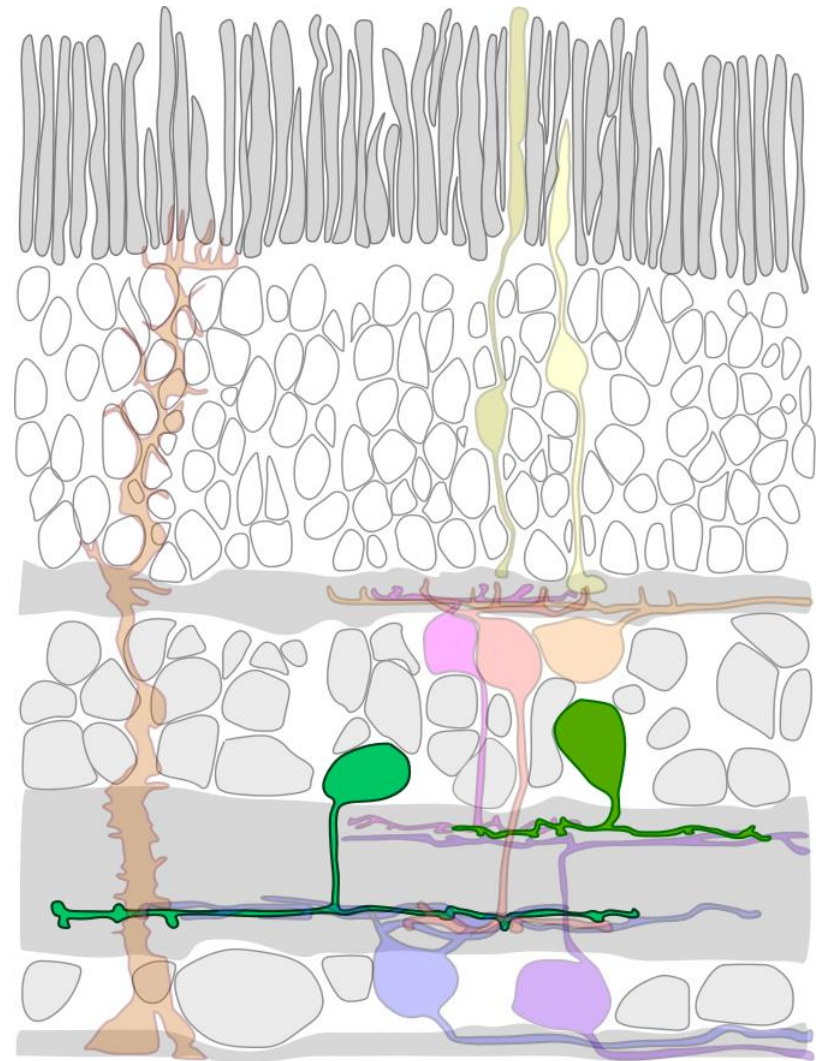
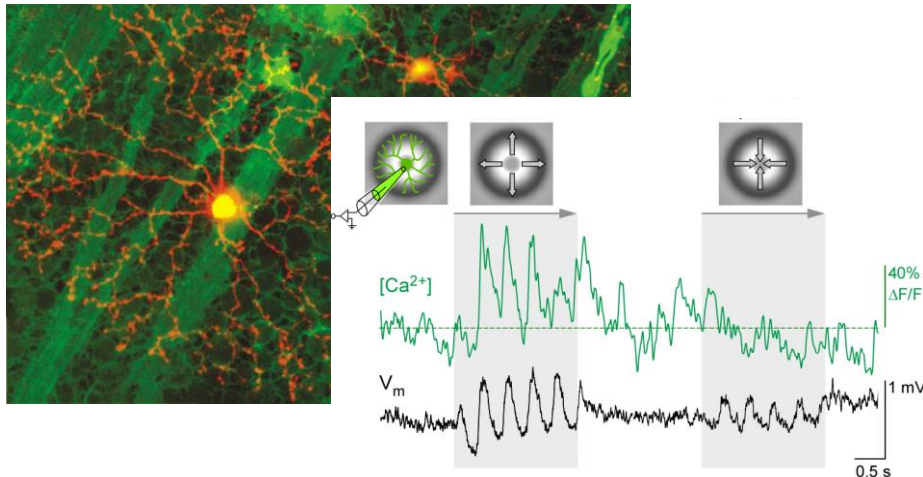
- 30-40 types of amacrine cells (or more)
- amacrine = “no axon” (Greek: a = “no” or “none”, makrós = “large” and ís (genitive of inós) = “fibre”)
- neuronal “hardware” in the inner retina
- graded, dual-transmitter neurons
(GABA or glycine + a “rare” transmitter, e.g. dopamine, ACh, serotonin?, neuropeptides, ...)
- most use dendrites for synaptic input and output
(dendritic processing)



Retinal cell classes – Amacrine cells



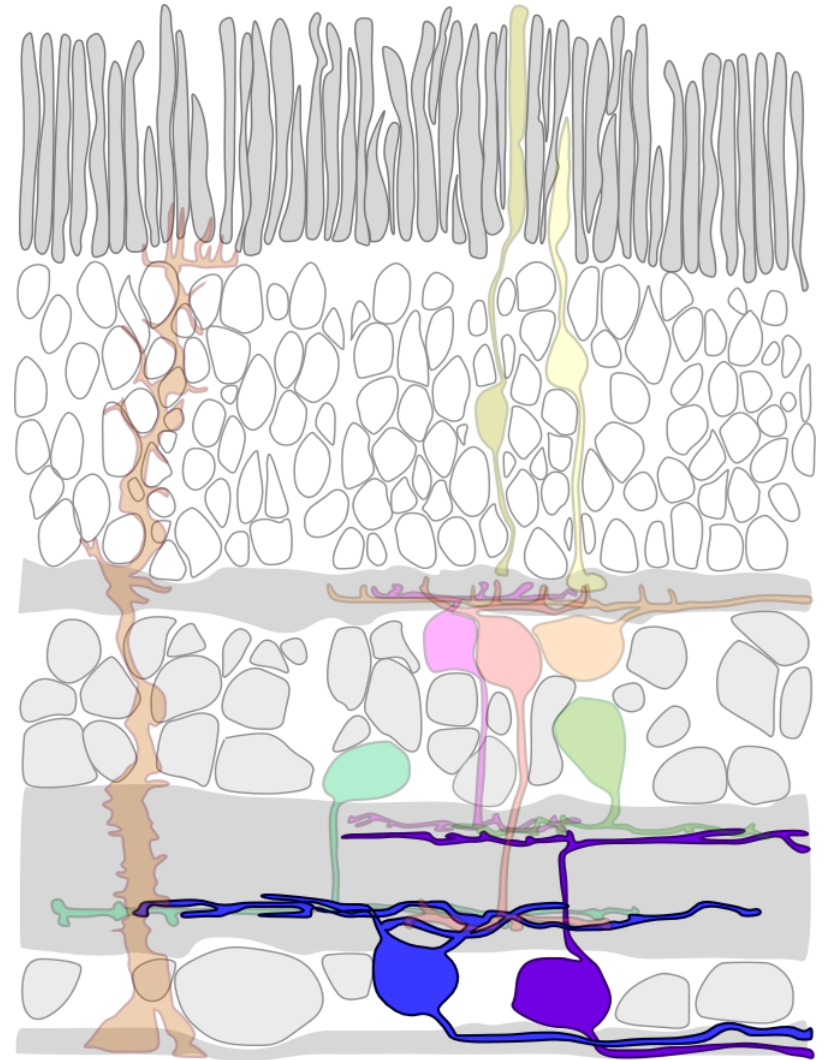
- 30-40 types of amacrine cells (or more)
- amacrine = “no axon” (Greek: a = “no” or “none”, makrós = “large” and ís (genitive of inós) = “fibre”)
- neuronal “hardware” in the inner retina
- graded, dual-transmitter neurons (GABA or glycine + a “rare” transmitter, e.g. dopamine, ACh, serotonin?, neuropeptides, ...)
- most use dendrites for synaptic input and output (dendritic processing)
- only few types functionally well understood (A2, A17, dopaminergic ACs, polyaxonal ACs, **starburst ACs**)



Retinal cell classes – Ganglion cells



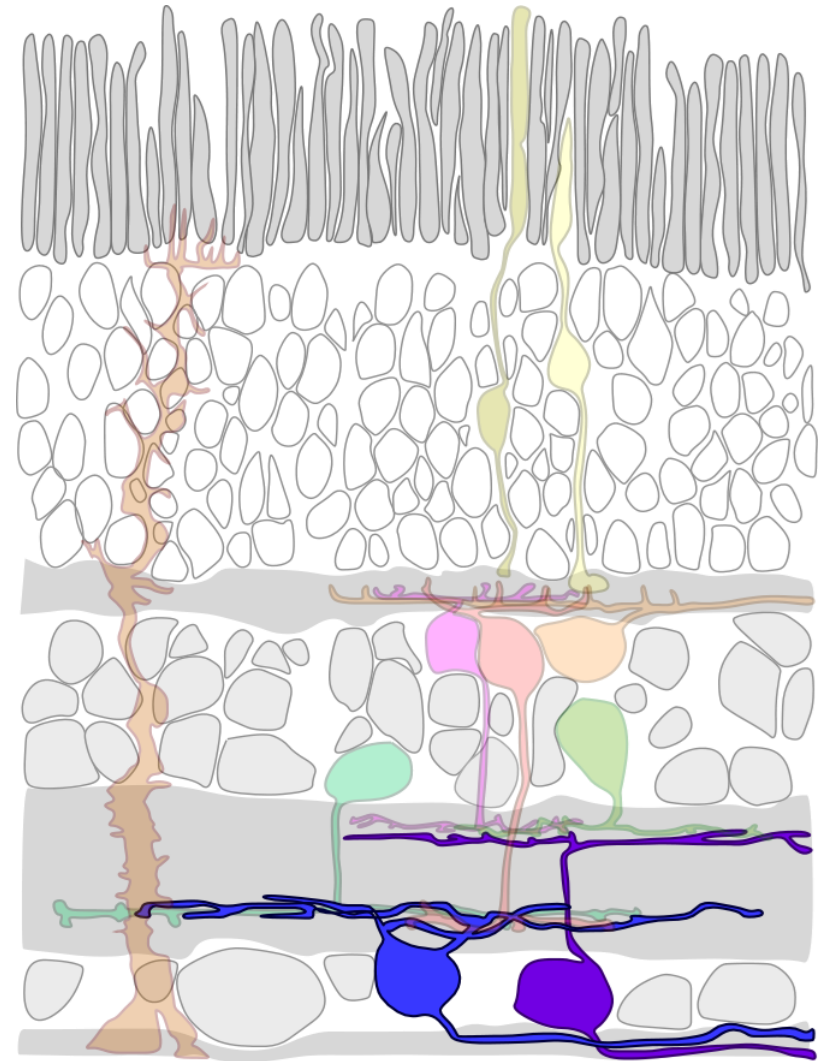
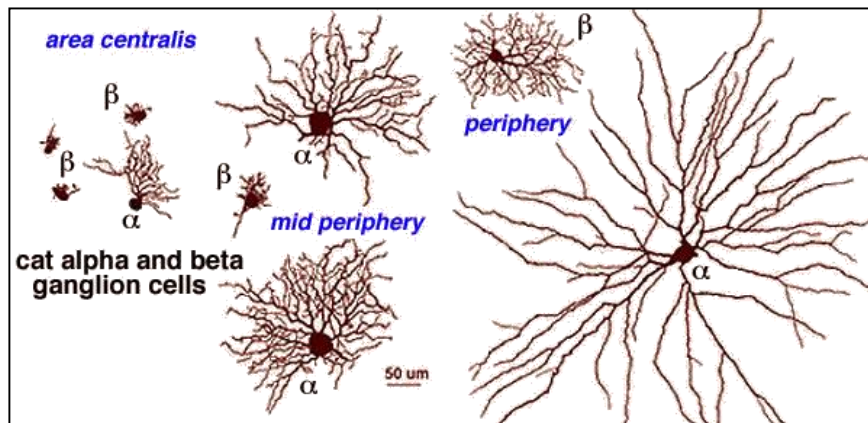
- 30-40 types of ganglion cells
- Retinal output neurons (no feed-back to the retinal interneurons); their axons compose the optic nerve
- Glutamatergic, spiking neurons (ganglion cells code the retinal output into spike trains)



Retinal cell classes – Ganglion cells



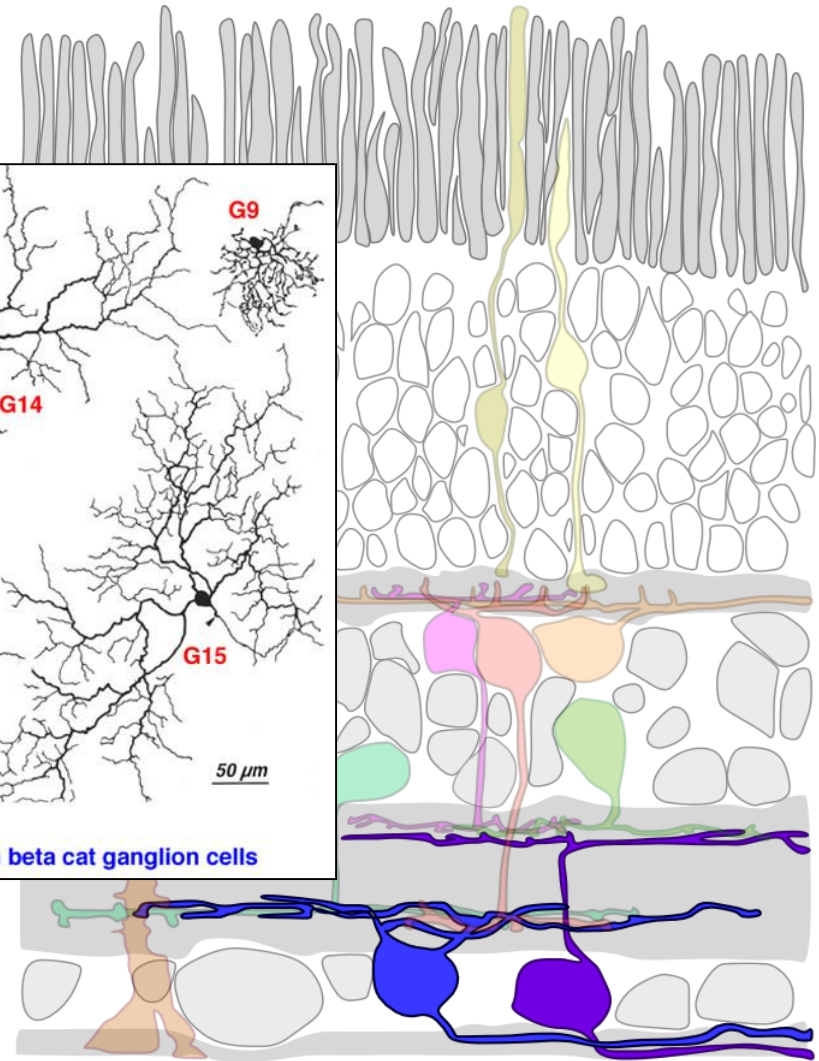
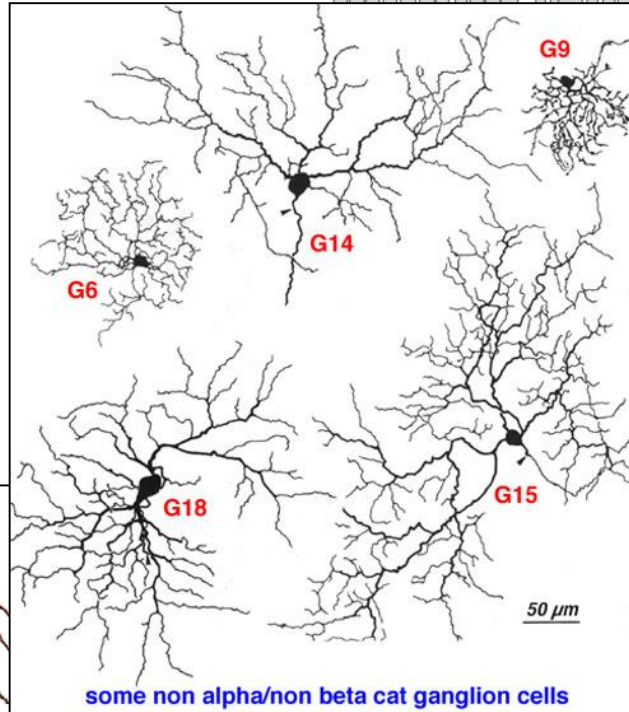
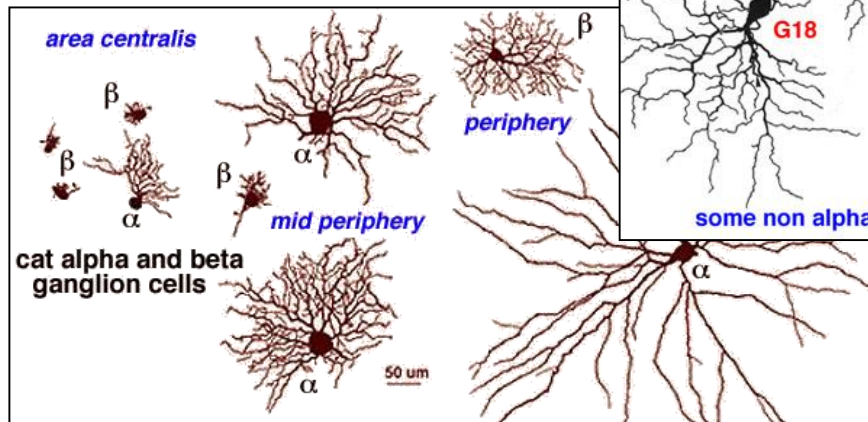
- 30-40 types of ganglion cells
- Retinal output neurons (no feed-back to the retinal interneurons); their axons compose the optic nerve
- Glutamatergic, spiking neurons (ganglion cells code the retinal output into spike trains)
- Dendritic field size/structure determines spatial resolution



Retinal cell classes – Ganglion cells



- 20-25 types of ganglion cells
- Retinal output neurons (no feed-back to the retinal interneurons); their axons compose the optic nerve
- Glutamatergic, spiking neurons (ganglion cells code the retinal output into spike trains)
- Dendritic field size/structure determines spatial resolution
- Ganglion cell types as feature detectors (e.g. edges, motion and its direction, orientation, absolute light level, “color”, ...)



Retina as a model system



Model system in three ways:

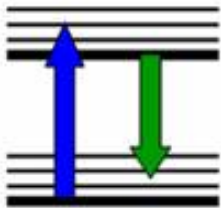
- 1) To understand how sensory, i.e. visual information is processed (the neuronal representation our brain uses to “understand” the visual world)
- 2) A “mini brain” in a dish, to understand neuronal computations
- 3) A convenient “brain slice” to study cellular functions of neurons (e.g. synaptic release, development of neurons etc.)

Two-photon laser microscopy

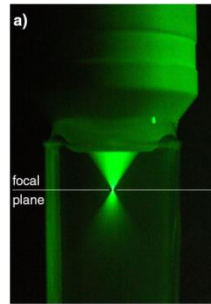


Problem: Use conventional light/confocal microscopy in a tissue that is light responsive → bleaching

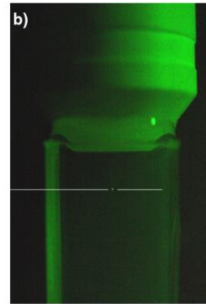
1-photon excitation



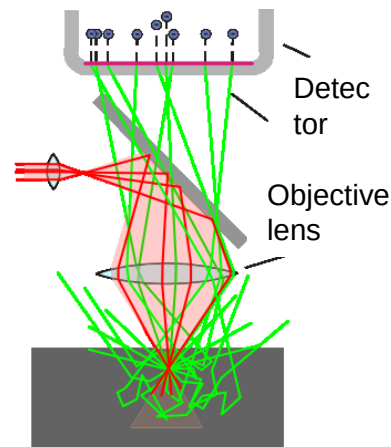
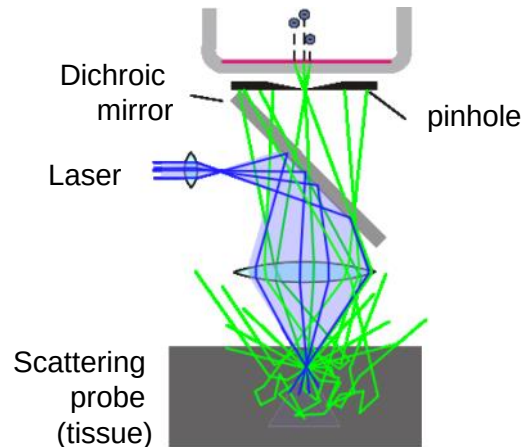
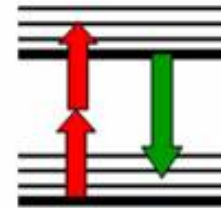
350-600 nm



700-1300 nm



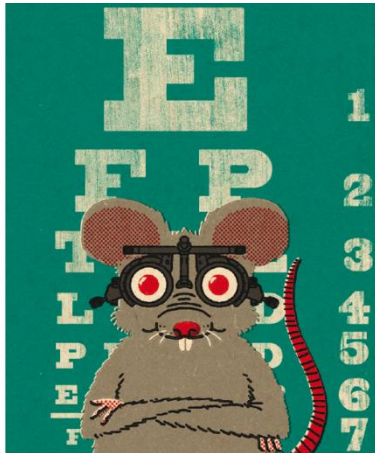
2-photon excitation



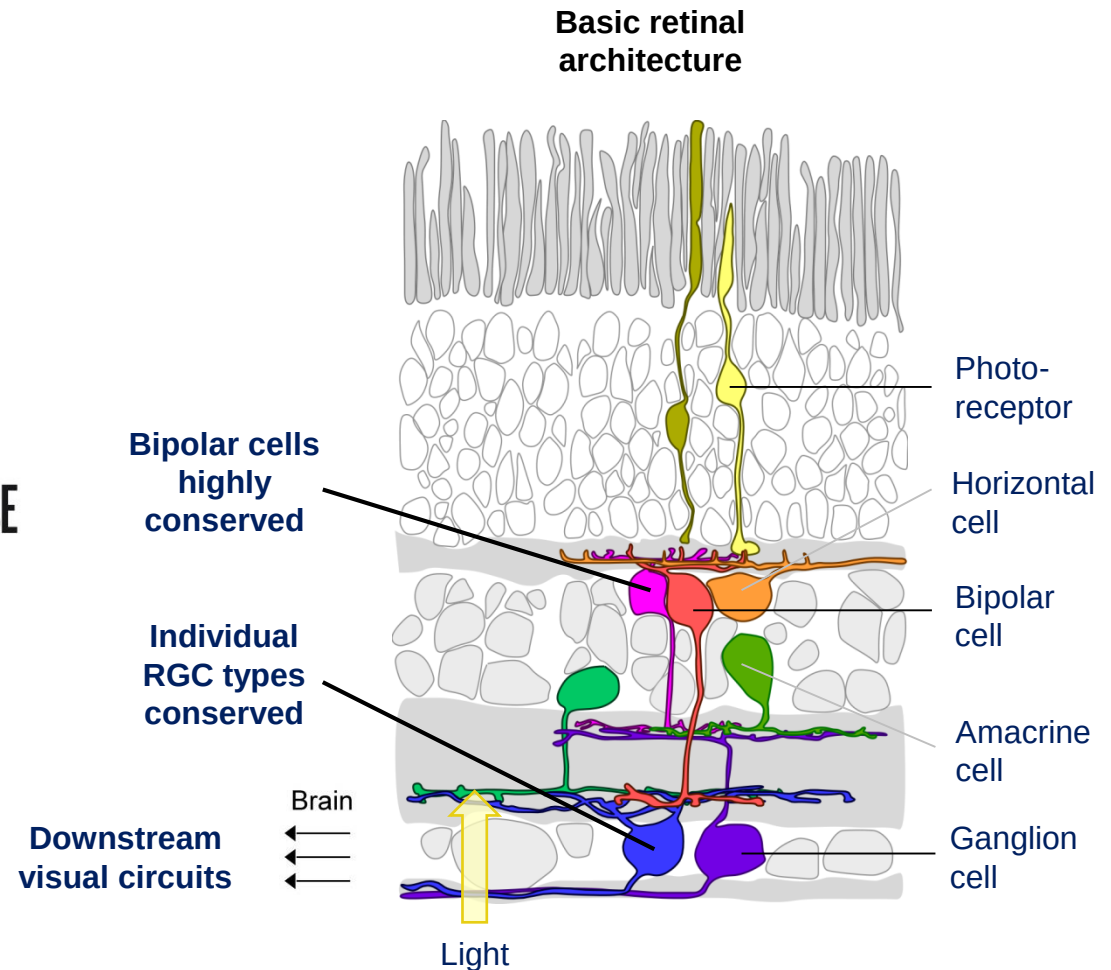
- Long wavelength: less direct activation of photoreceptors
- Requires very high power: 2-photon events only in focal volume, less indirect activation of photoreceptors
- Less scattering: deep imaging possible (not relevant for retina)

Species specific differences in retinal processing

The mouse is a good model system for the mammalian visual system and an adequate model for the human peripheral retina.



THROUGH THE EYES OF A MOUSE

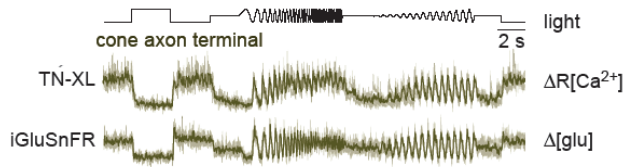


Species specific differences in retinal processing



Two-photon imaging of retinal activity

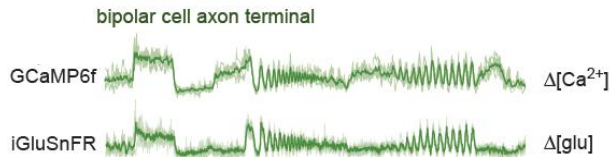
1) Output dynamics in cone photoreceptors



2) Feedback inhibition from horizontal cells



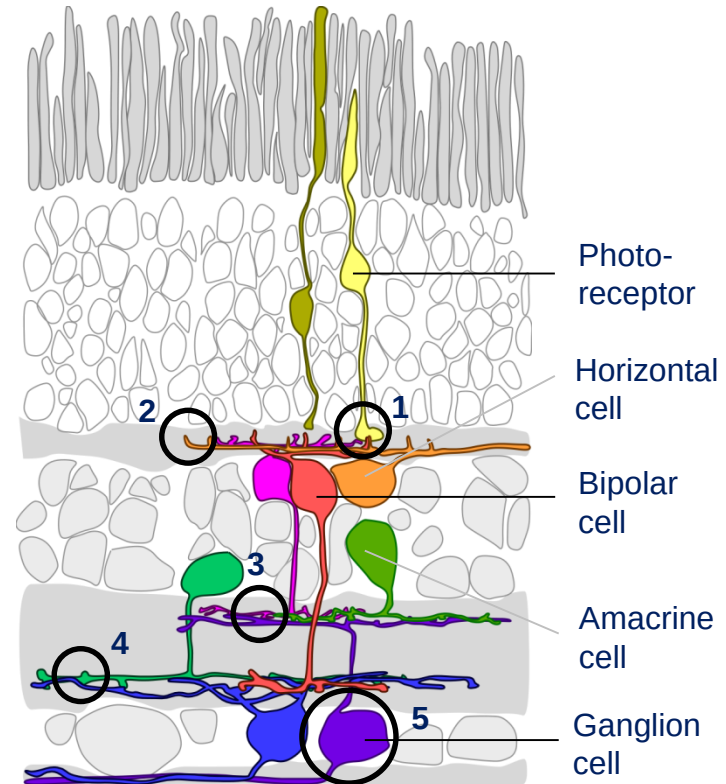
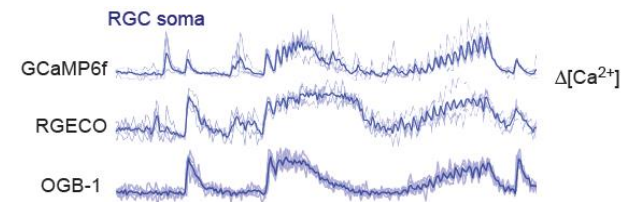
3) Bipolar cells as parallel channels



4) Mechanisms of dendritic computations in retinal ganglion cells

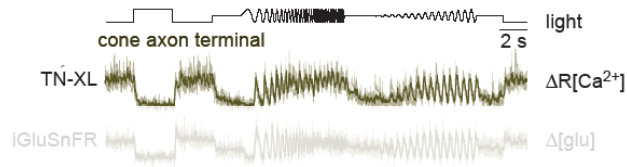


5) "Fingerprinting" retinal output



Two-photon imaging of retinal activity – Example 1

1) Output dynamics in cone photoreceptors



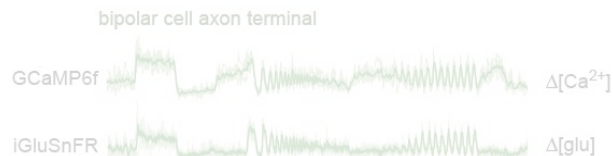
Cone outer segments

2) Feedback inhibition from horizontal cells



Cone somata

3) Bipolar cells as parallel channels



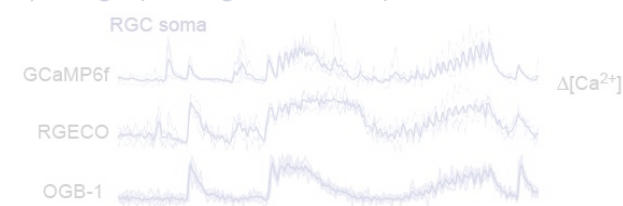
Cone axon terminals

4) Mechanisms of dendritic computations in retinal ganglion cells

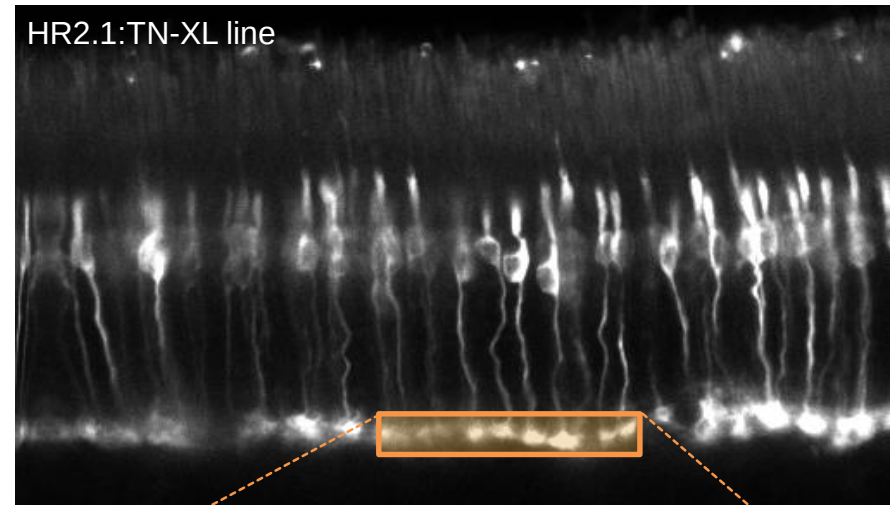


Calcium changes

5) "Fingerprinting" retinal output



Spectral identity (functional)

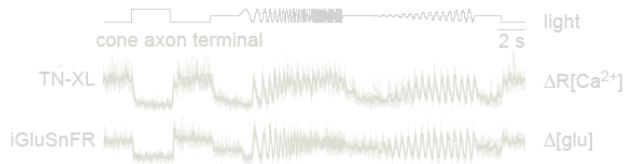


Average image



Two-photon imaging of retinal activity – Example 2

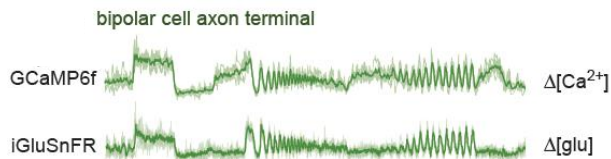
1) Output dynamics in cone photoreceptors



2) Feedback inhibition from horizontal cells



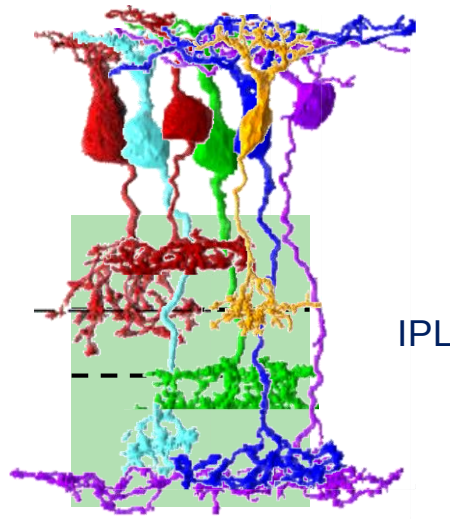
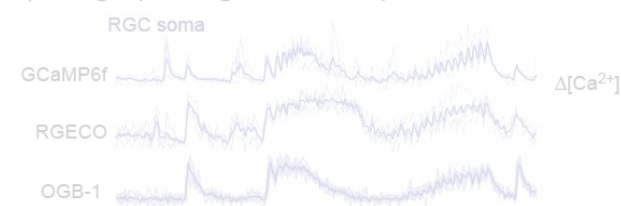
3) Bipolar cells as parallel channels



4) Mechanisms of dendritic computations in retinal ganglion cells



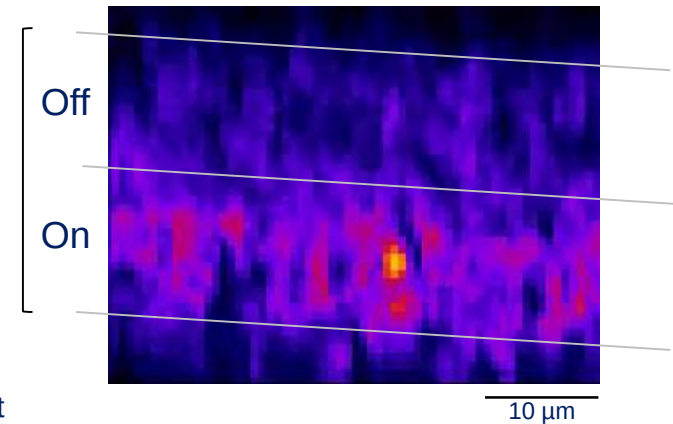
5) “Fingerprinting” retinal output



→ Record from all bipolar cell types at the same time across the whole synaptic layer

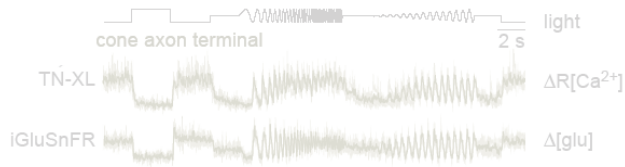
Chirp stimulus

Vertical optical slice of IPL using electrically tunable lens (ETL)



Two-photon imaging of retinal activity – Example 3

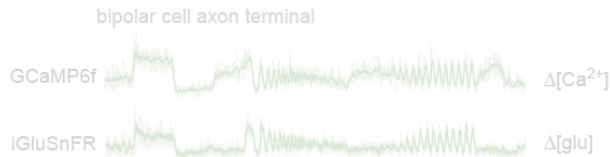
1) Output dynamics in cone photoreceptors



2) Feedback inhibition from horizontal cells



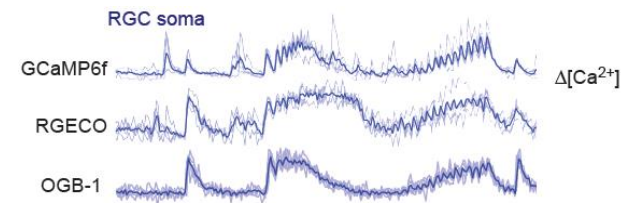
3) Bipolar cells as parallel channels



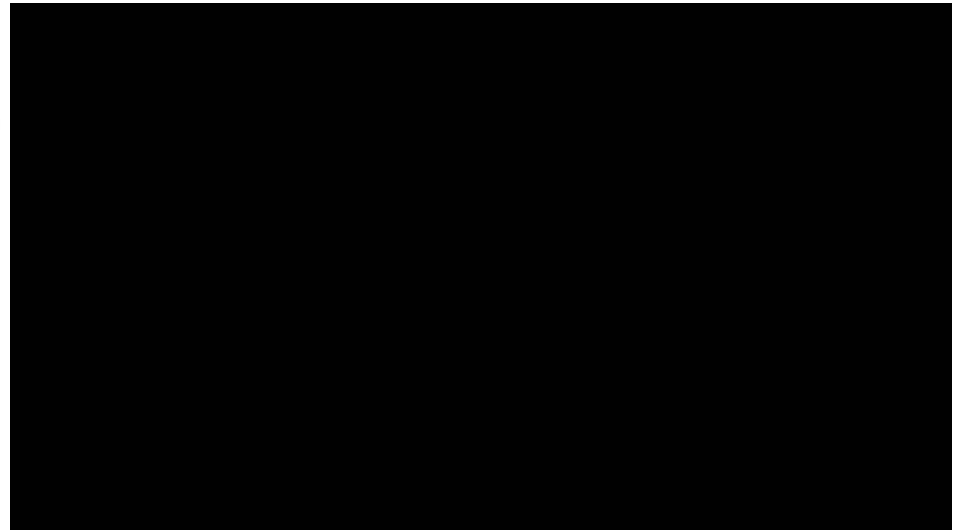
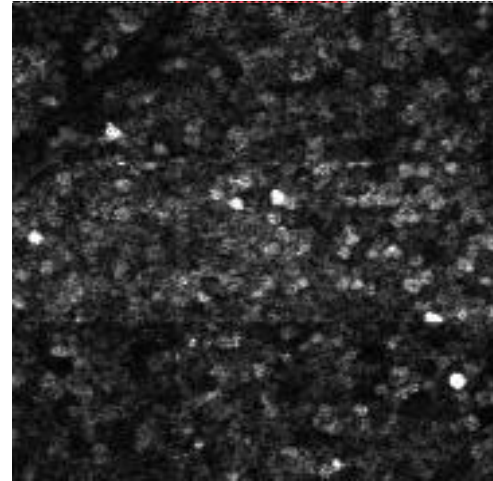
4) Mechanisms of dendritic computations in retinal ganglion



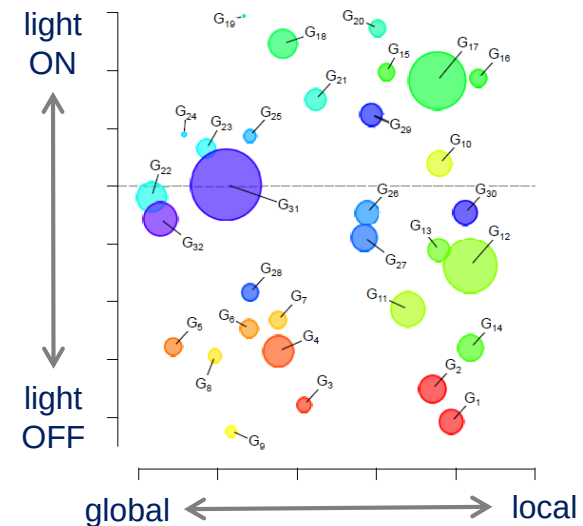
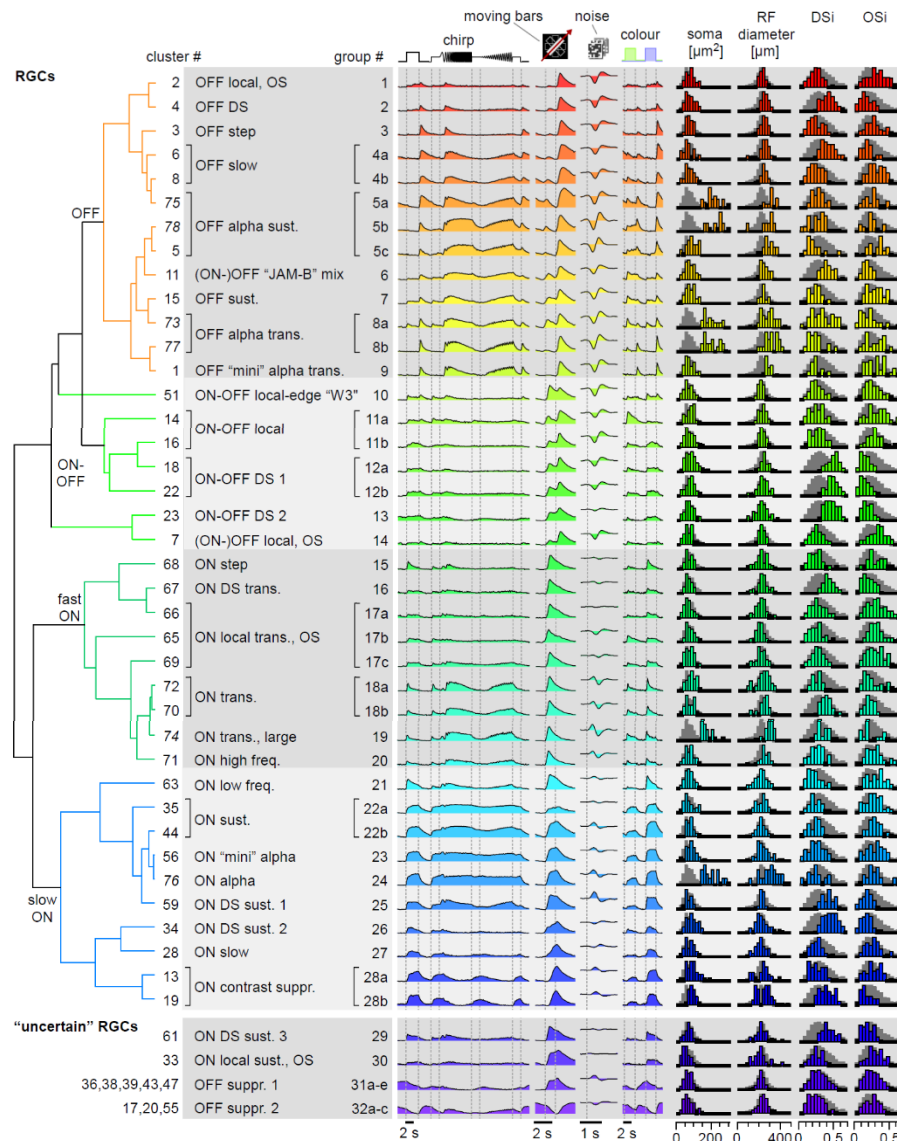
5) “Fingerprinting” retinal output



Ganglion cell layer cells labeled
with calcium dye OGB-1



Why >32 retinal channels to the brain?



Why >32 retinal channels to the brain?

PROCEEDINGS OF THE IRE

November

What the Frog's Eye Tells the Frog's Brain*

J. Y. LETTVIN†, H. R. MATURANA‡, W. S. McCULLOCH||, SENIOR MEMBER, IRE,
AND W. H. PITTS||

The “bug detector”:

“The operations thus have much more the flavor of perception than of sensation if that distinction has any meaning now. That is to say that the language in which they are best described is the language of complex abstractions from the visual image. We have been tempted, for example, to call the convexity detectors “bug perceivers.” Such a fiber responds best when a dark object, smaller than a receptive field, enters that field, stops, and moves about intermittently thereafter. The response is not affected if the lighting changes or if the background (say a picture of grass and flowers) is moving, and is not there if only the background, moving or still, is in the field. Could one better describe a system for detecting an accessible bug?”

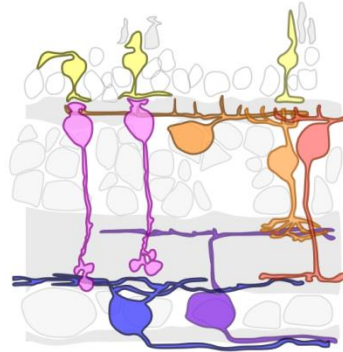
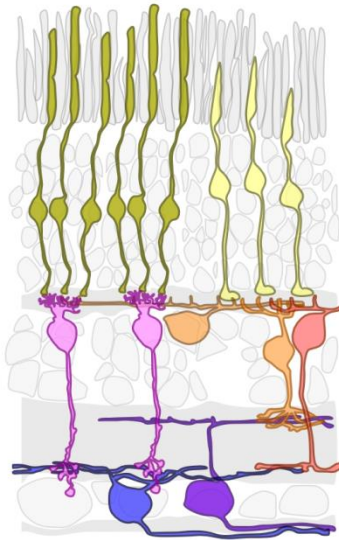


Retinal degeneration



Wild type retina

Degenerated retina



← Photoreceptor cell death

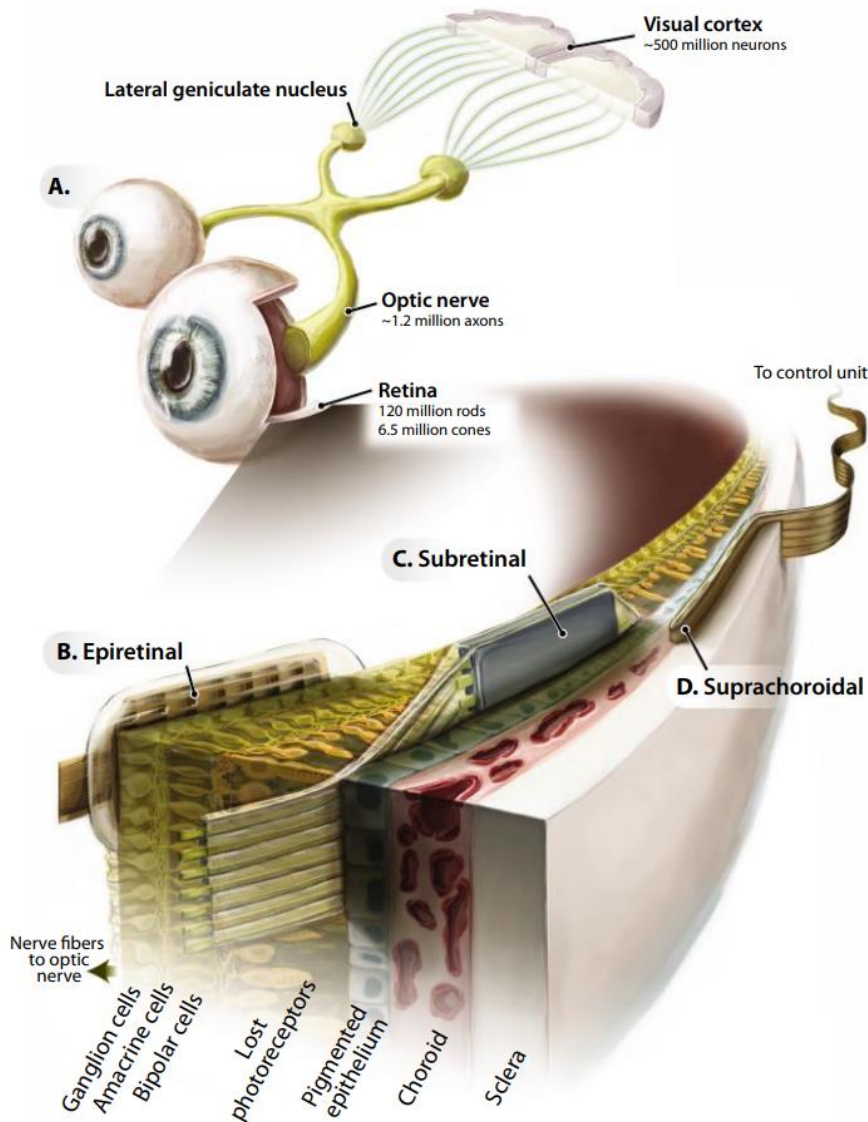
← Intact inner retinal circuits

← Optogenetic and implant approaches for vision repair

Retinal degeneration: Retinitis pigmentosa



<http://www.pro-retina.de/simulation/retinitis-pigmentosa>



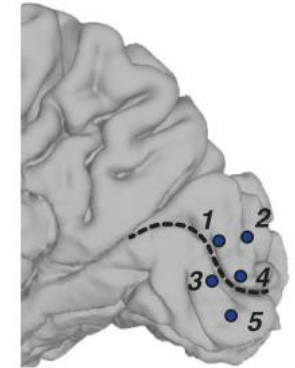
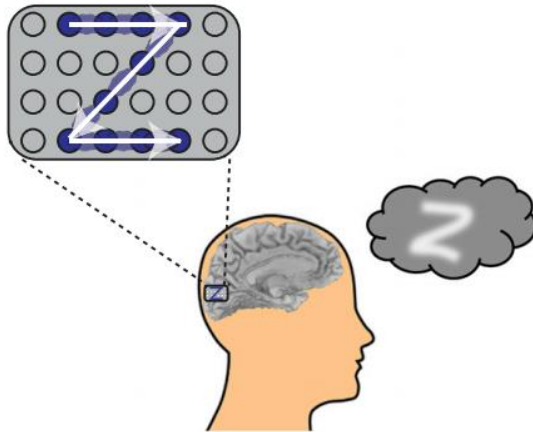
Epiretinal:
Stimulate retinal ganglion cell layer

Subretinal:
Stimulate remaining photoreceptors
and bipolar cells

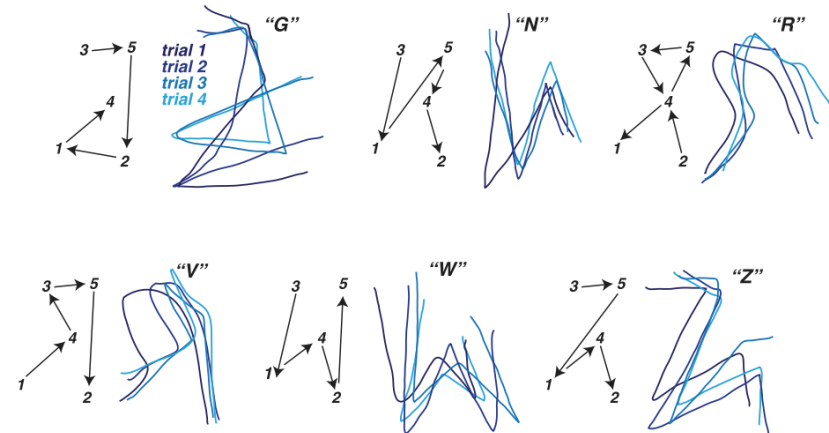
Retinal degeneration: Cortical implants



Dynamic current steering



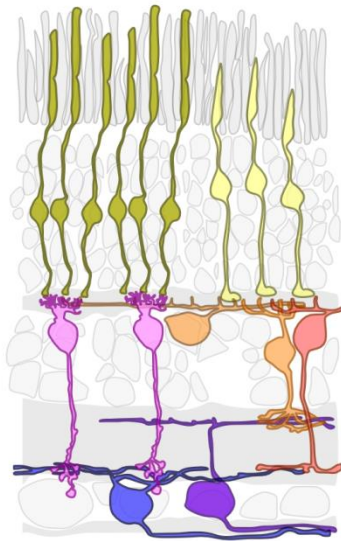
stimulation drawing



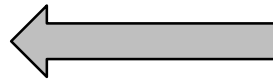
Treating the diseased retina requires basic research



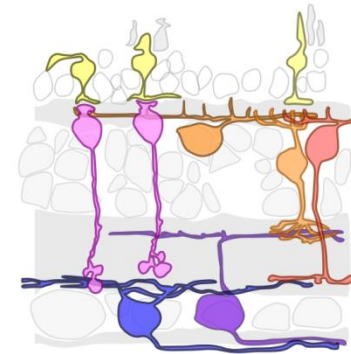
Wild type retina



Restoring physiological function
requires to thoroughly understand
signal processing in the healthy retina!



Degenerated retina



Watching experiments:

On Thursday (30.6.22) at 9:30 am

The meeting point is at the entrance of the CIN building

→ Read the script

