Neural coding in the retina

Olivier Marre

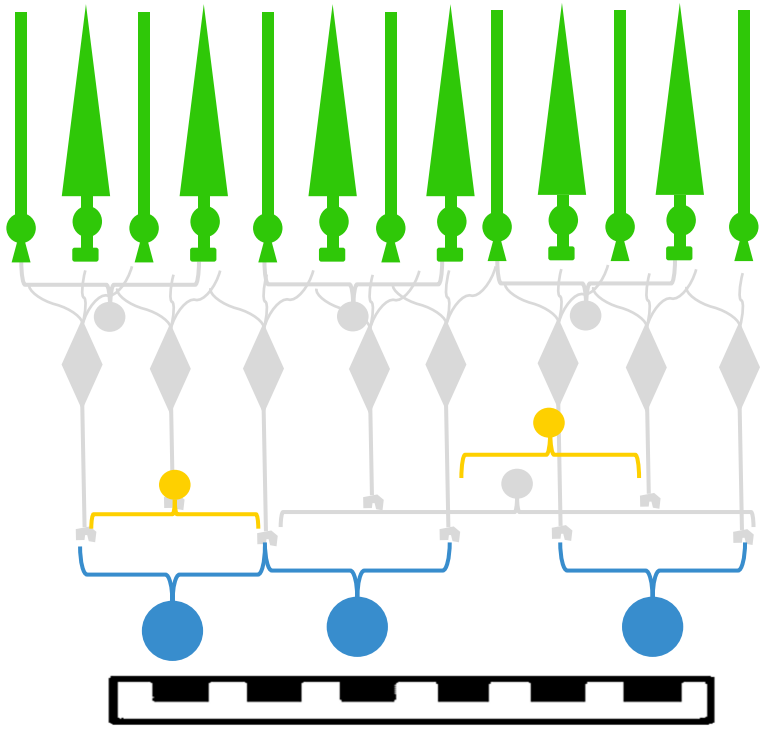
Institut de la Vision, INSERM – Sorbonne Université, Paris

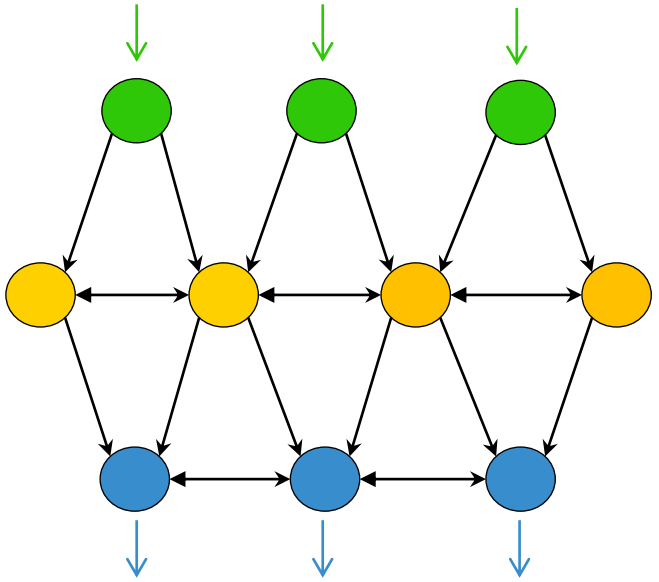


Retinal circuit and computations











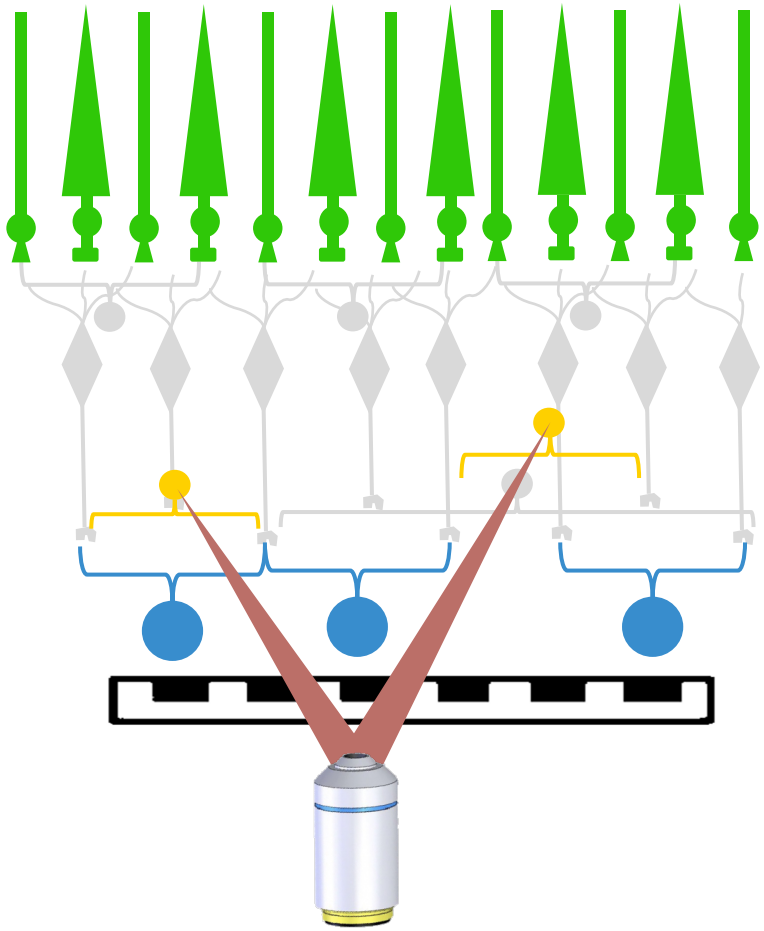


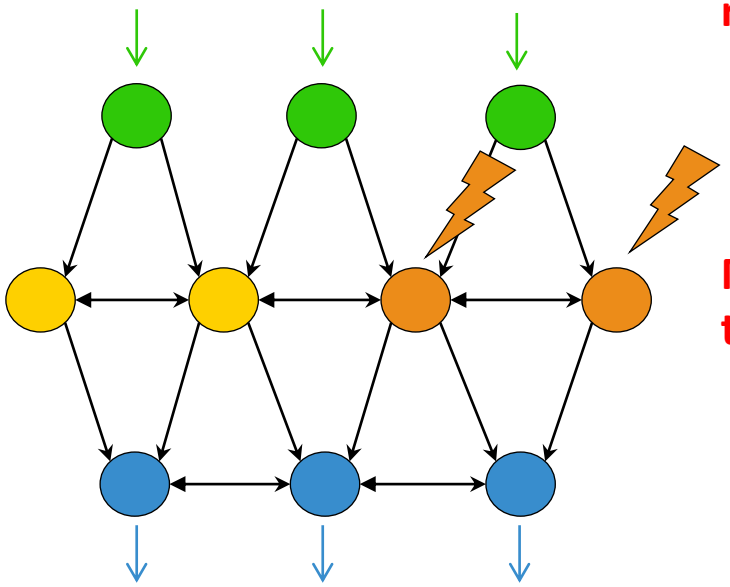
Predict how ganglion cells respond to natural stimuli.

Retinal circuit and computations













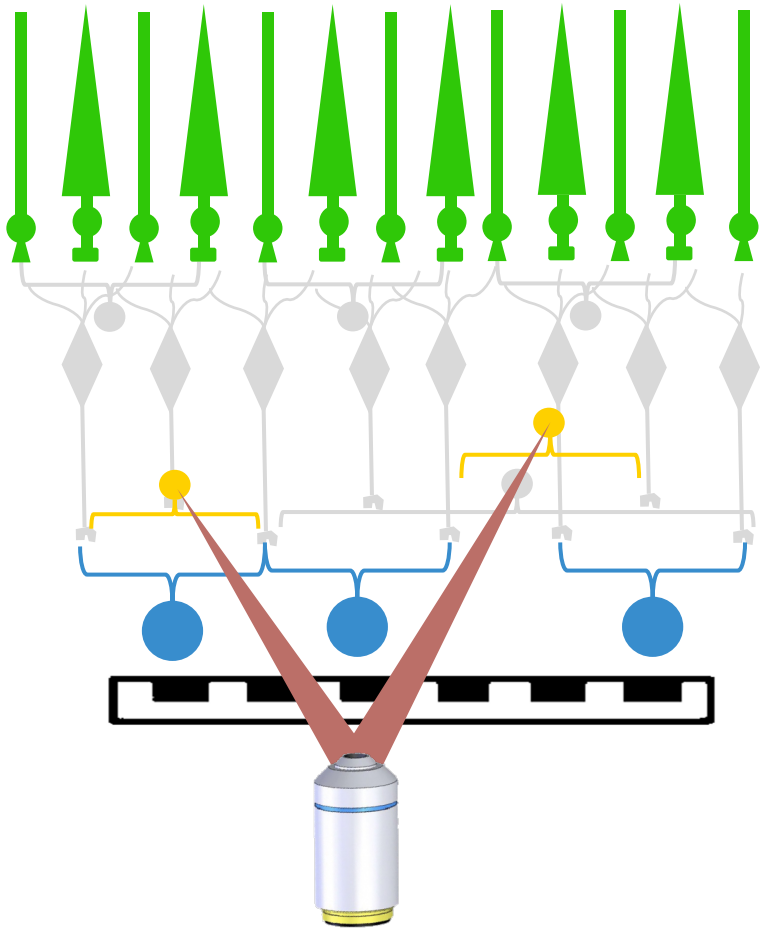
Predict how ganglion cells respond to natural stimuli.

Map the model component to the retinal circuit.

Retinal circuit and computations

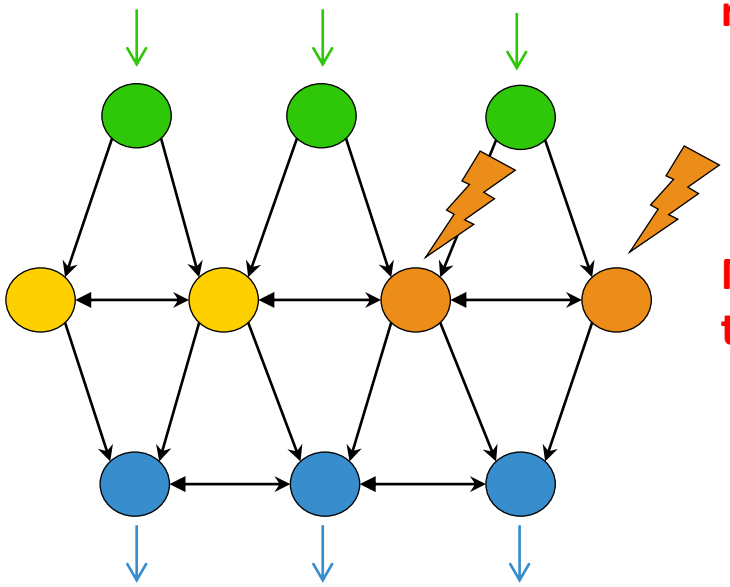












Predict how ganglion cells respond to natural stimuli.

Map the model component to the retinal circuit.

Also: preventing and curing blindness (myopia control and vision restoration with optogenetics)

V1: Hubel and Wiesel

https://www.youtube.com/watch?v=8VdFf3egwfg&t=118s

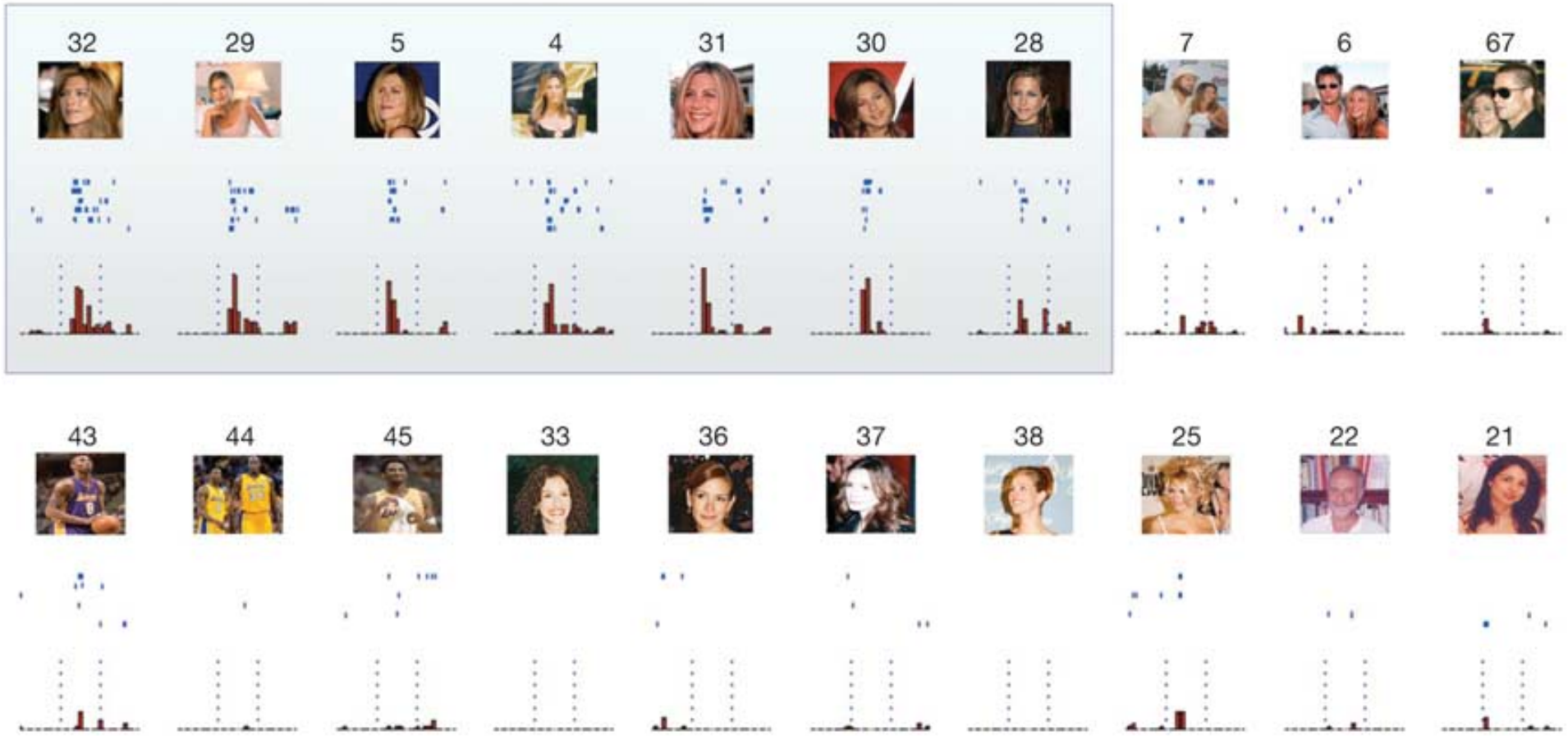
2 problems

2 problems

- How much do responses to bars tell us about responses in natural environment ?

- Is this really selectivity ?

Limits of single cell selectivity



Quian-Quiroga et al, 2005

2 problems

- How much do responses to bars tell us about responses in natural environment ?
- Is this really selectivity ?
- You also need invariance.
- Modeling is essential.

Why do we need models of sensory computation?

Why do we need models of sensory computation?

- We want a **compact** mathematical description of how neurons process stimuli, that can **generalize to complex stimuli** (ideally natural scenes).

- From this mathematical description we can derive predictions (responses to specific stimuli) and we can ask questions about implementation (mechanisms, circuits…example: Direction Selective ganglion cells).

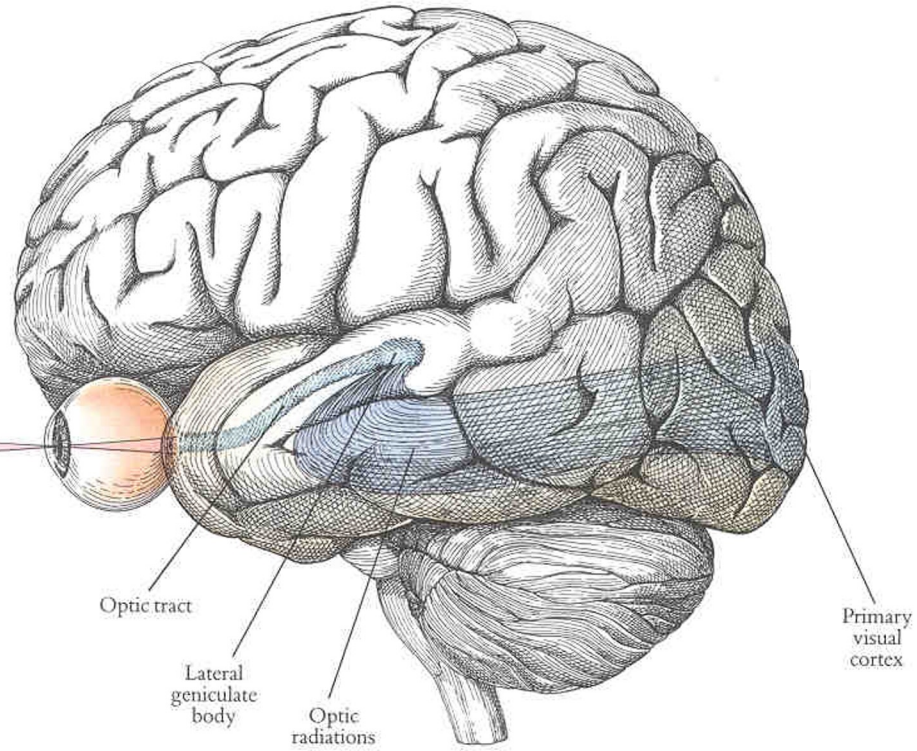
Barlow and Levick, 1965
Euler et al, 2002
Briggman et al, 2011

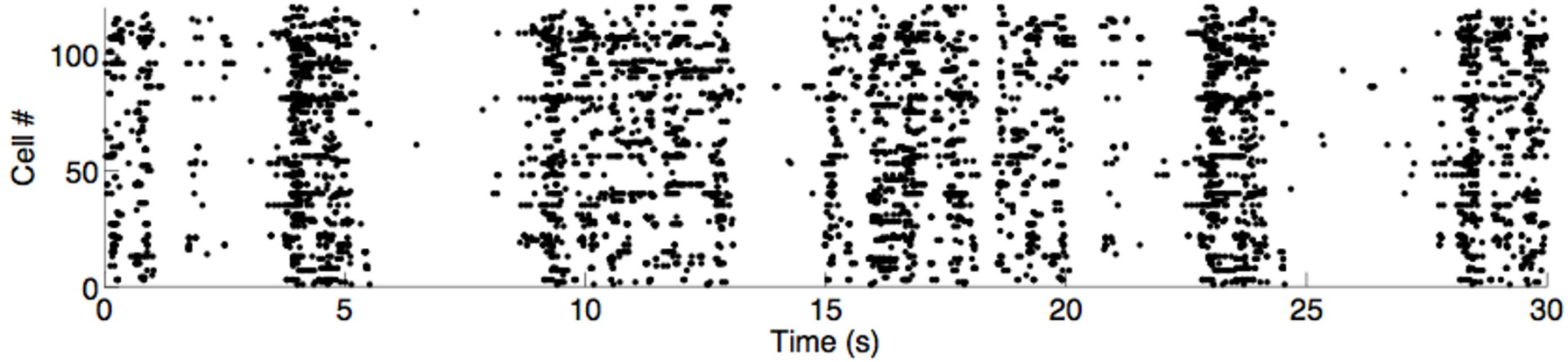
- We might be able to relate them to some behaviours.

Neural coding

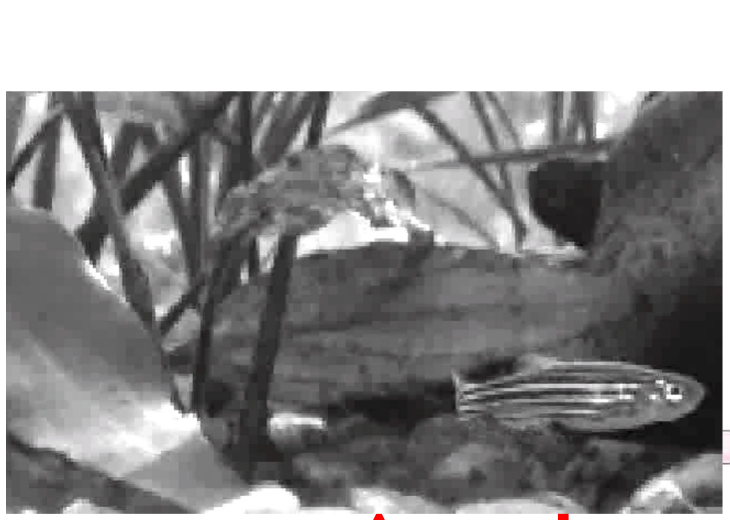


?

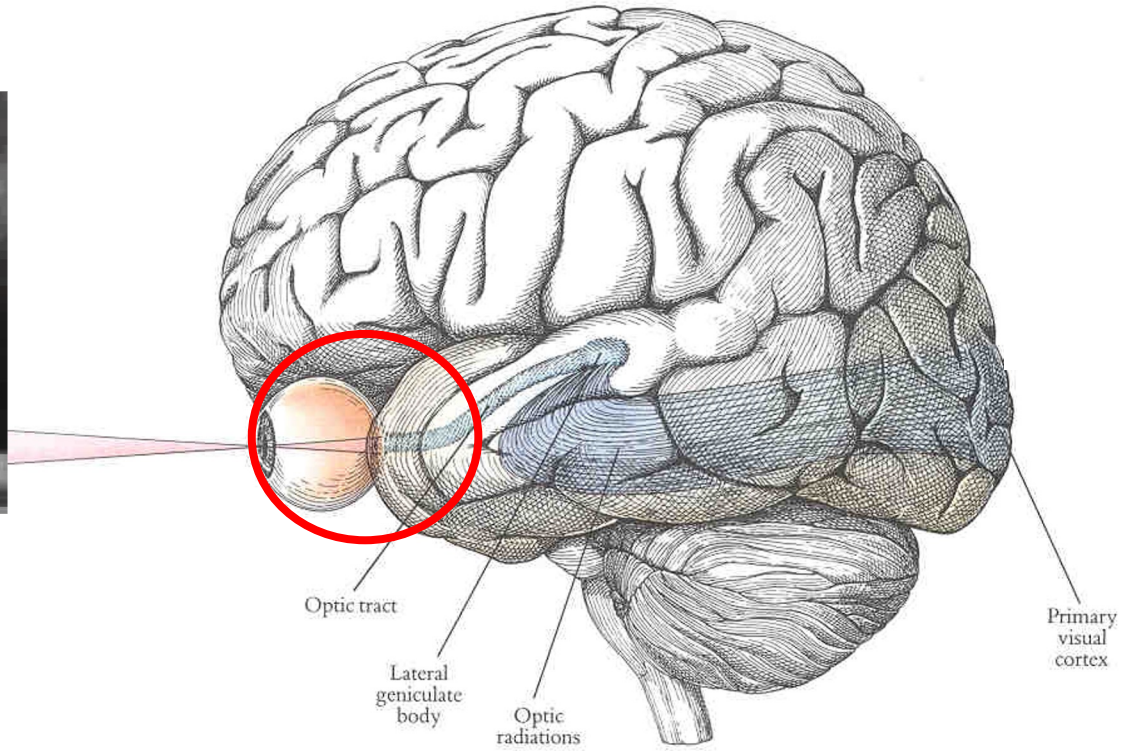


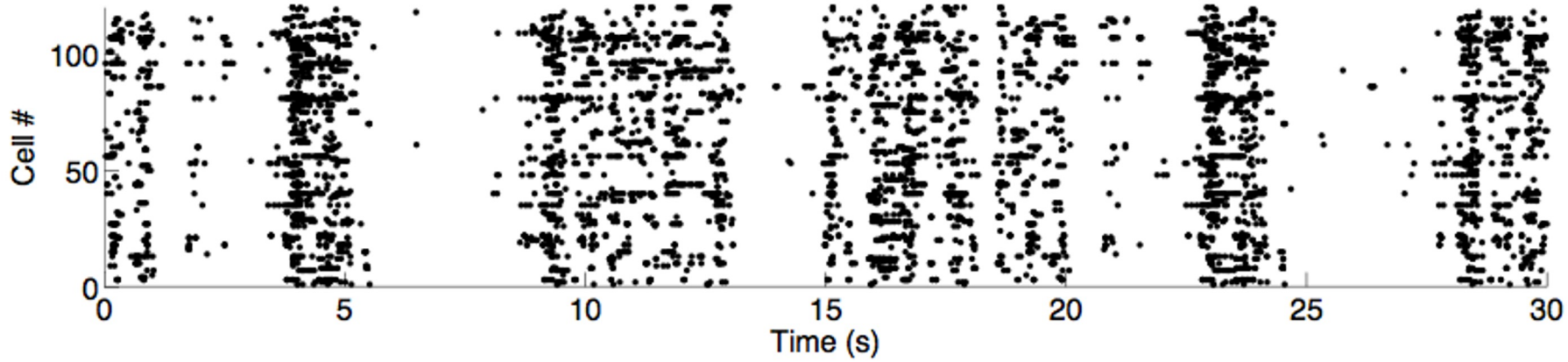


Neural coding in the retina



?

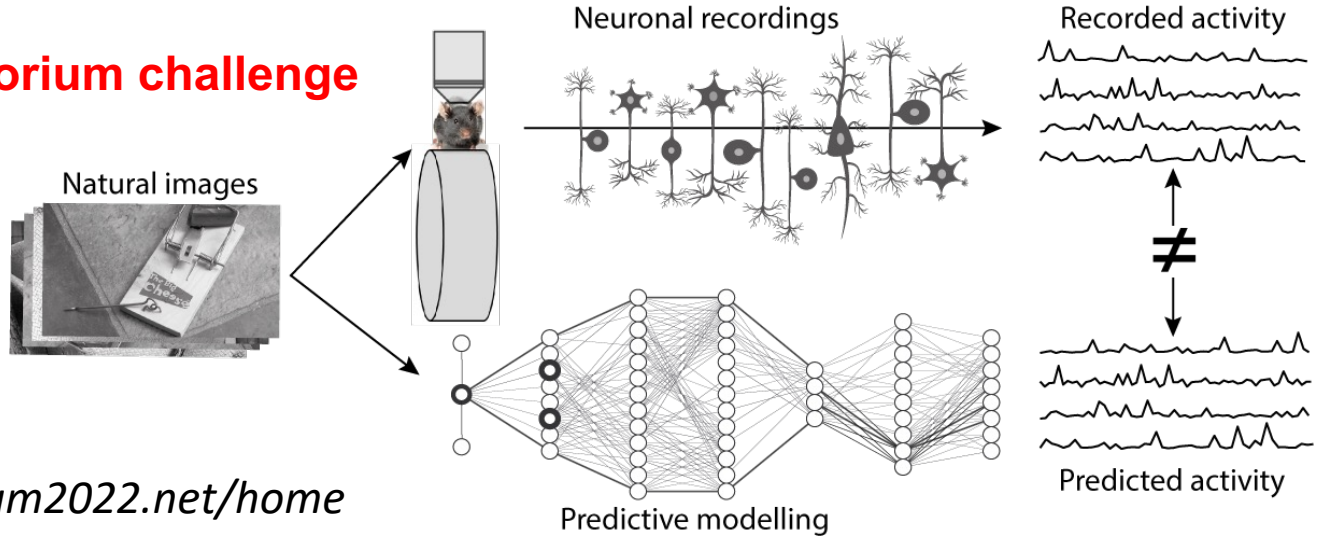




Two complementary approaches

- Define the architecture of the model, learn the parameters, then test it on responses to other stimuli.

The sensorium challenge



https://sensorium2022.net/home

- Design stimuli to exclude some model architecture (and find what is missing).

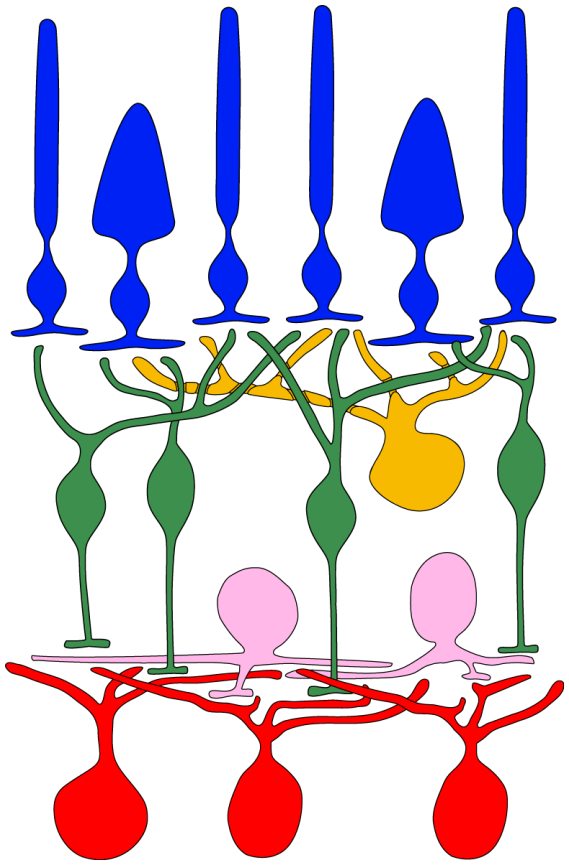
The classical view of the retina

Side view



Visual Input

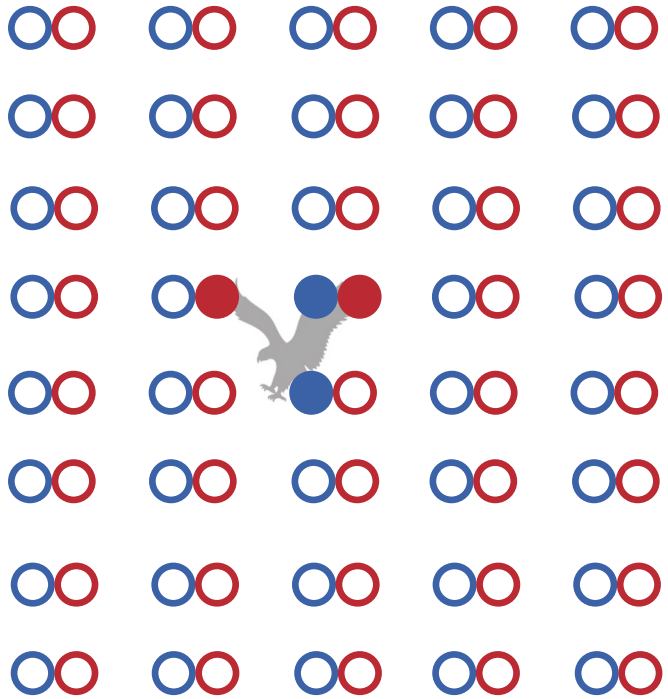




Response Output



Flat view (ganglion cells)



Ganglion cells encode different visual features.

What are these features?

The classical view of the retina

Side view



Visual Input

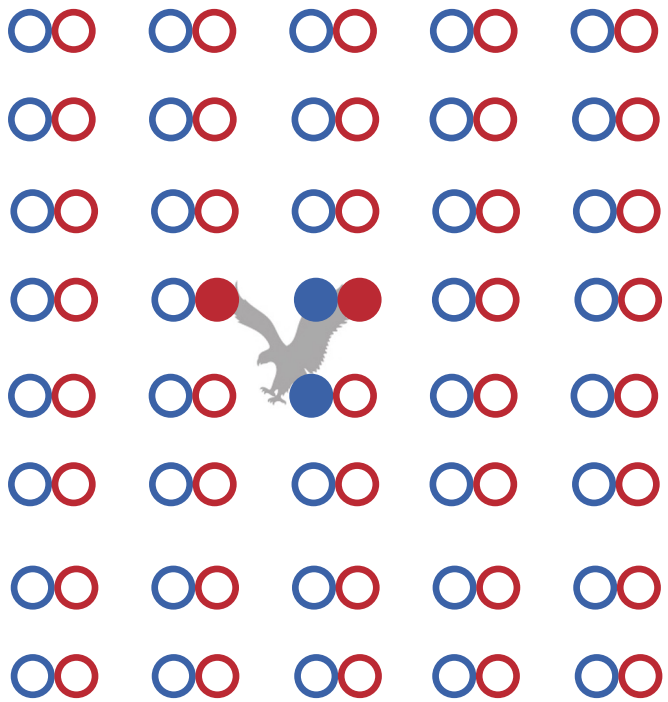
photo-receptors

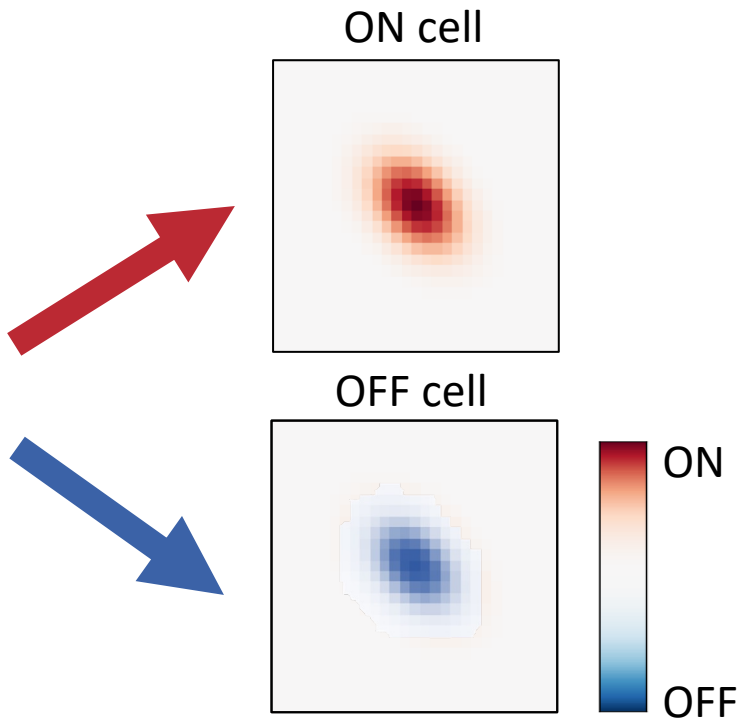
Bipolar
Horizontal
Amacrine
cells

ganglion cells

Response Output

Flat view (ganglion cells)



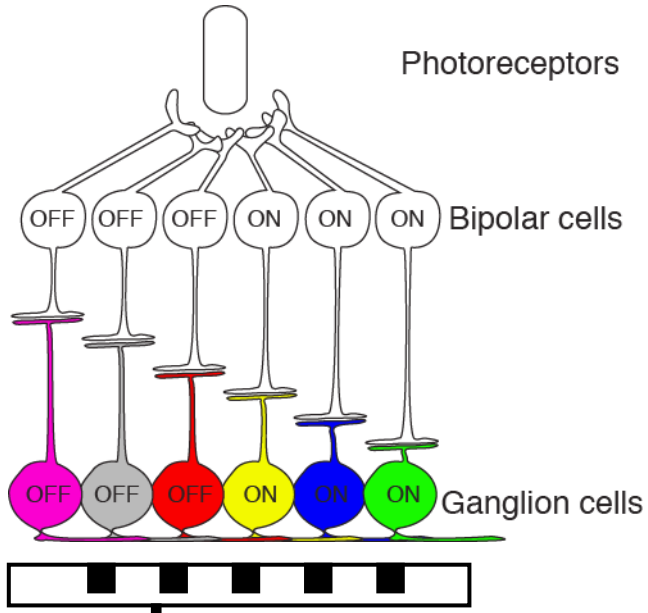


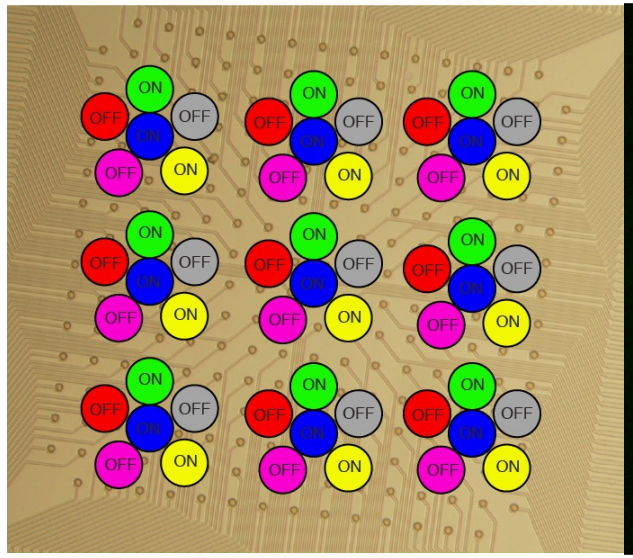
Different ganglion cell types.
Different selectivities for polarity and size.

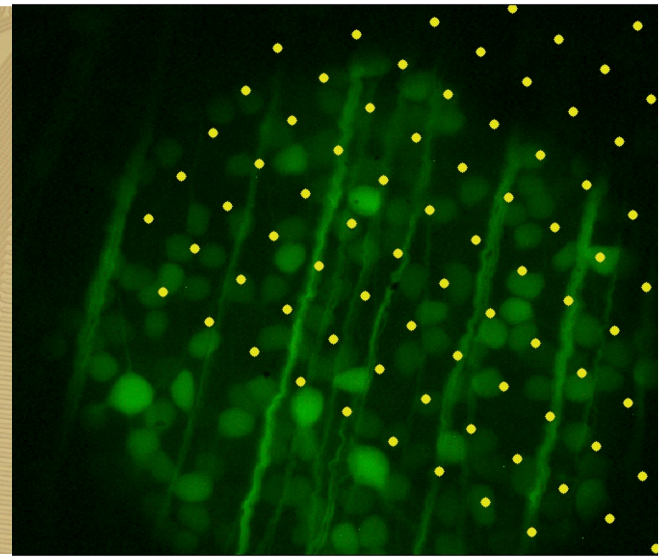
Large-scale recordings in the retina

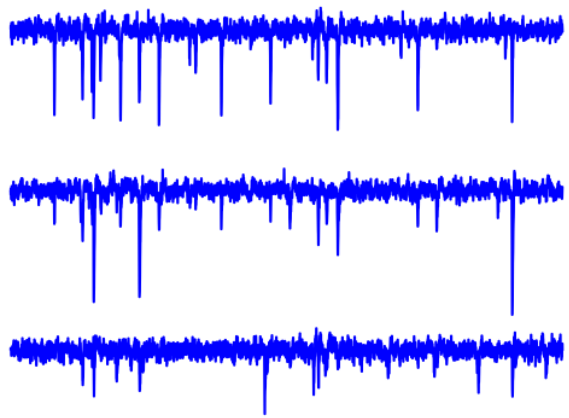




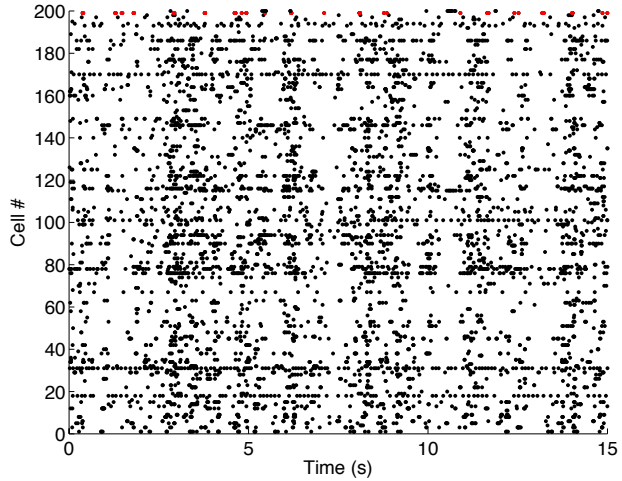








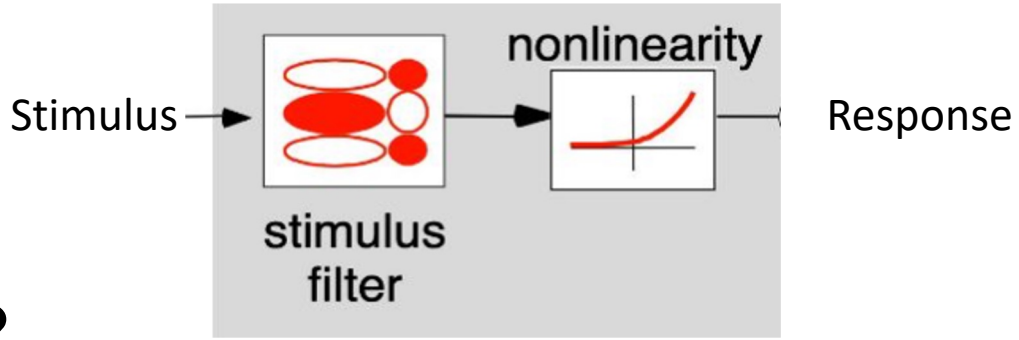




Yger et al, 2018

The LN model

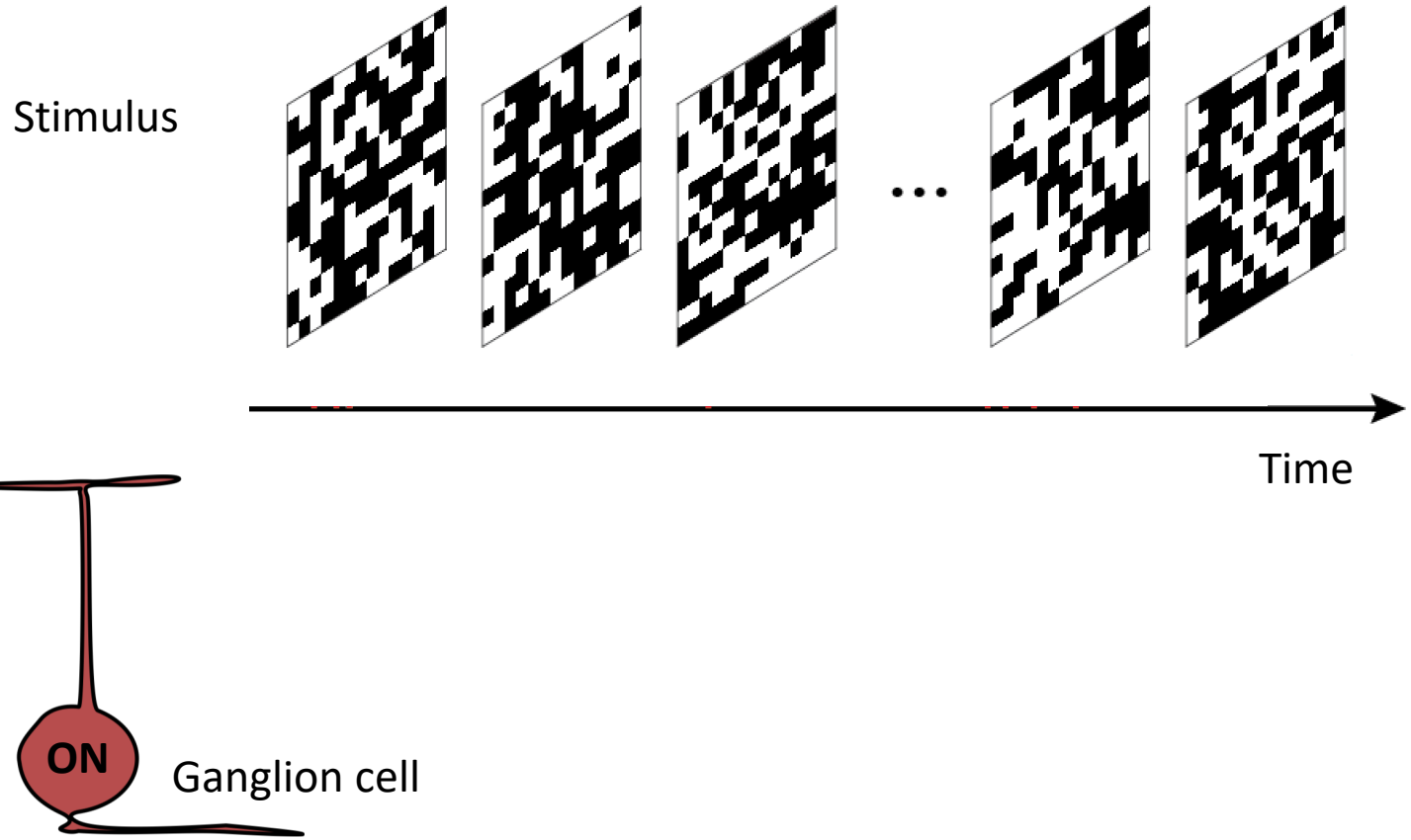
- Linear filter + non linearity



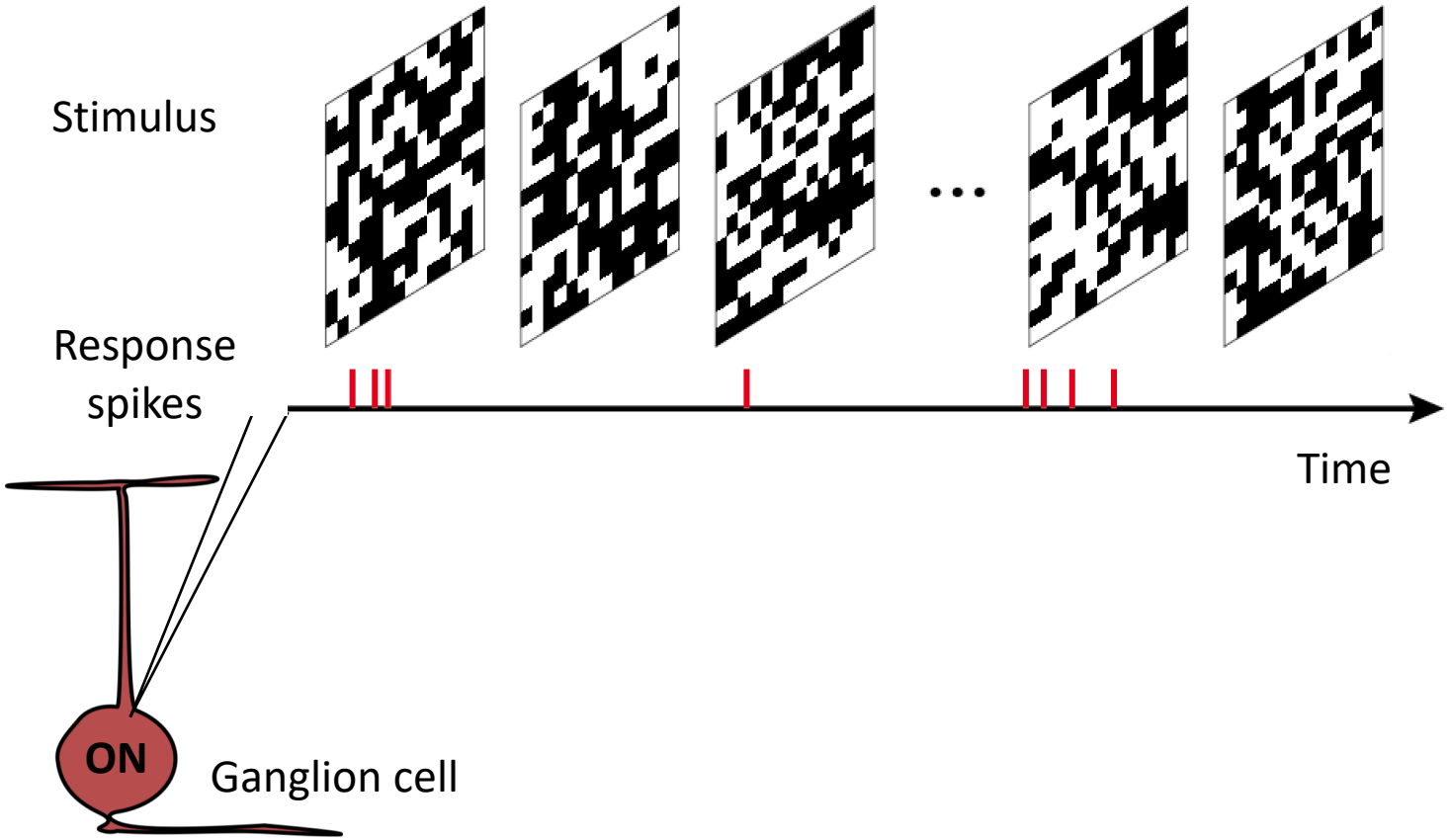
- How to estimate its parameters ?

- If the stimulus is a white noise, estimate the Spike Triggered Average.

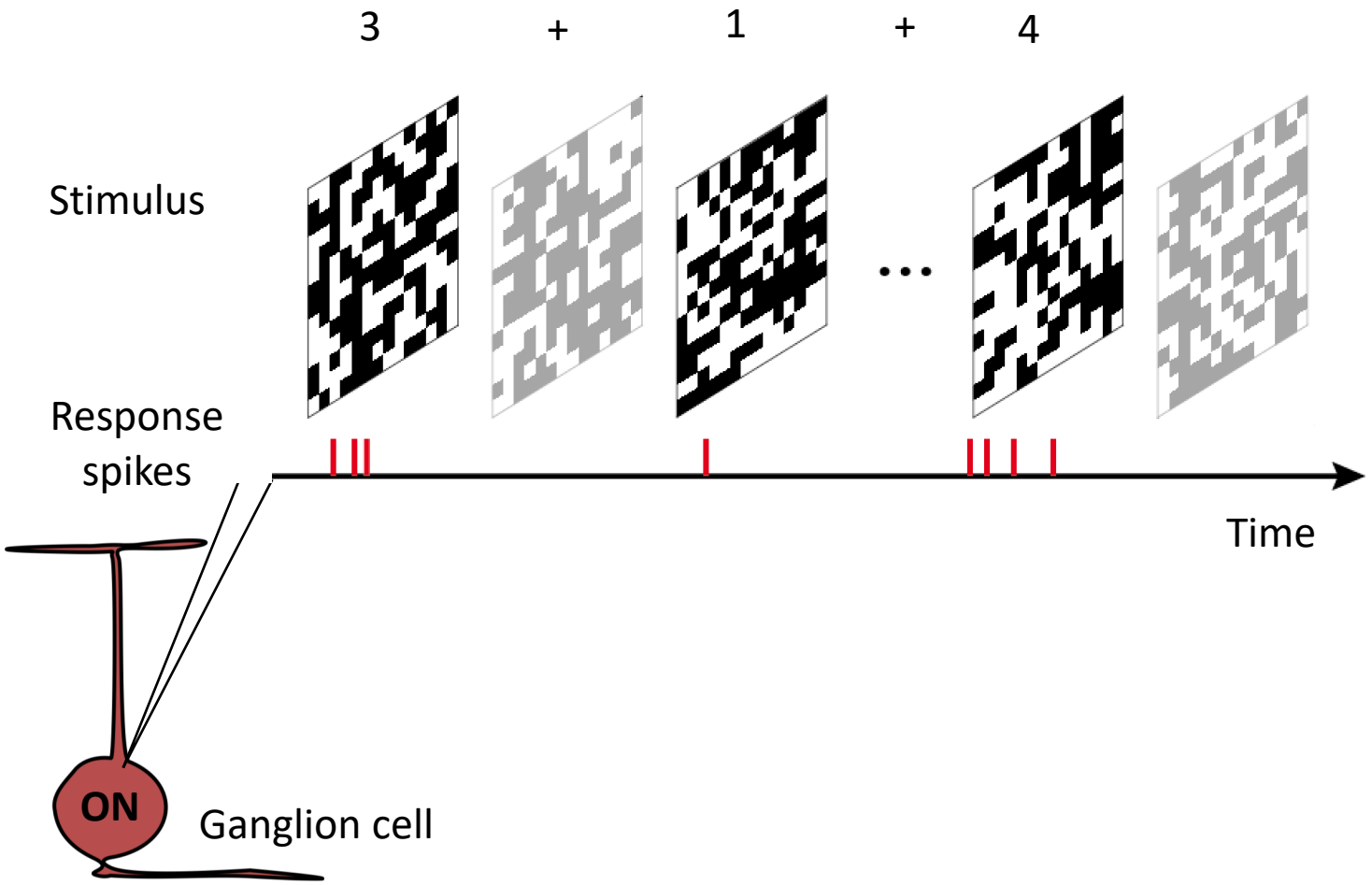
How to measure receptive fields?



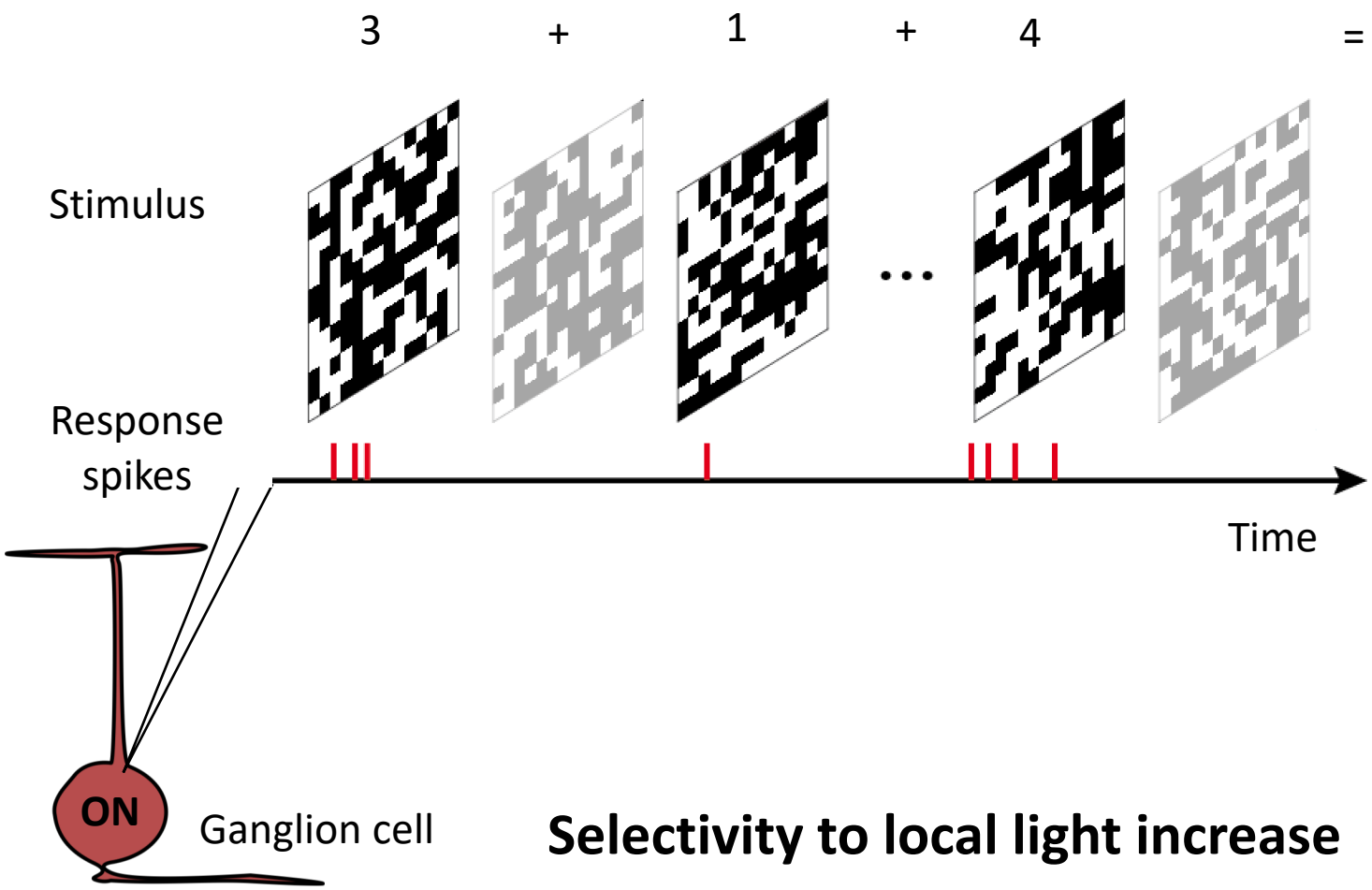
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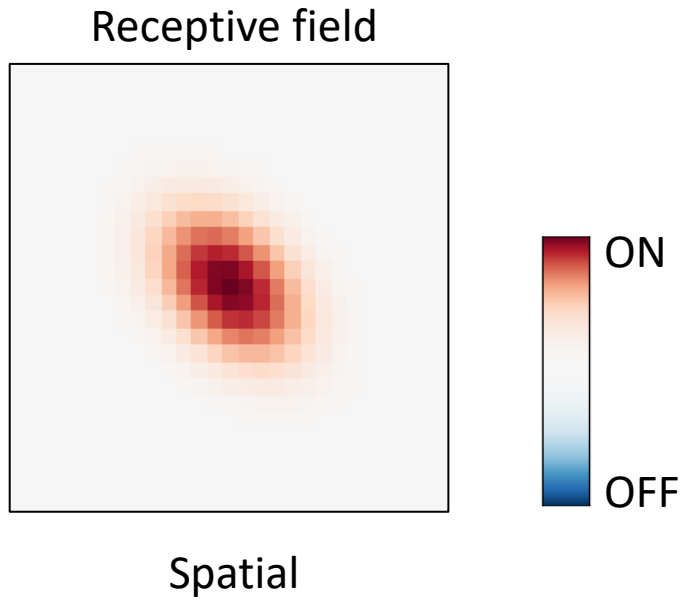


How to measure receptive fields?



How to measure receptive fields?



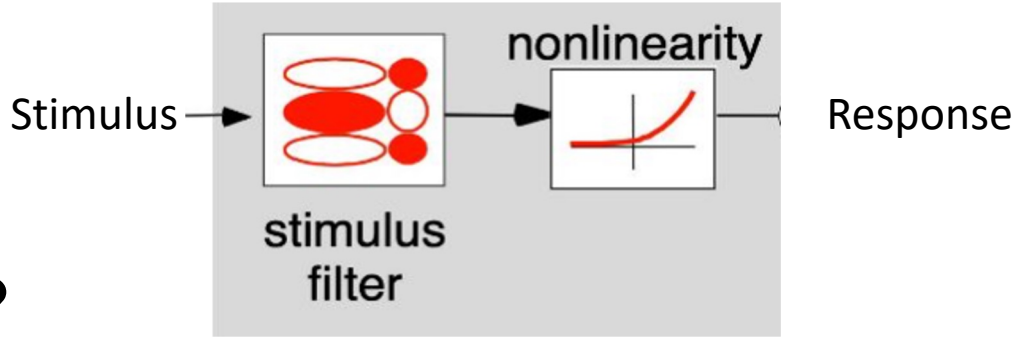


This is called STA
(Spike Triggered Average)

Selectivity to local light increase

The LN model

- Linear filter + non linearity



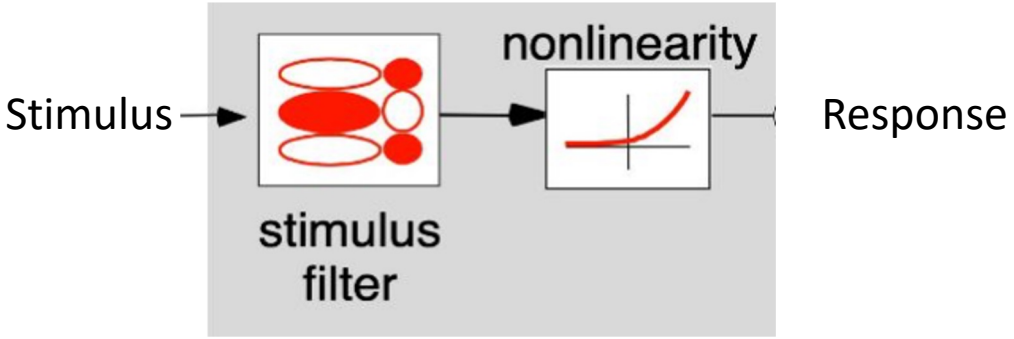
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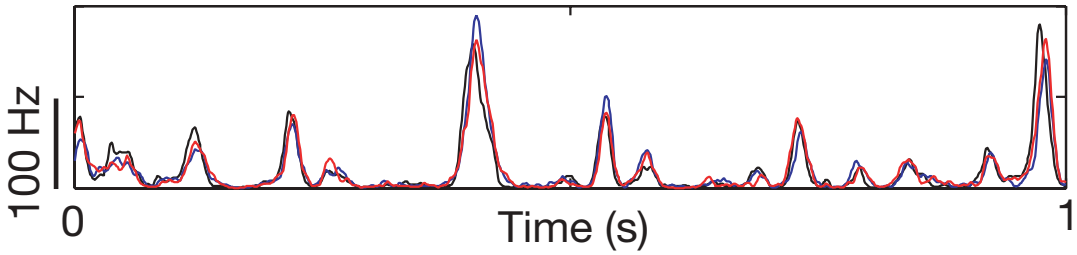
- If not, beware of stimulus correlations ! MLE estimator or related methods (https://pillowlab.princeton.edu/pubs/Pillow_BBchap07.pdf).

The LN model: does it work ?

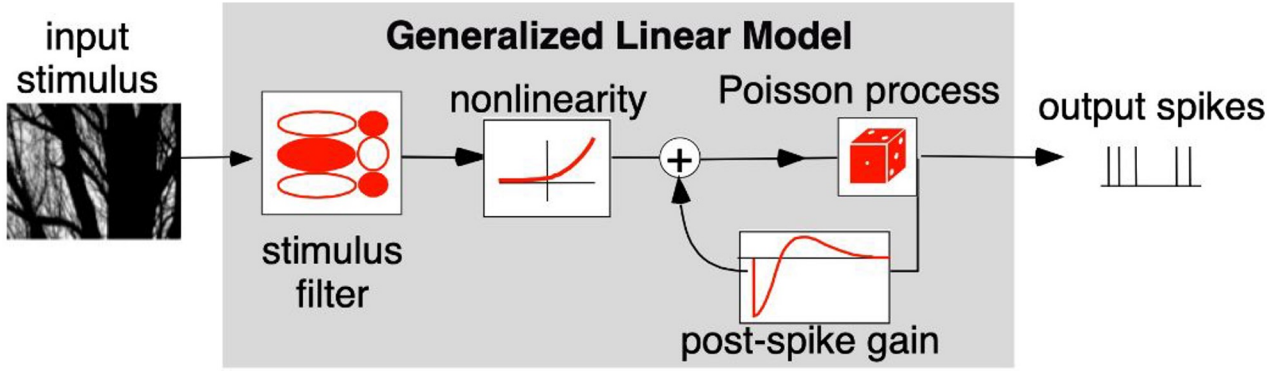
- Yes, if the stimulus is full-field or coarse grained (Berry and Meister, 1998).

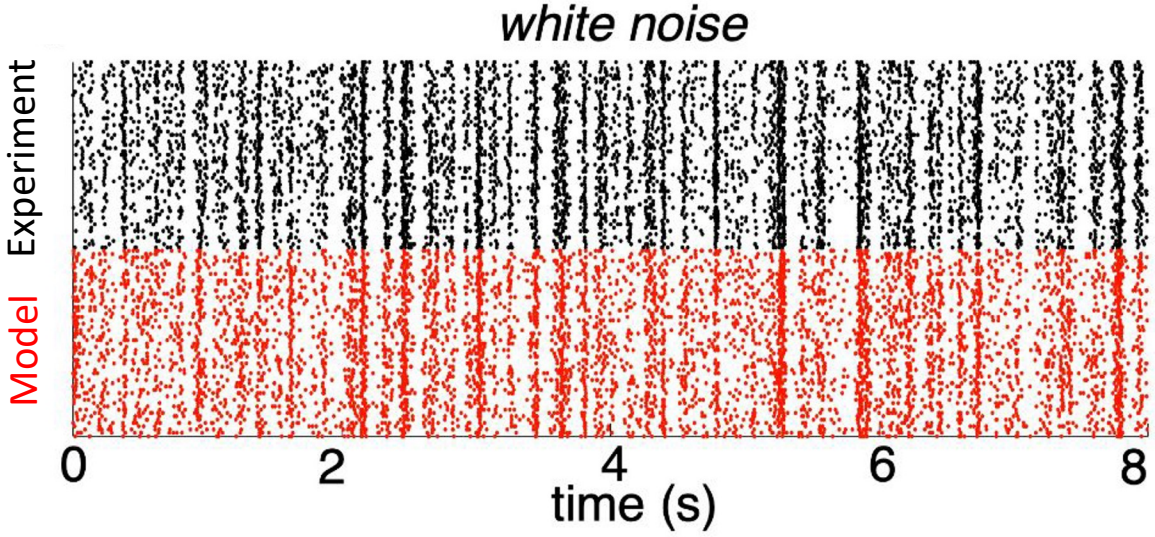


- Generalization: the GLM model (Pillow et al, 2008, with some additional interactions between cells).



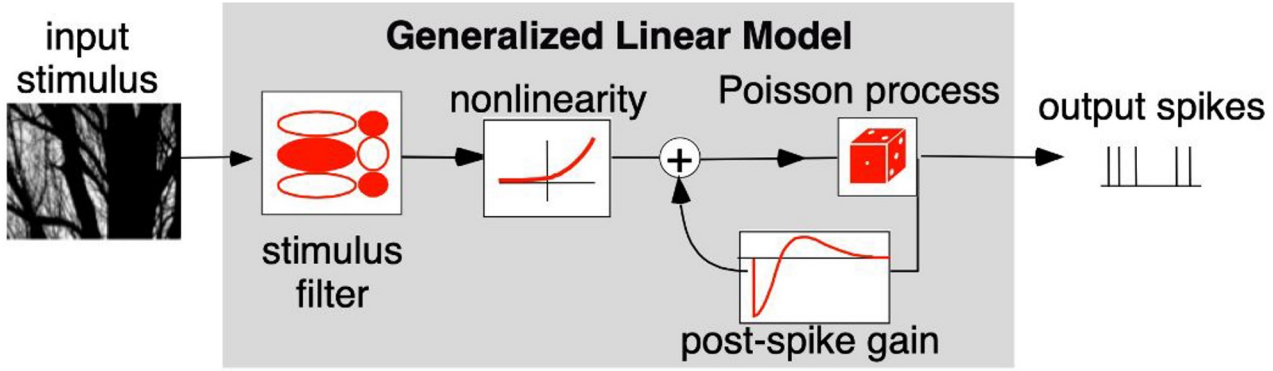
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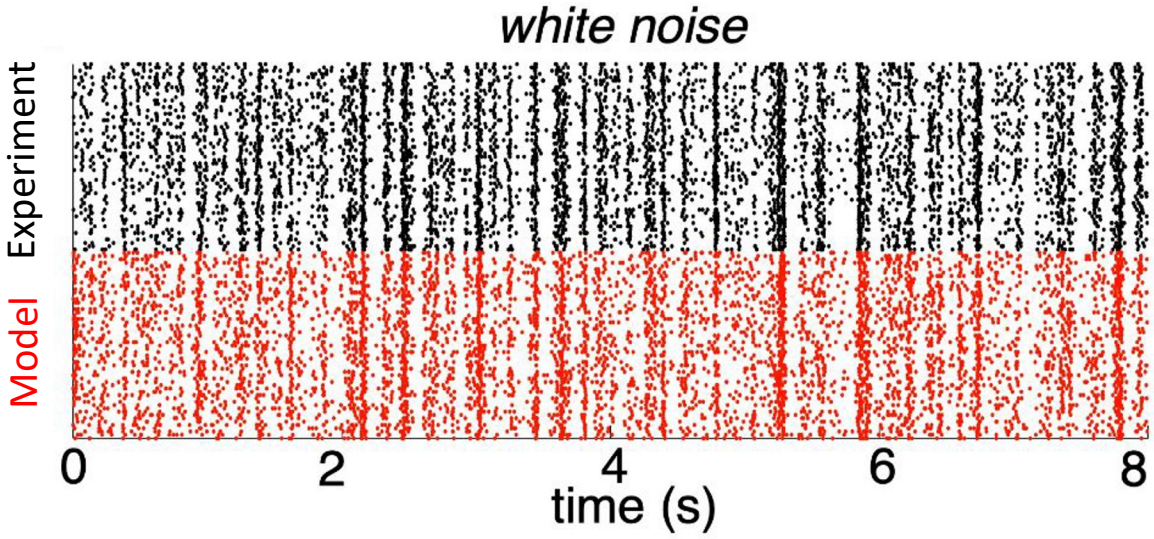


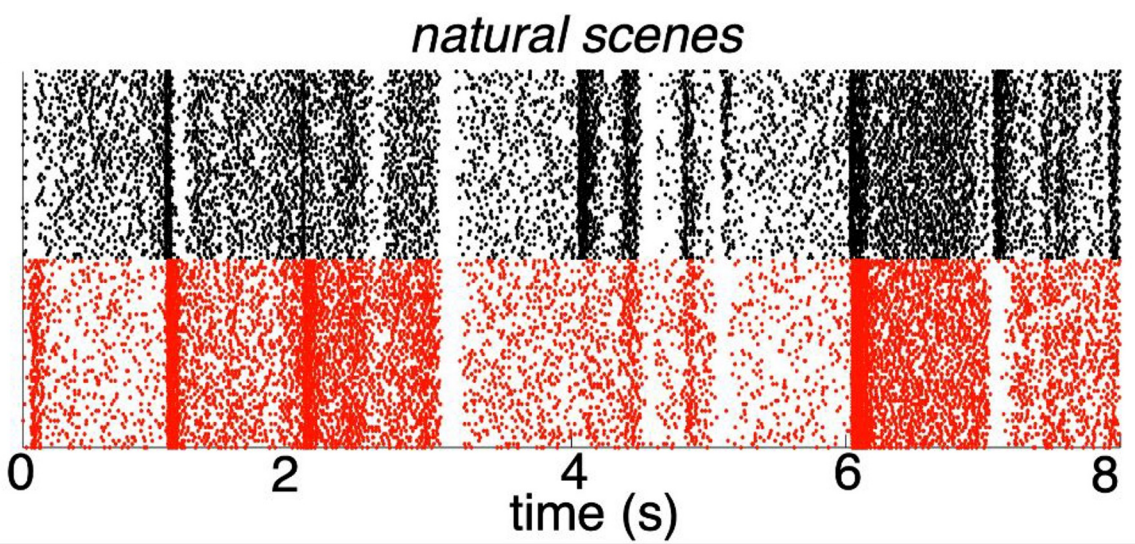


Heitman et al, 2016
See also: Deny et al, 2017

The LN model: does it work ?



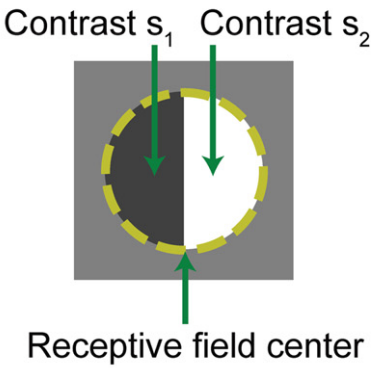




Heitman et al, 2016

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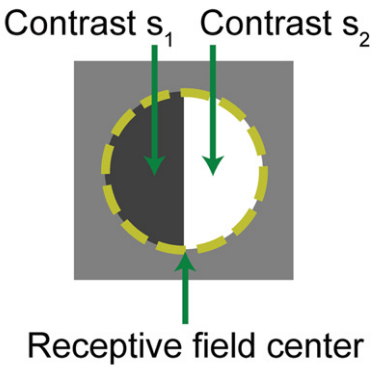
What is missing ?



Two different regions in the receptive field center.

If you assume a LN model:
R(s1 and s2) = R(s1 and 0) + R(0 and s2) ?

What is missing ?

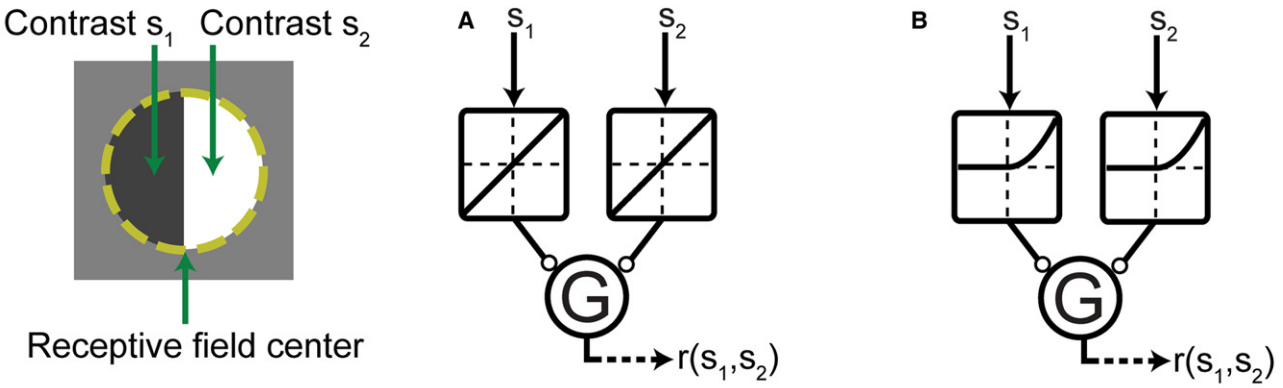


Two different regions in the receptive field center.

If you assume a LN model:
R(s1 and s2) = R(s1 and 0) + R(0 and s2) ?

No !
The non linearity can already induce deviations.
Is there a way around ?

Iso-firing rate curves

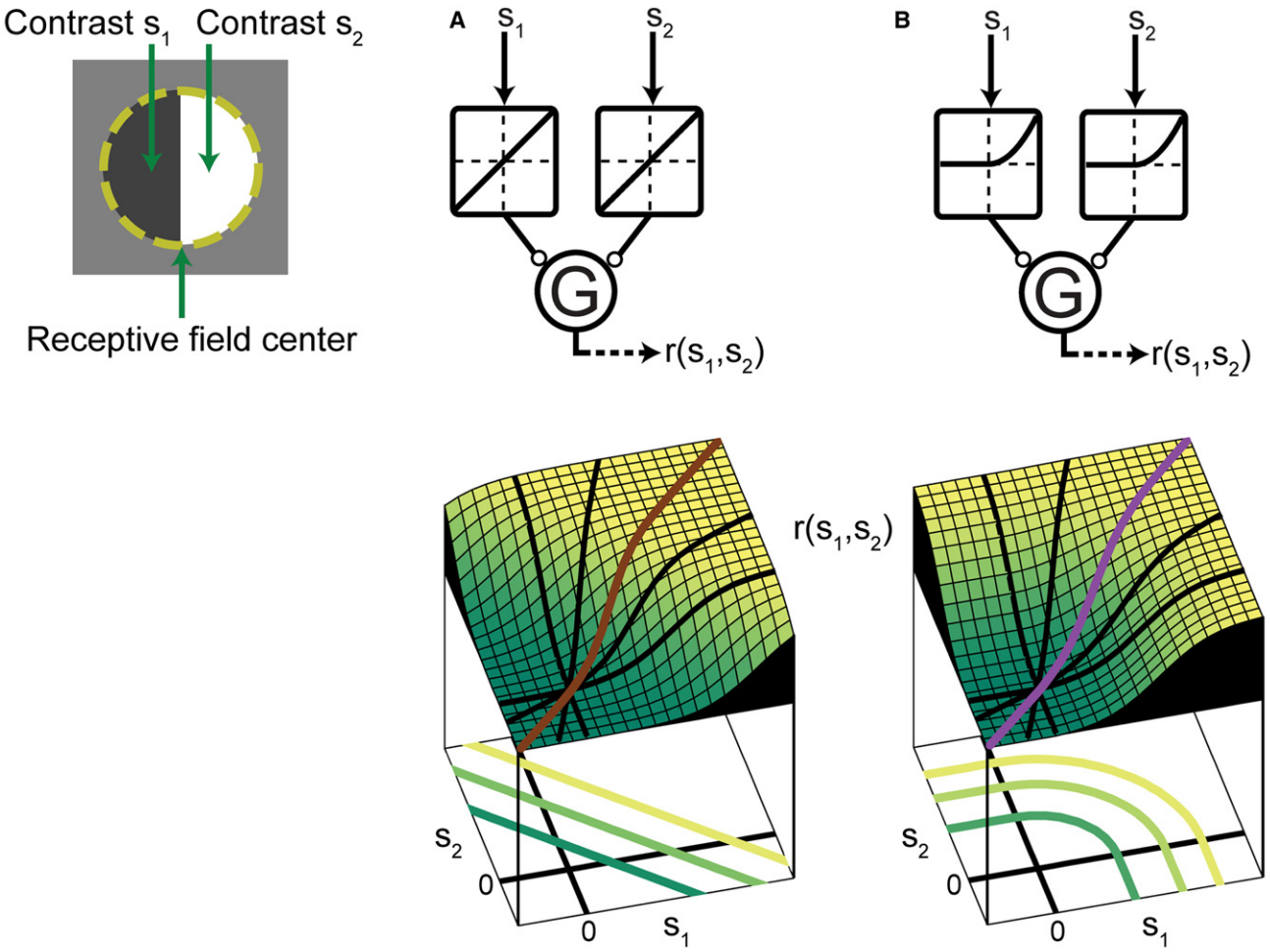


In a LN model, r(s1,s2) = r(s1+s2)

What are the combinations of s1 and s2 that give the same firing rate ?

Boelinger and Gollisch, 2012

Iso-firing rate curves



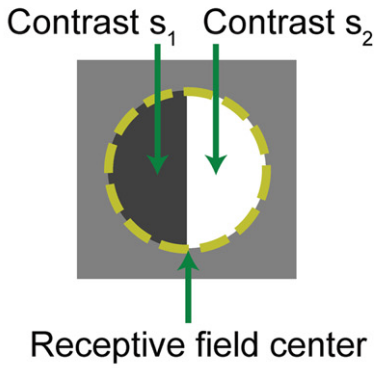
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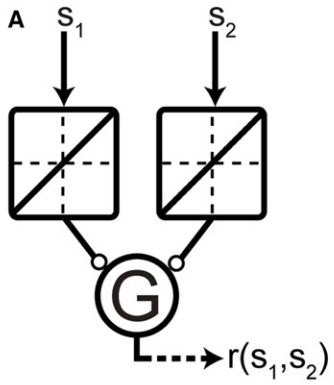
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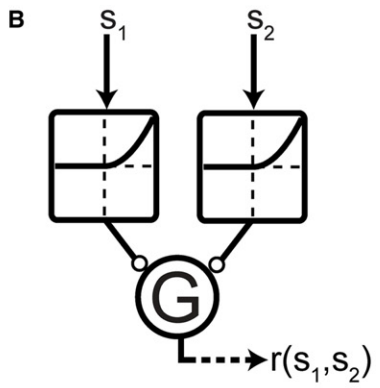
A signature of non-linear behaviour beyond LN model.

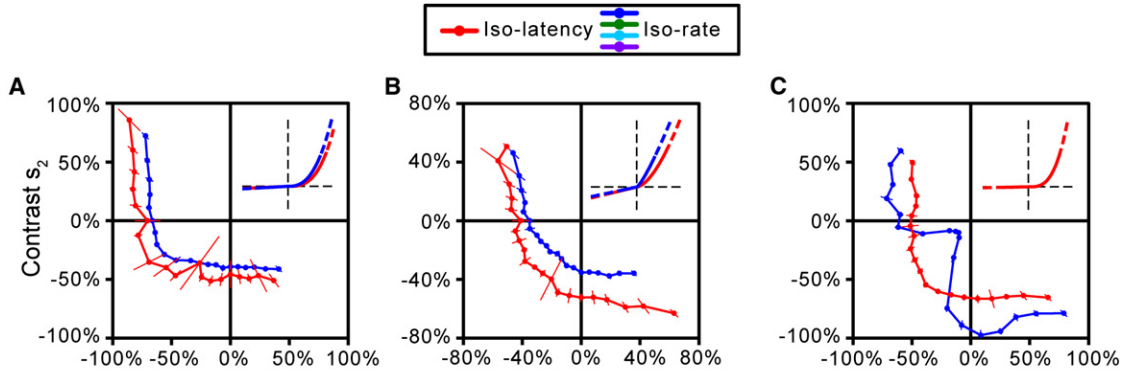
Boelinger and Gollisch, 2012

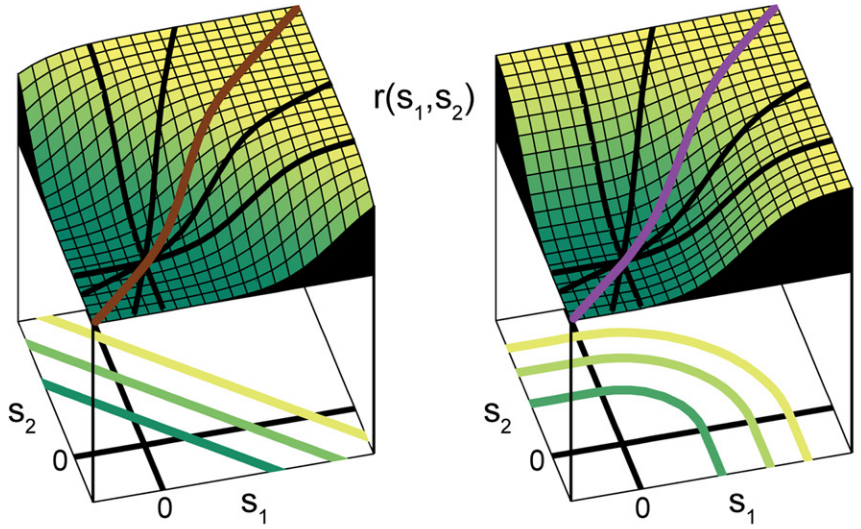
Iso-firing rate curves







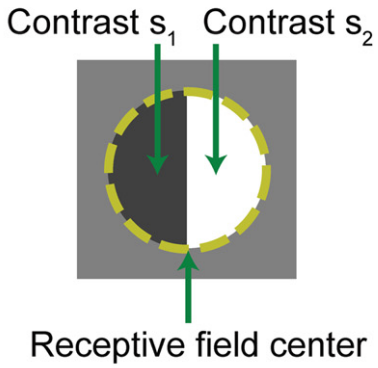


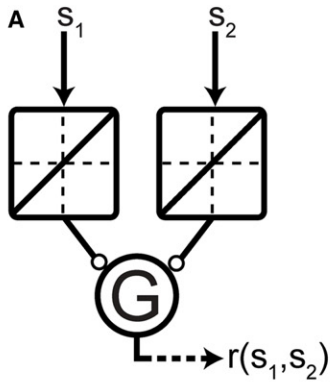


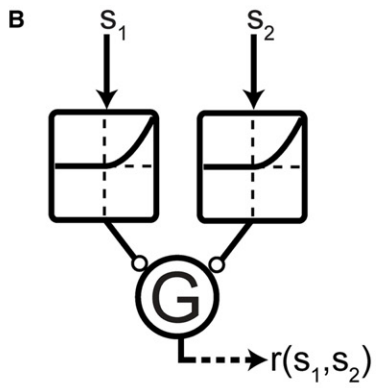
This is what is found experimentally !

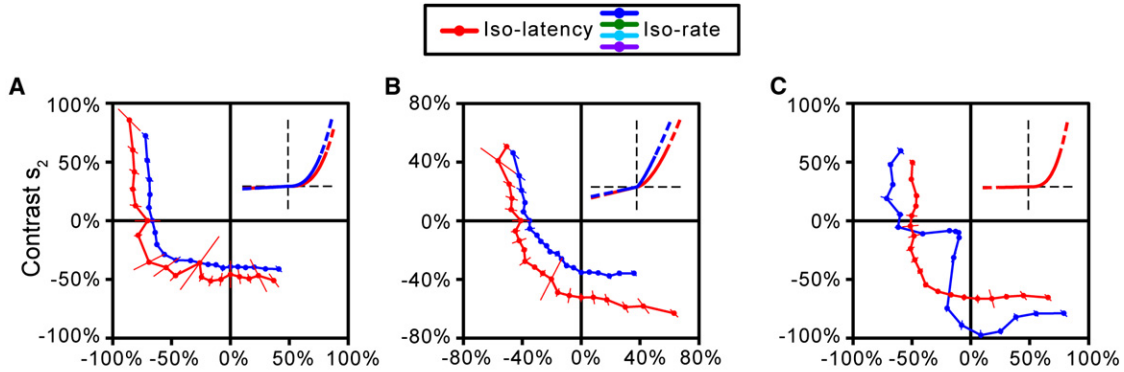
Boelinger and Gollisch, 2012

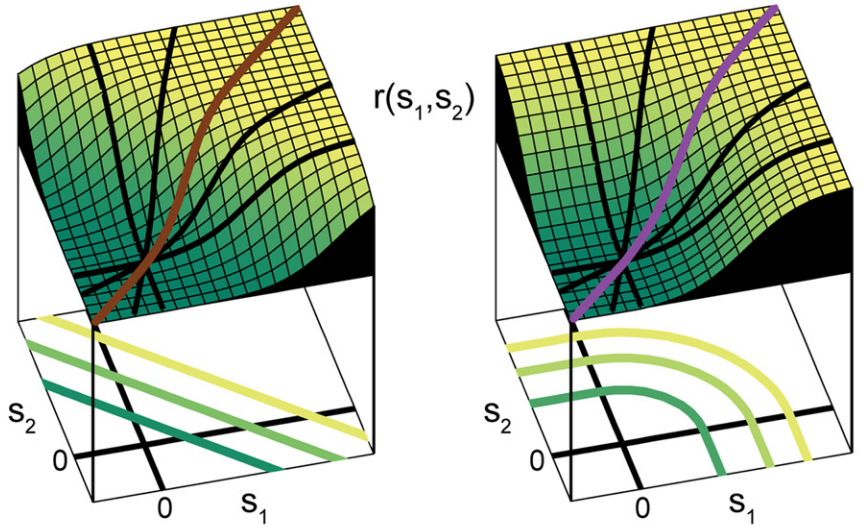
Iso-firing rate curves









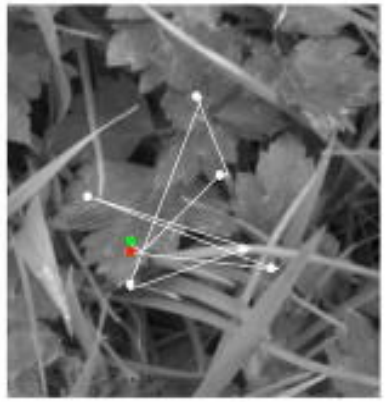


This is what is found experimentally !

Caveat: far from natural stimuli.

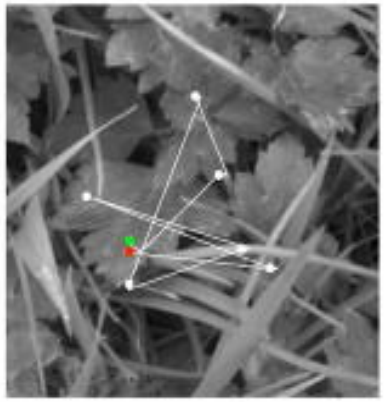
Boelinger and Gollisch, 2012

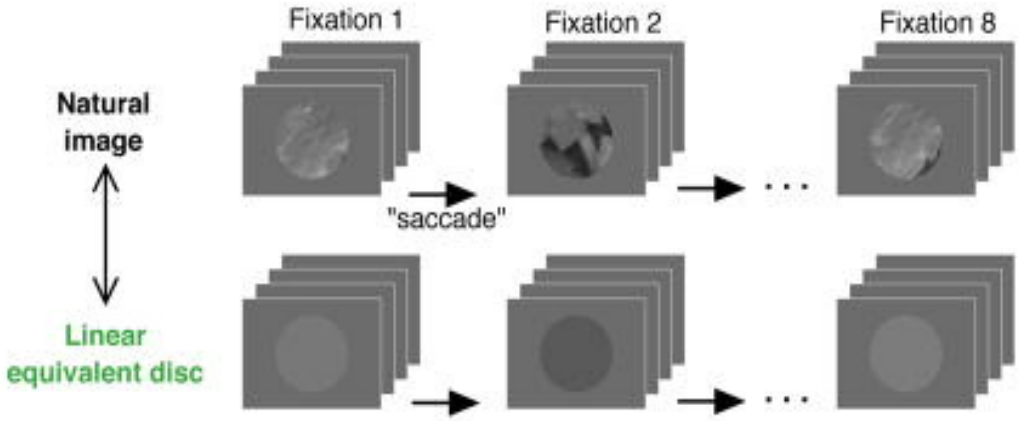
With natural scene stimulation



Turner and Rieke, 2016

With natural scene stimulation

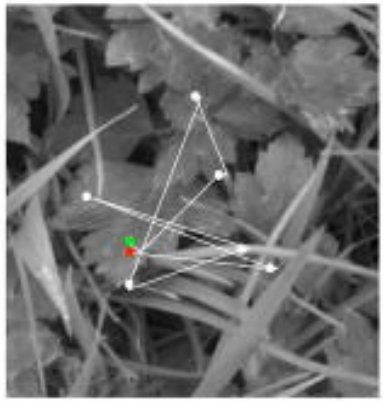


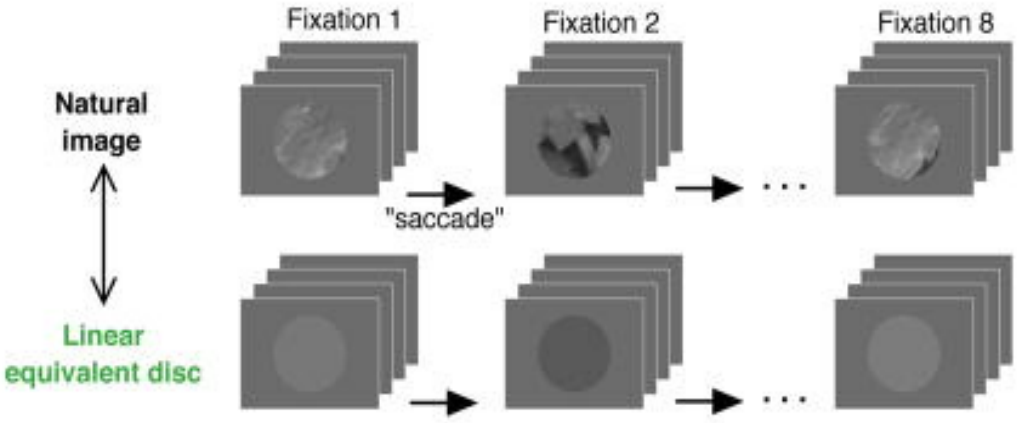


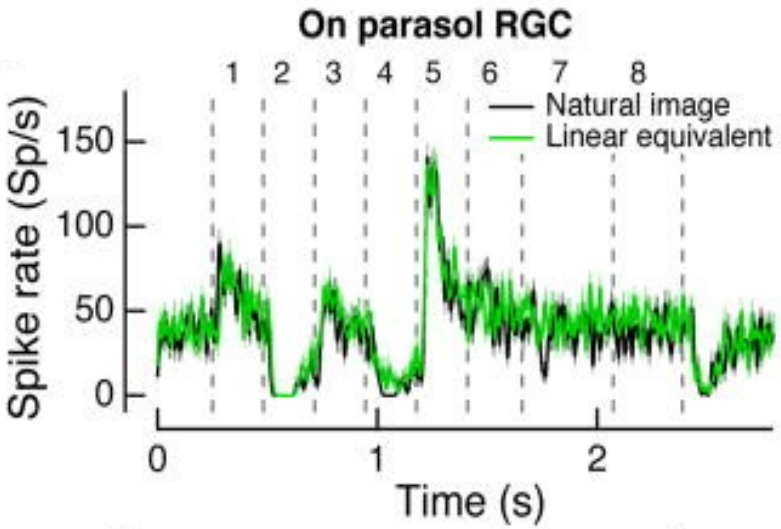
What would happen if it was a LN model ?

Turner and Rieke, 2016

With natural scene stimulation

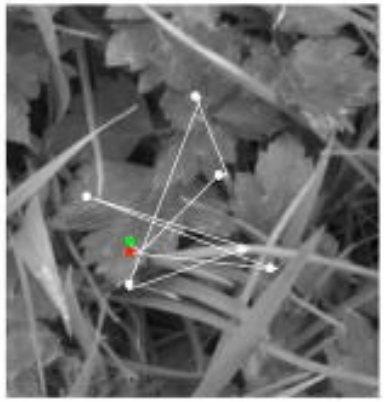


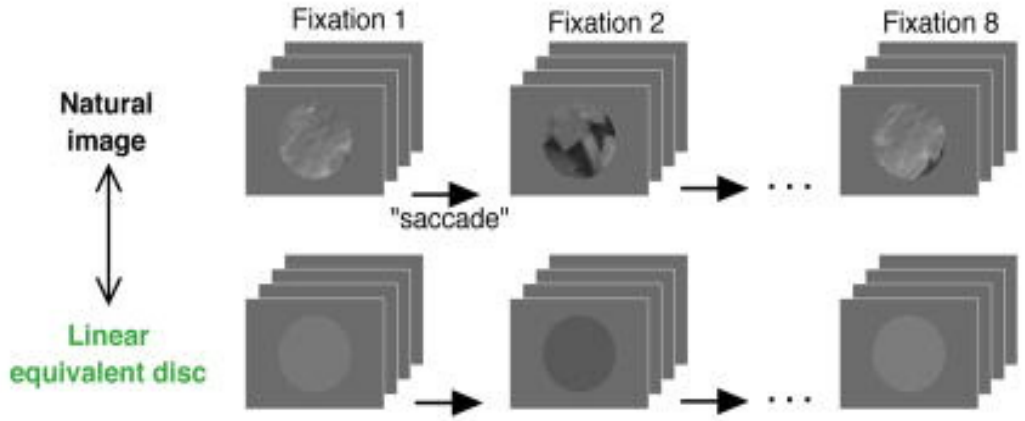


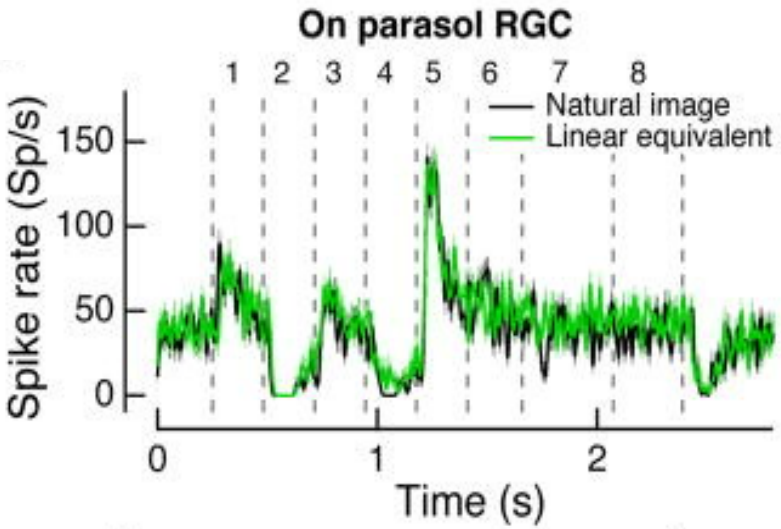


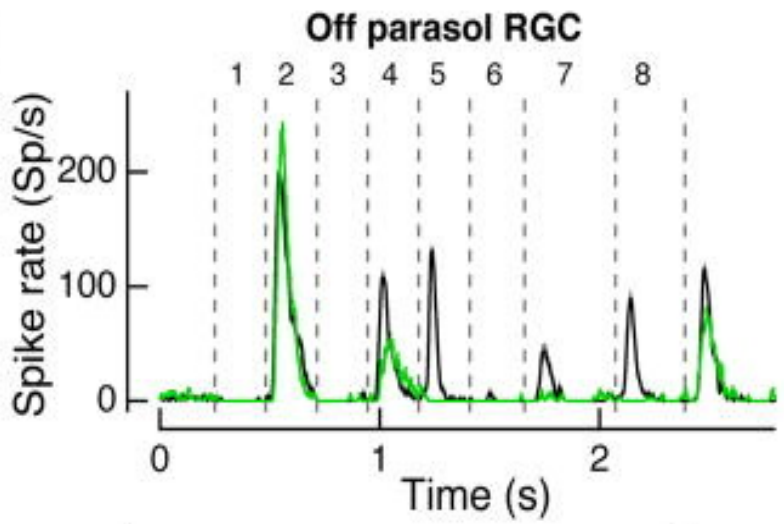
Turner and Rieke, 2016

With natural scene stimulation



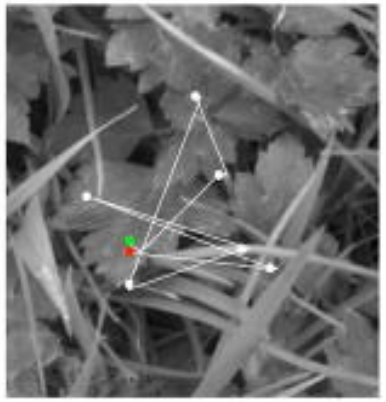


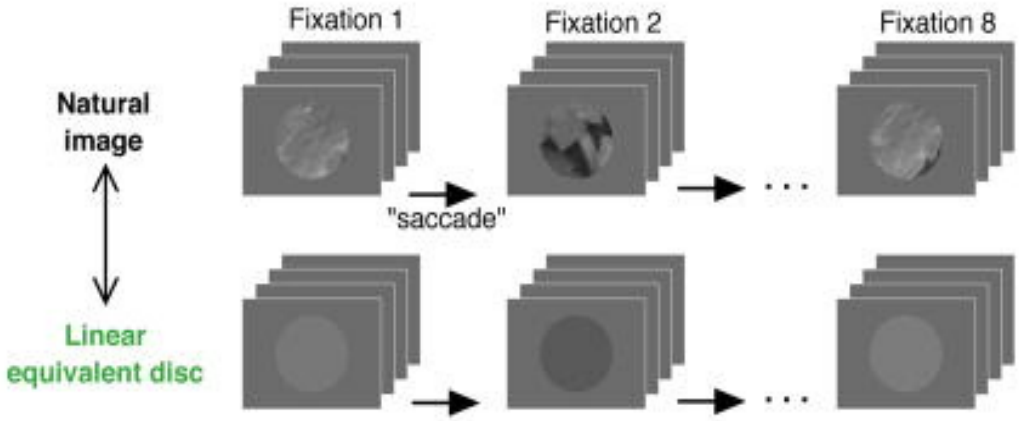


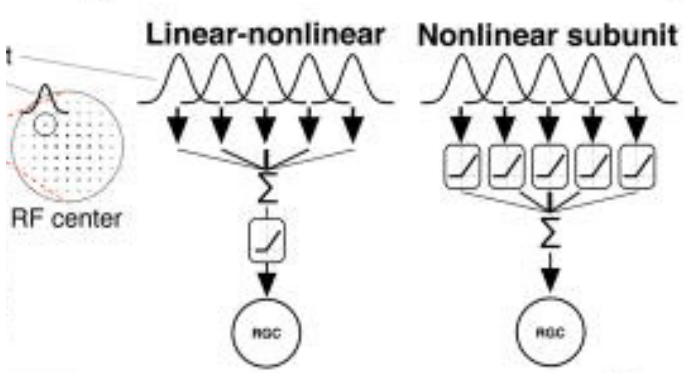


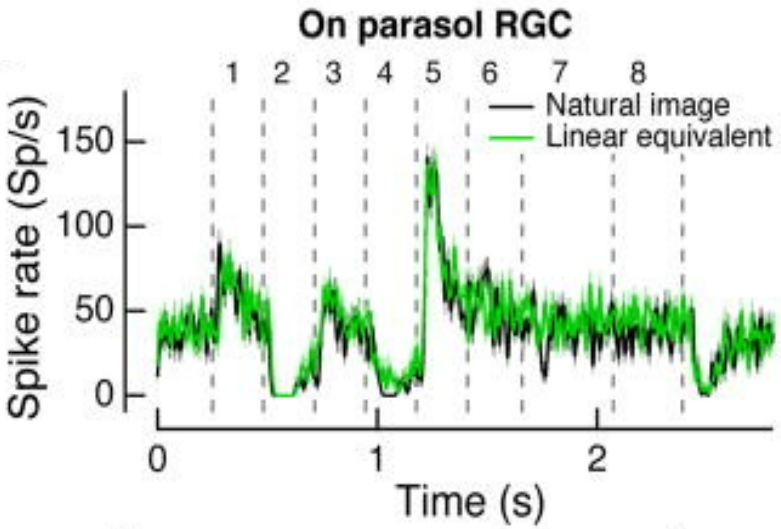
Turner and Rieke, 2016

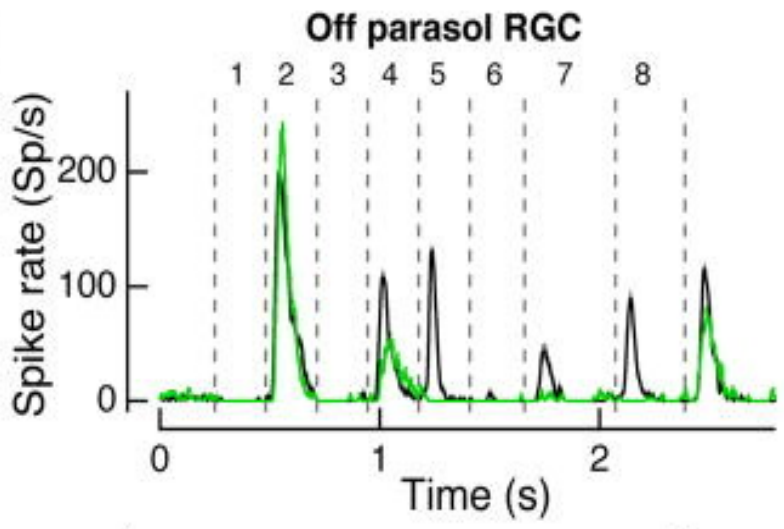
With natural scene stimulation











Turner and Rieke, 2016

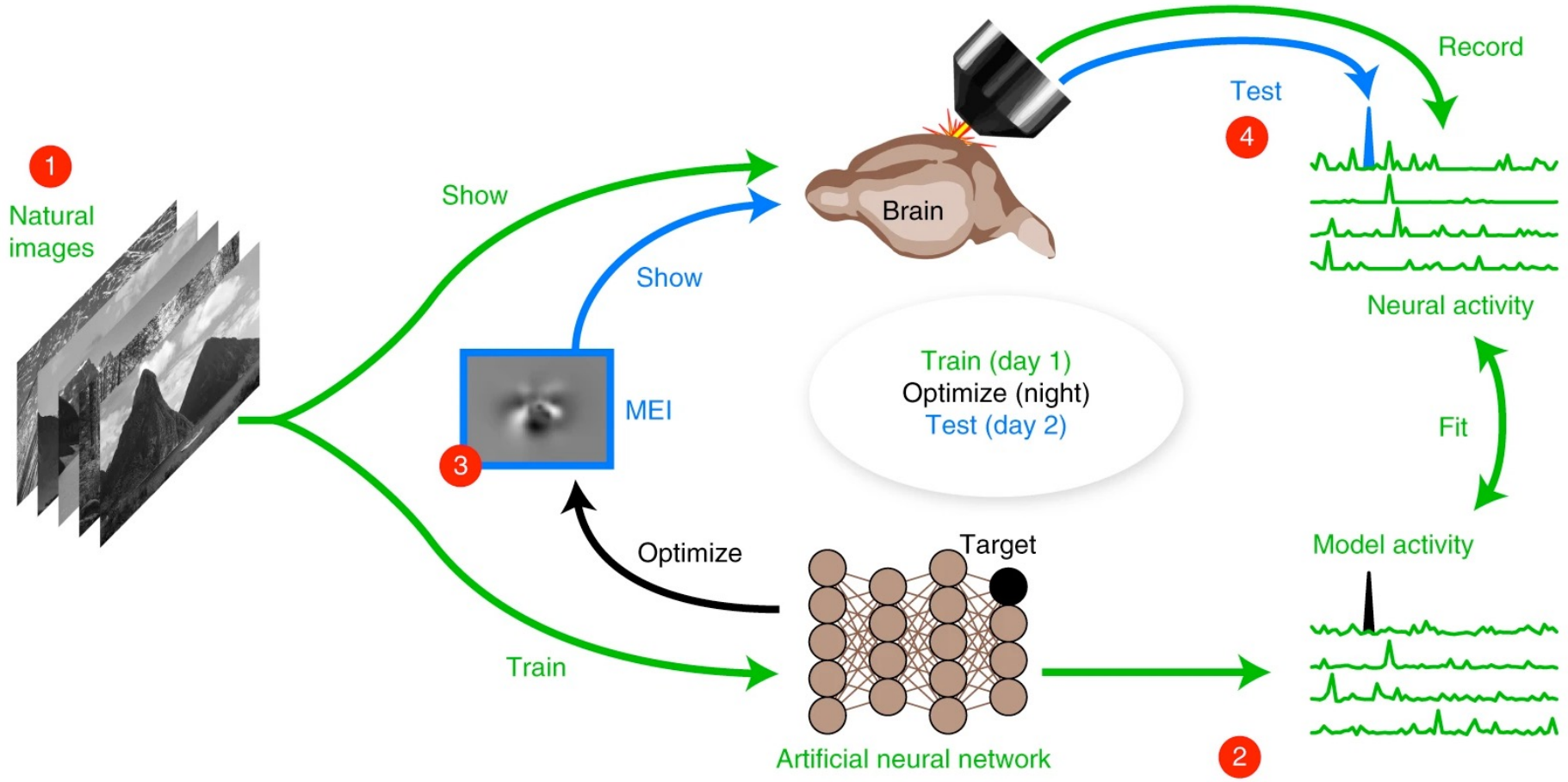
A “LNLN” model can explain these differences.

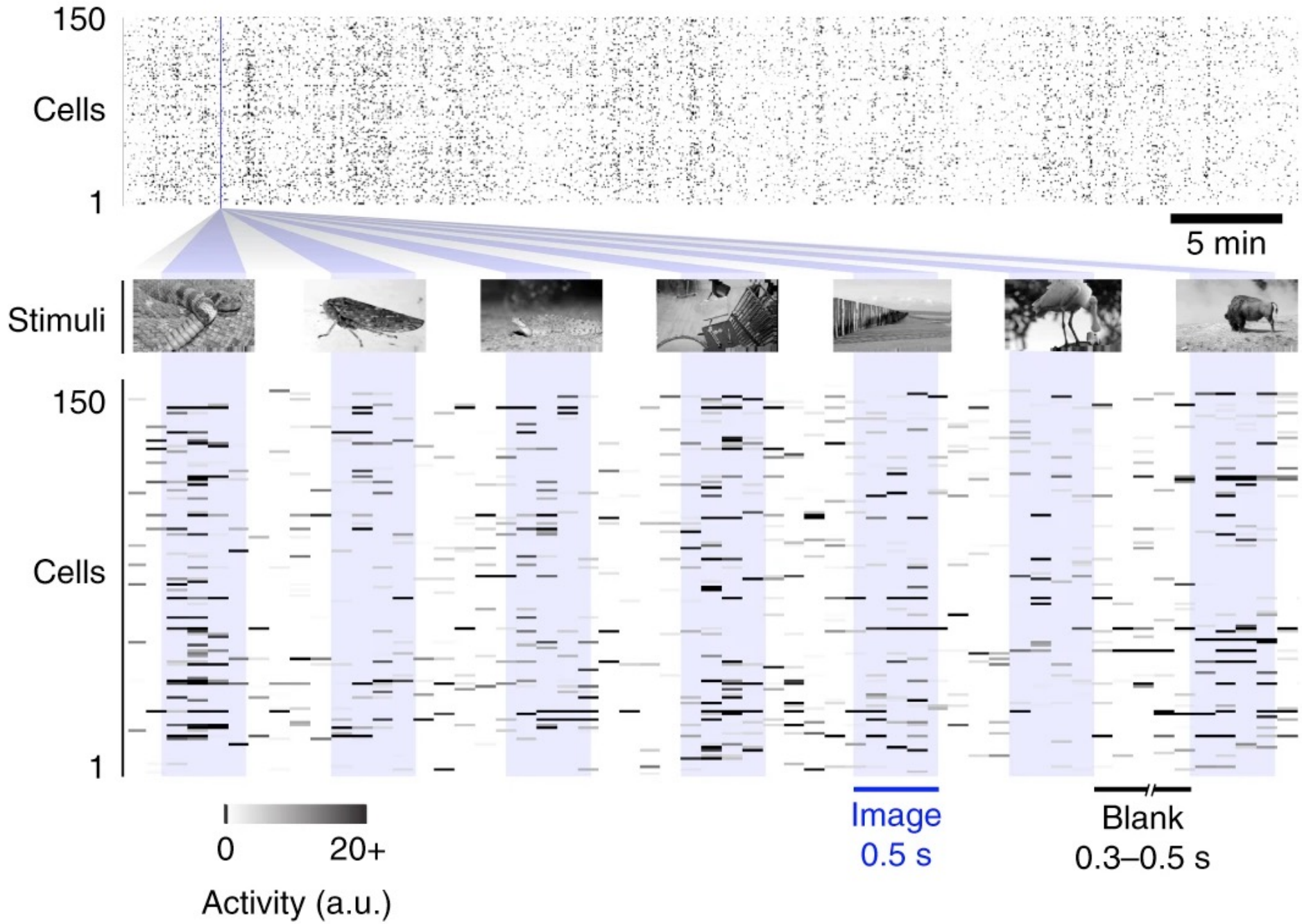
In later work they could show the non-linearity was from photoreceptors (Yu et al, 2022)

The inception experiment

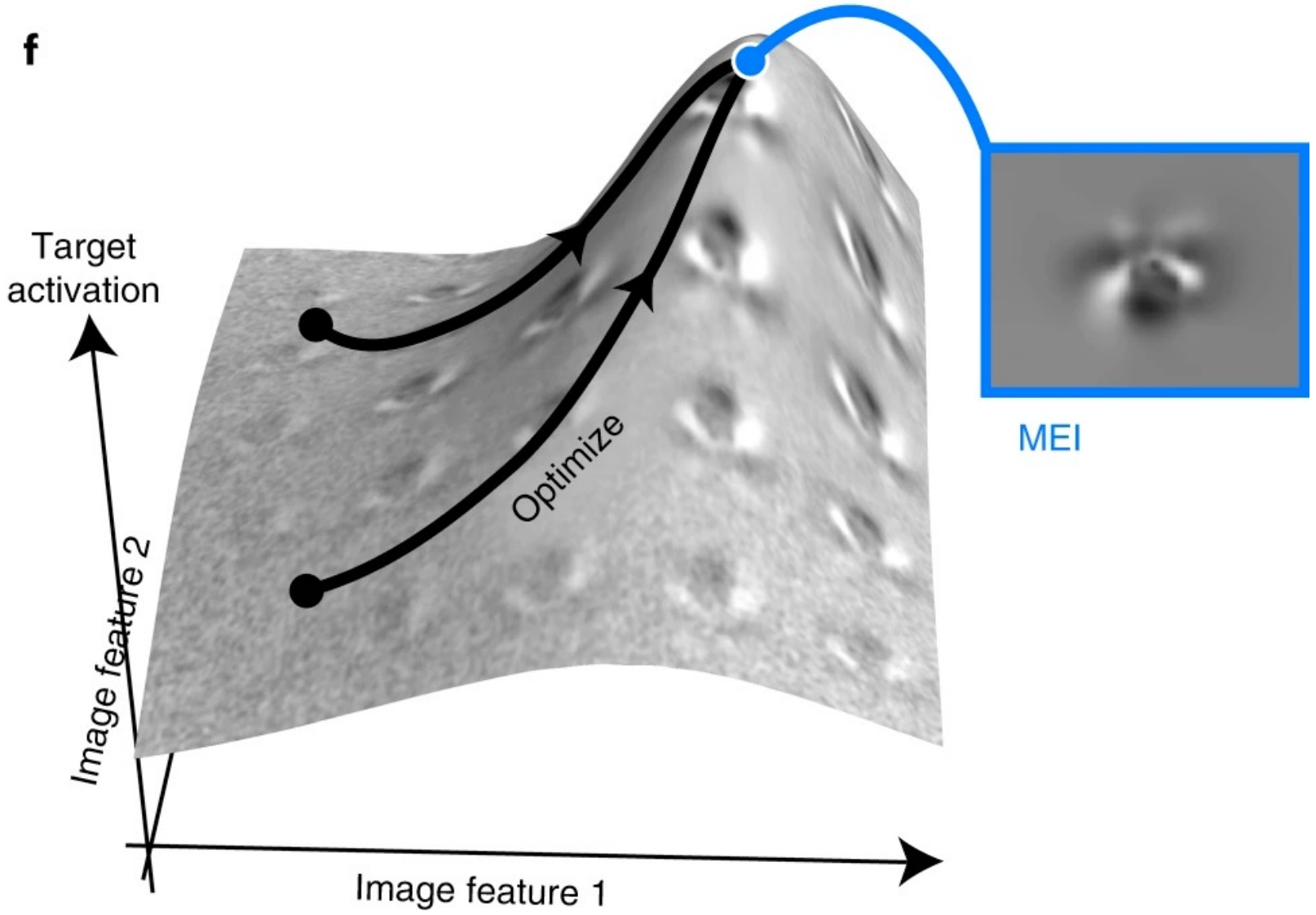
- Walker et al, Nature Neuroscience 2019
- https://www.nature.com/articles/s41593-019-0517-x?proof=t

Protocol

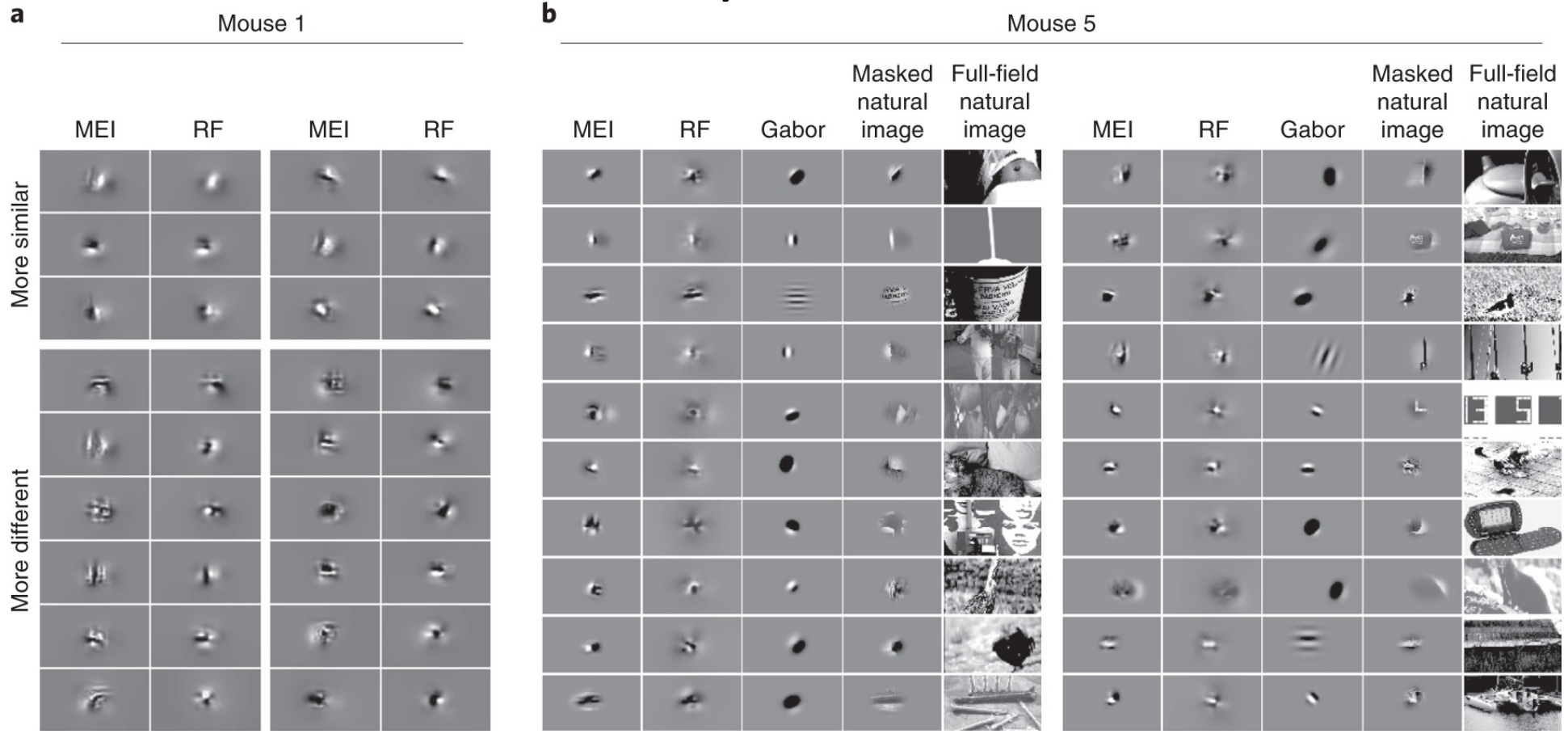

1
Natural images
Show
Show
MEI
3
Brain
Record
Test
4
Neural activity
Train (day 1)
Optimize (night)
Test (day 2)
Fit
Optimize
Target
Model activity
Train
Artificial neural network
2


150
Cells
1
5 min
Stimuli
150
Cells
1
0
20+
Activity (a.u.)
Image
0.5 s
Blank
0.3–0.5 s

Finding the stimulus with maximal activation



Stimuli that maximally excite a cell

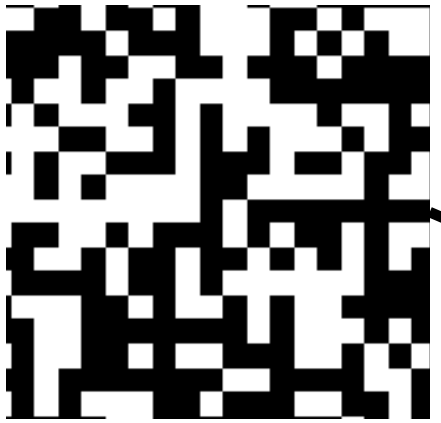


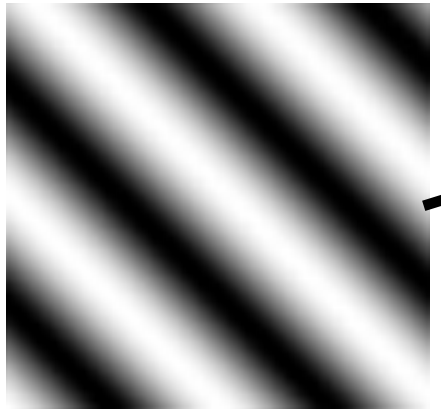
The inception experiment

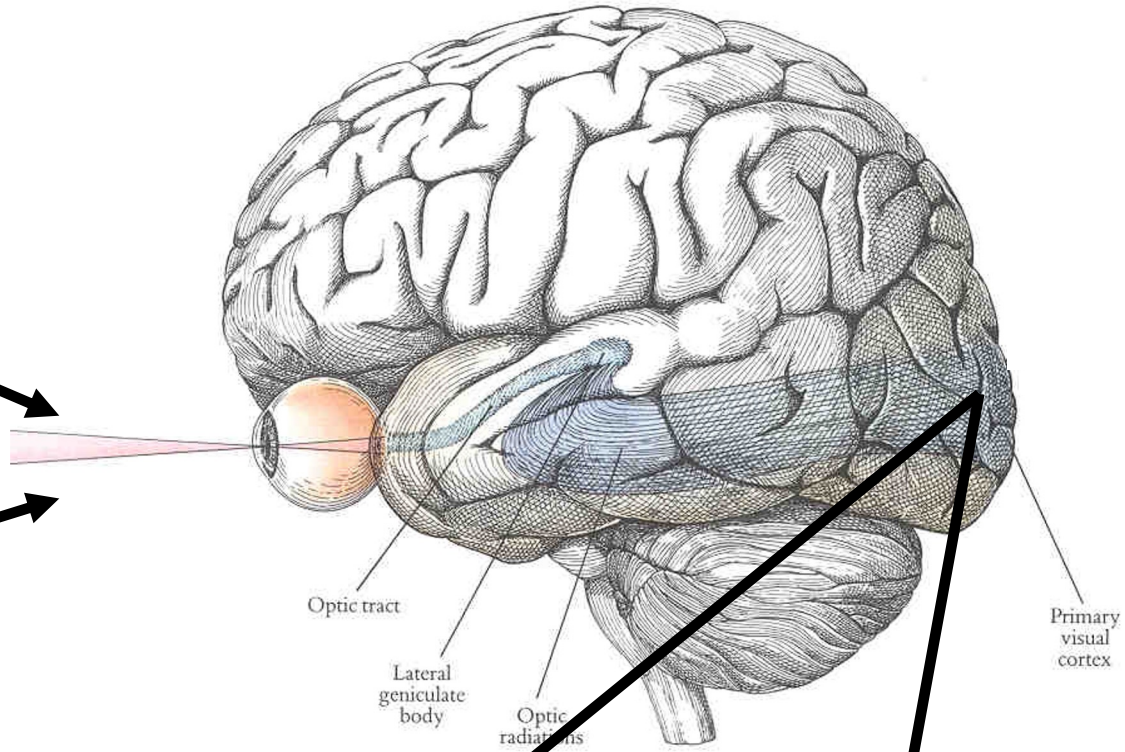
- Better activation with this stimulus than with any other.

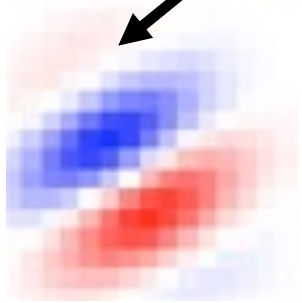
- What does it tell about neural coding ?

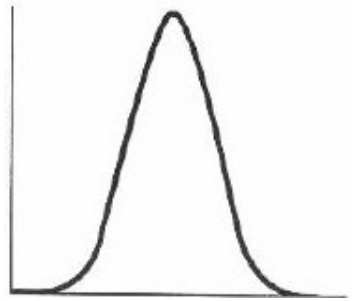
Simple stimuli





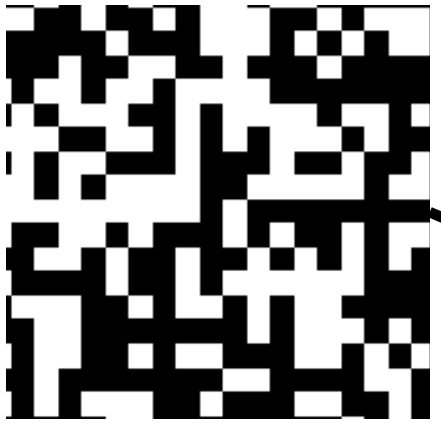


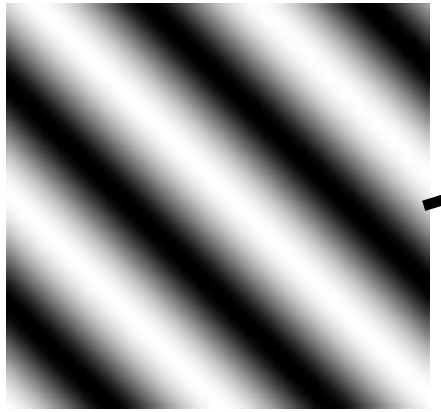


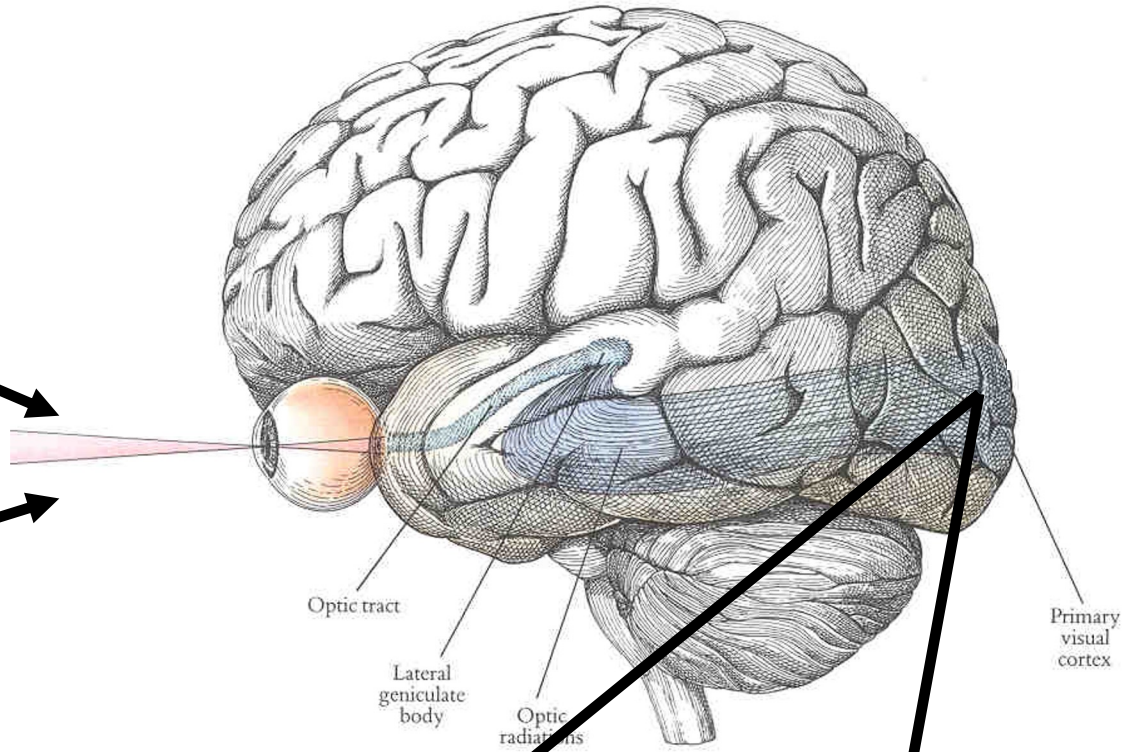


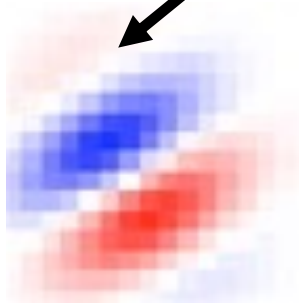
Hartline, Kuffler
Hubel & Wiesel, 1962
Rowe & Stone, 1980
DeAngelis & Freeman, 1995
"In praise of artifice" Rust and Movshon (2005)

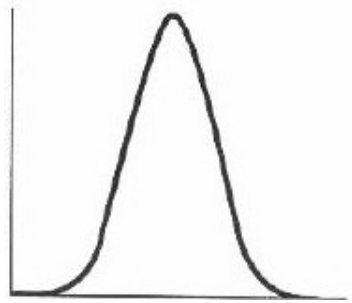
Simple stimuli: usually don't generalize to natural scenes







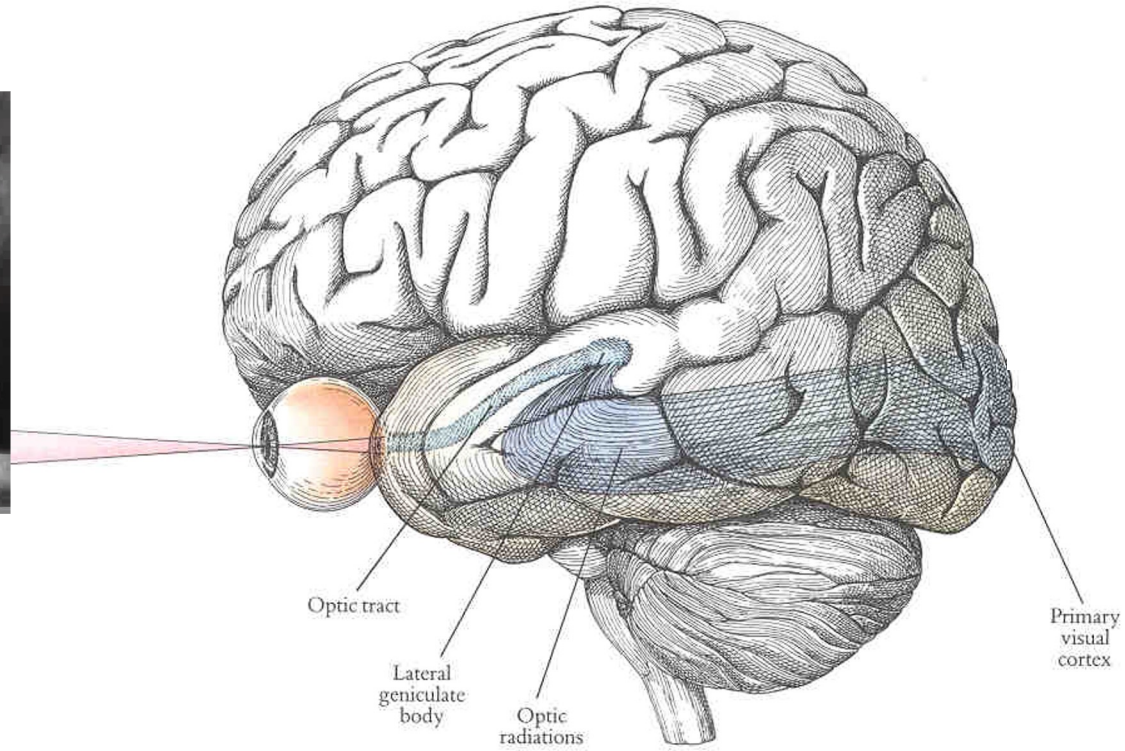




Hartline, Kuffler
Hubel & Wiesel, 1962
Rowe & Stone, 1980
DeAngelis & Freeman, 1995
"In praise of artifice" Rust and Movshon (2005)

Complex, natural stimuli



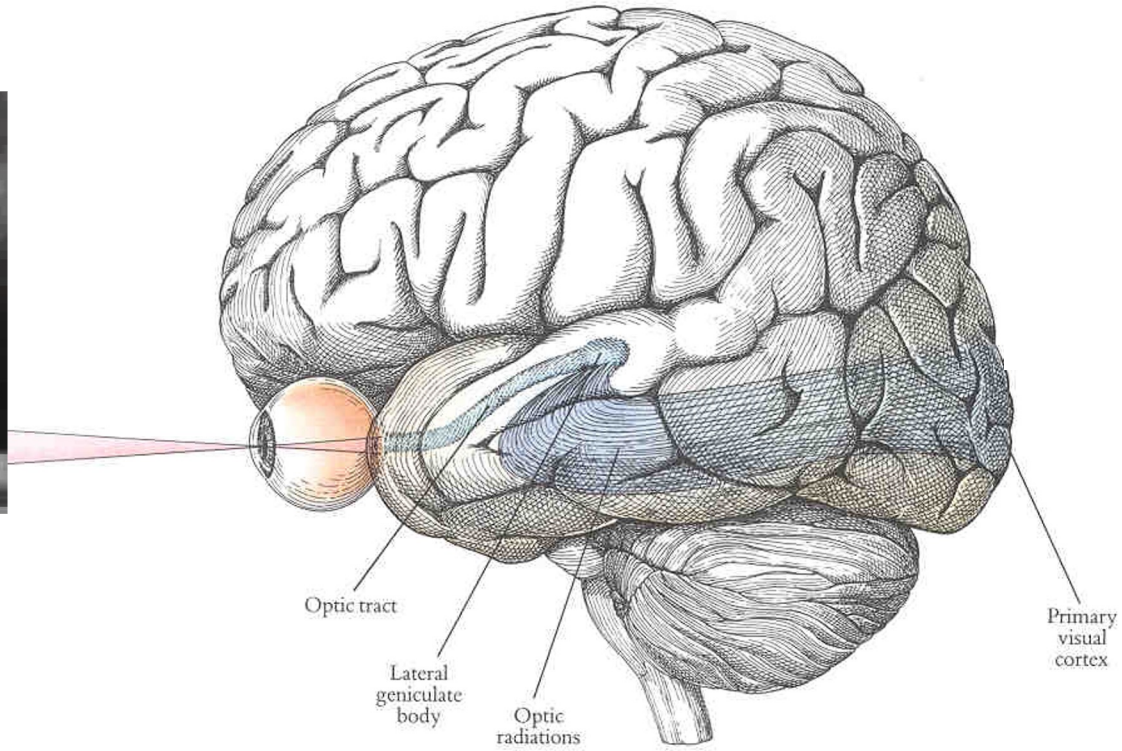




Lettvin et al, 1959
Carandini et al, 2005
Gollisch & Meister, 2010
Yamins & DiCarlo, 2016
McIntosh et al, 2016
Walker et al, 2019

Complex, natural stimuli: curse of dimensionality



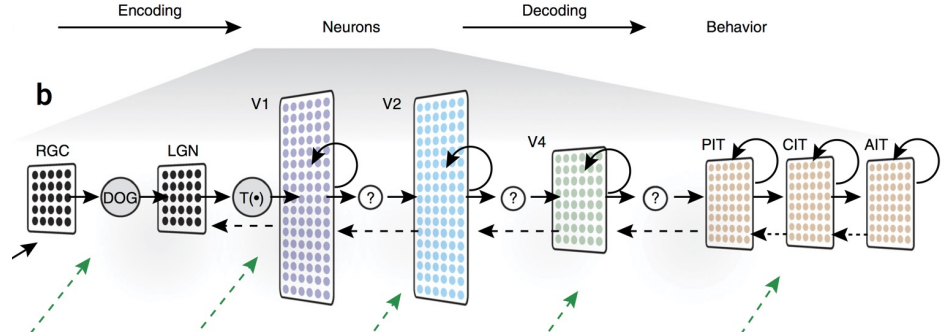


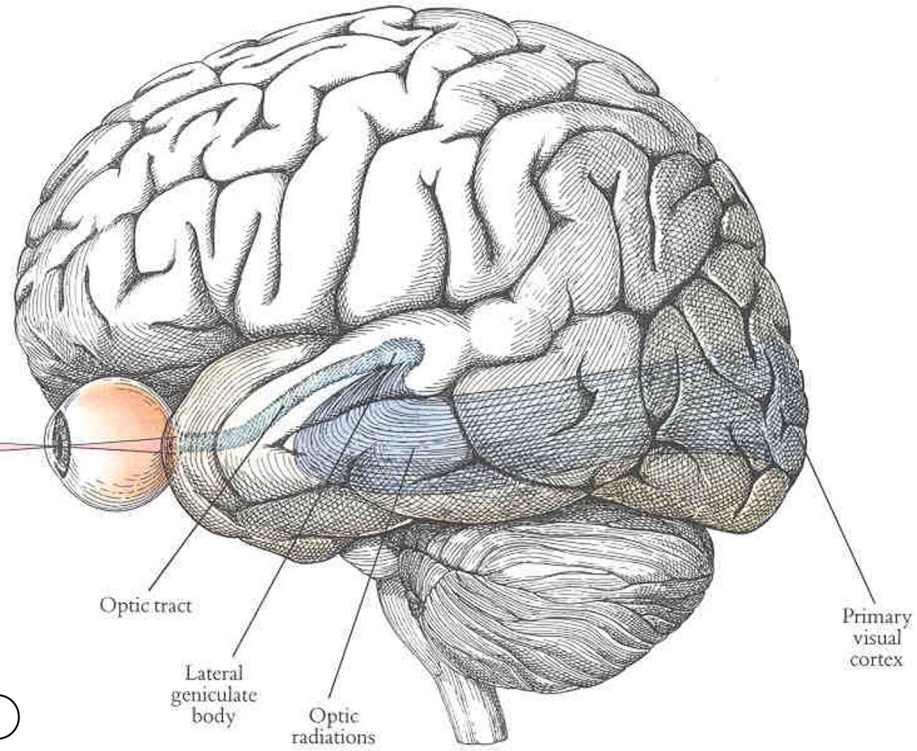


Lettvin et al, 1959
Carandini et al, 2005
Gollisch & Meister, 2010
Yamins & DiCarlo, 2016
McIntosh et al, 2016
Walker et al, 2019

Complex, natural stimuli







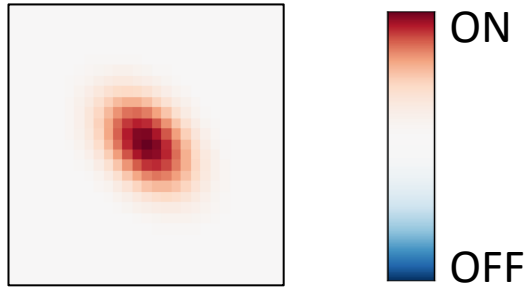
Is there a middle ground ?

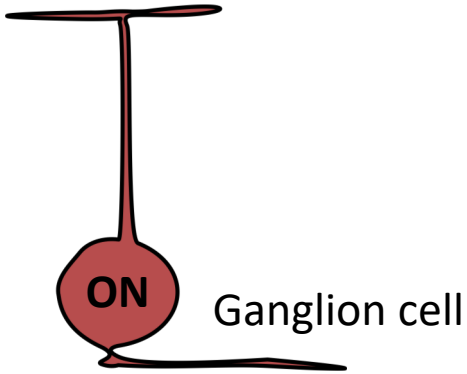


Lettvin et al, 1959
Carandini et al, 2005
Gollisch & Meister, 2010
Yamins & DiCarlo, 2016
McIntosh et al, 2016
Walker et al, 2019

Selectivity in natural contexts

- ON ganglion cell: selectivity to local light increase.

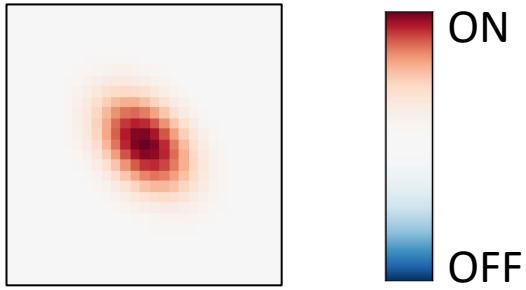




Ganglion cell

Selectivity in natural contexts

- ON ganglion cell: selectivity to local light increase.

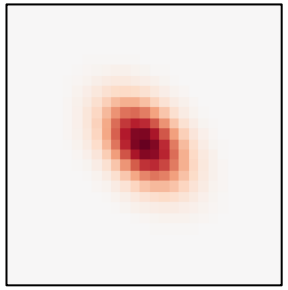


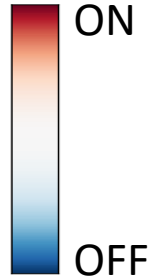
- With a natural image:



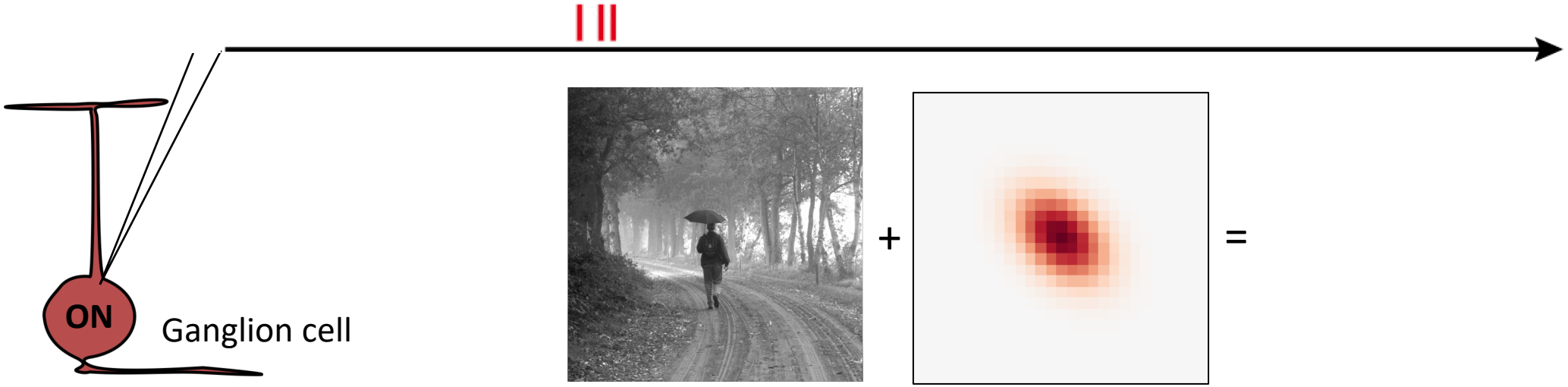
Selectivity in natural contexts

- ON ganglion cell: selectivity to local light increase.



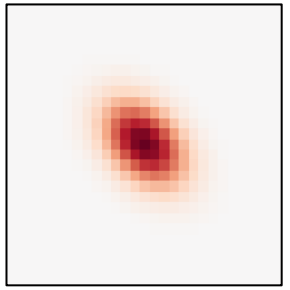


- With a natural image:

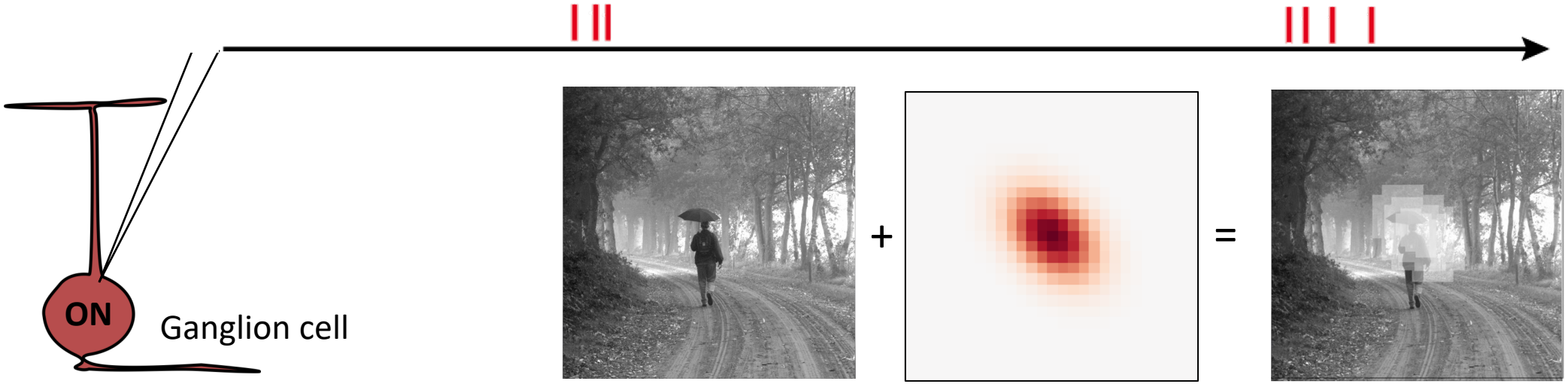


Selectivity in natural contexts

- ON ganglion cell: selectivity to local light increase.



- With a natural image: **local light increase is the best way to increase the firing rate?**



Probing selectivity in natural contexts



reference image

Probing selectivity in natural contexts



reference image

+



checkerboard pattern

Probing selectivity in natural contexts



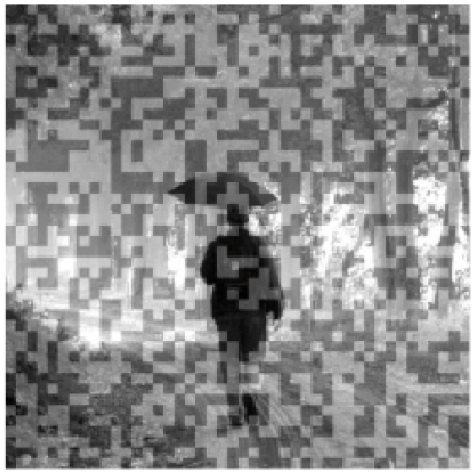
reference image

+



checkerboard pattern

=



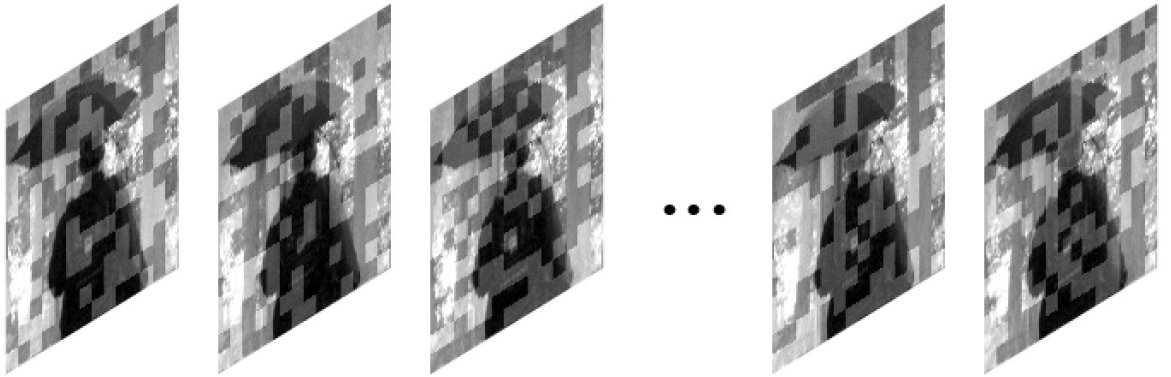
perturbed image

Probing selectivity in natural contexts



Reference image

Stimulus

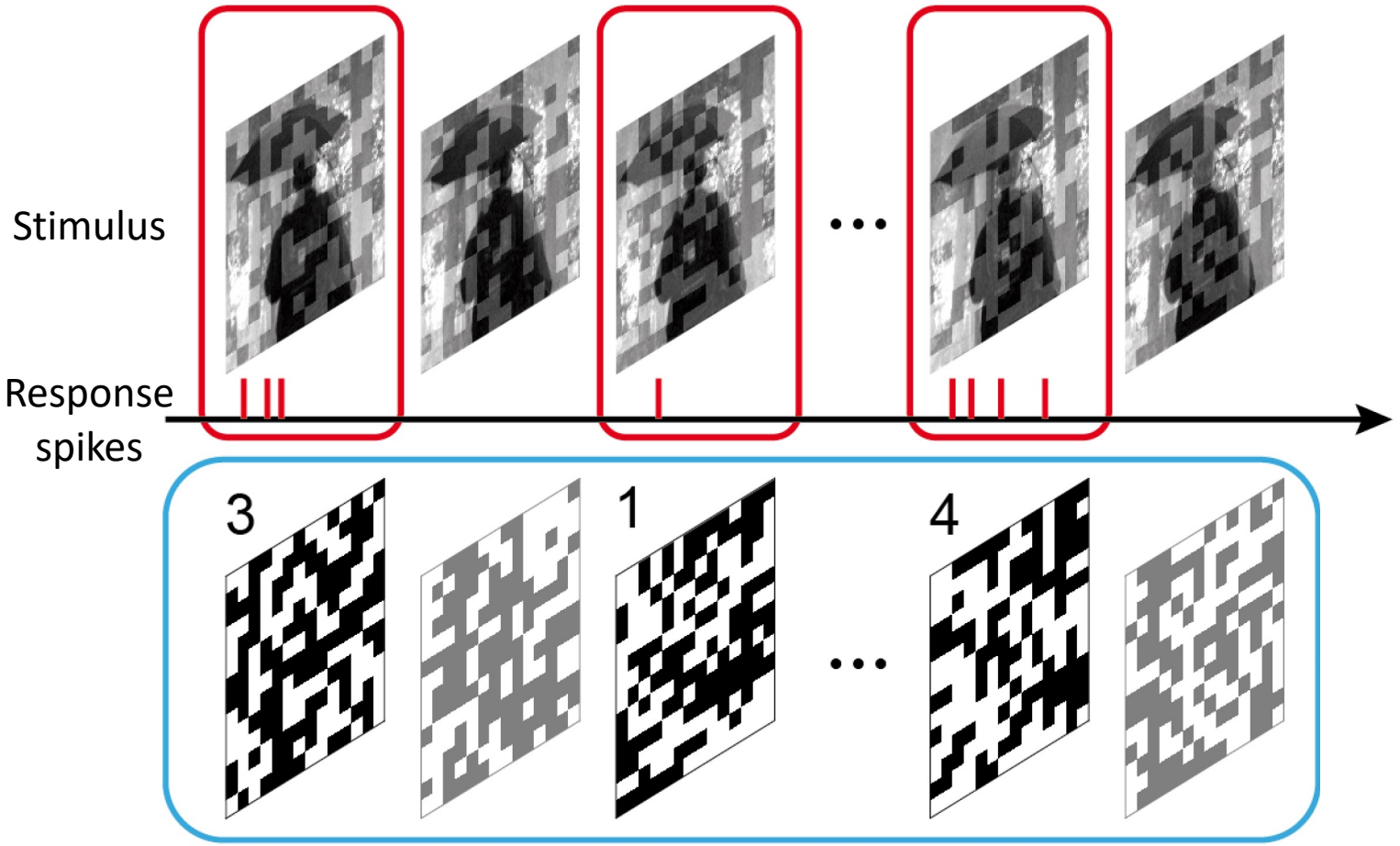


Many perturbations for each reference image.

Probing selectivity in natural contexts



Reference image



Many perturbations for each reference image.

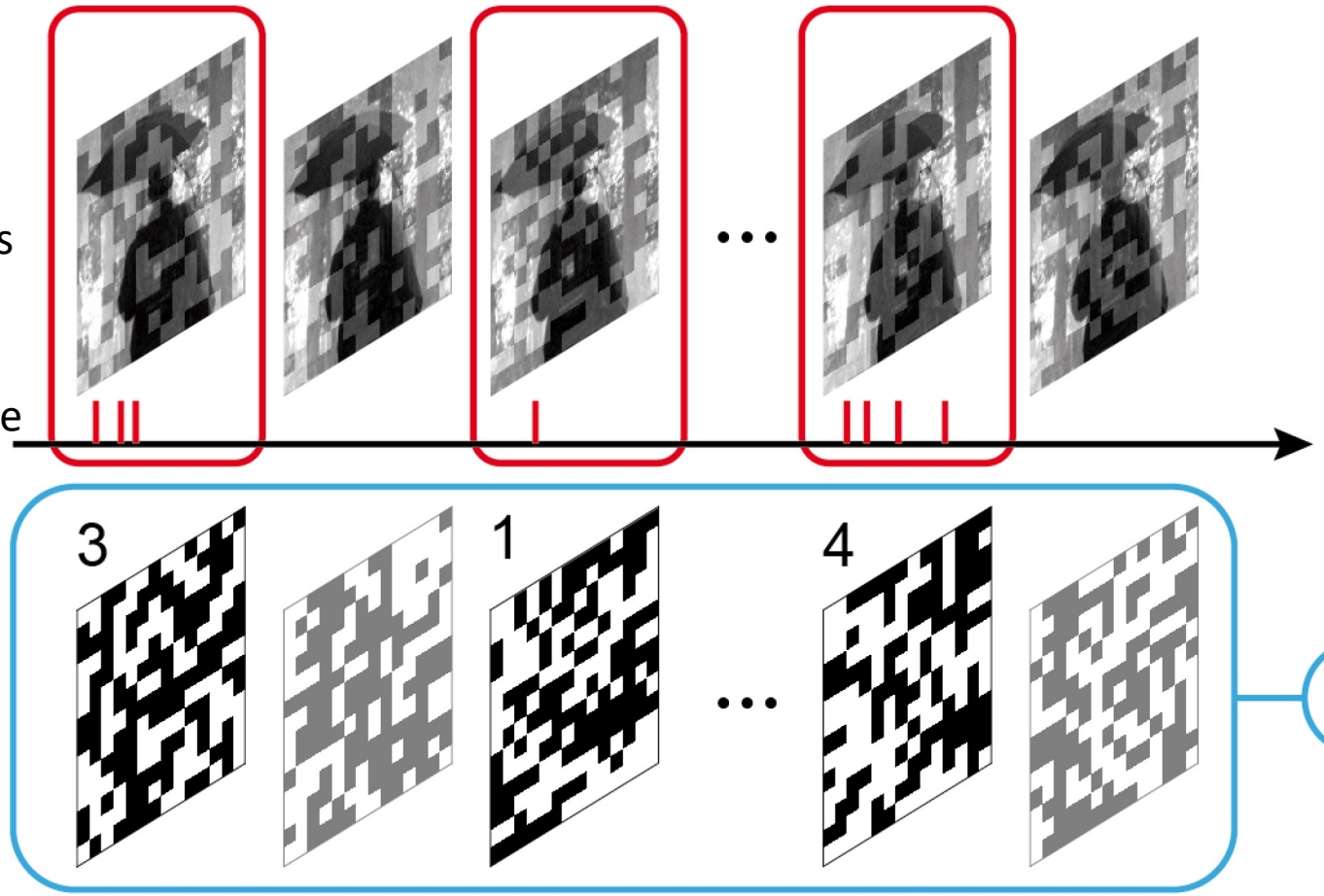
Probing selectivity in natural contexts



Reference image

Stimulus

Response spikes



Many perturbations for each reference image.

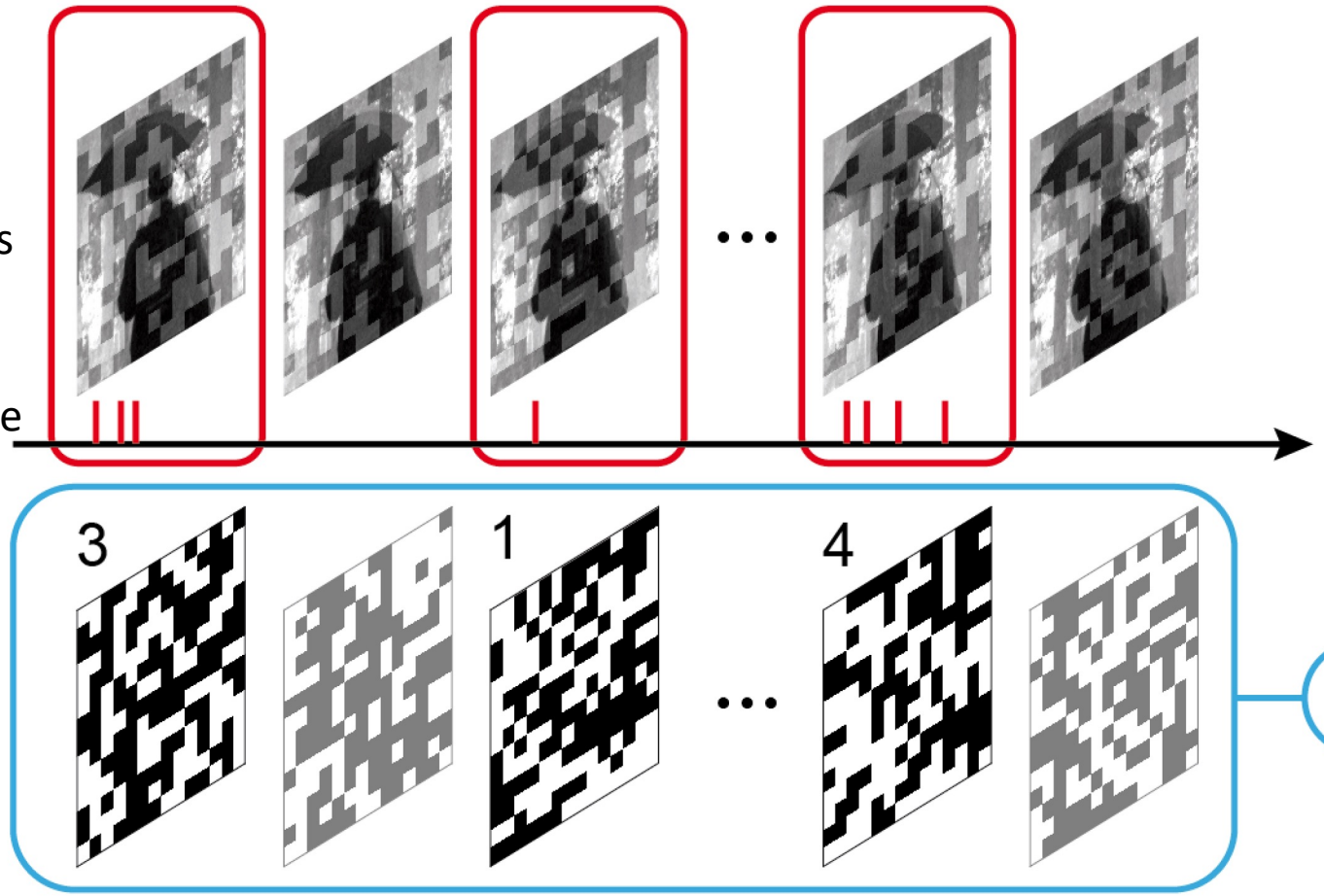
Probing selectivity in natural contexts



Reference image

Stimulus

Response spikes

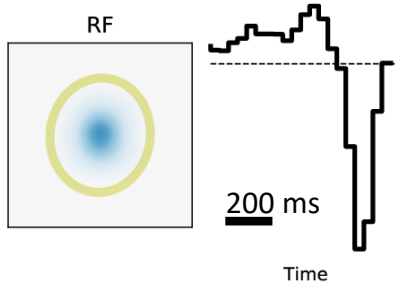


Many perturbations for each reference image.

Local STA

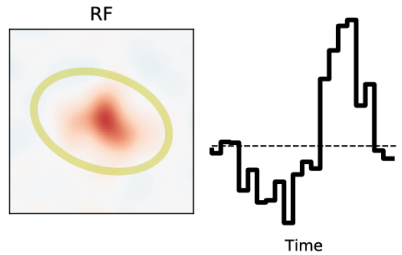
Variations in polarity for the same cell





Classical OFF cell

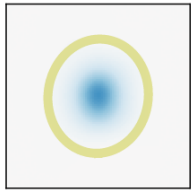


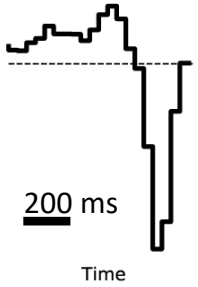


Classical ON cell

Variations in polarity for the same cell

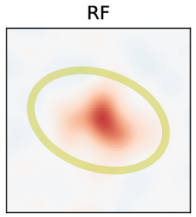


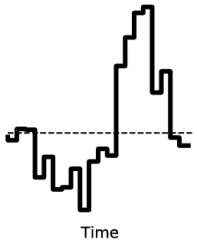




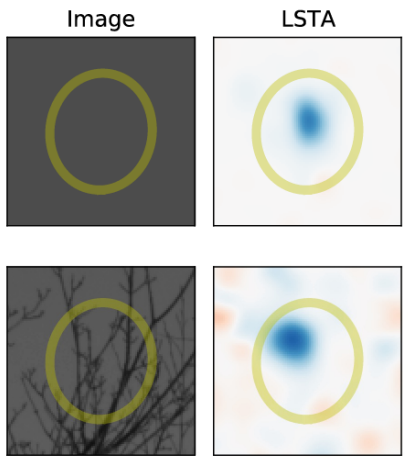
Classical OFF cell



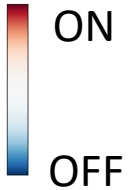


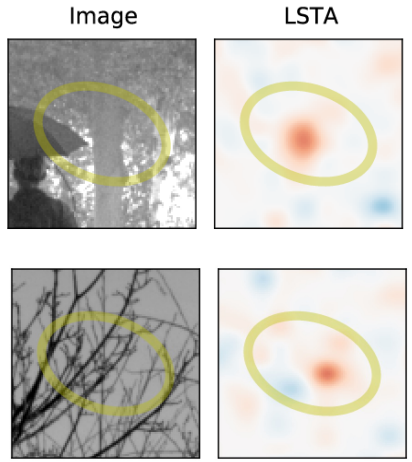


Classical ON cell



OFF

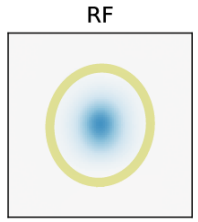


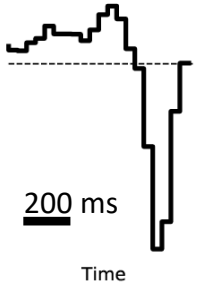


ON

Variations in polarity for the same cell

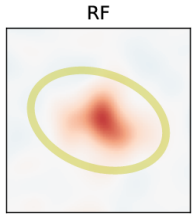


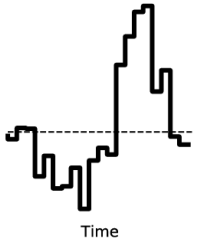




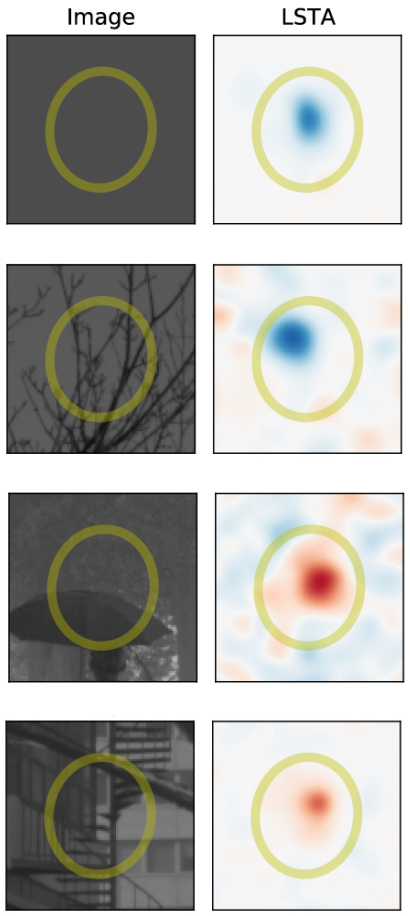
Classical OFF cell





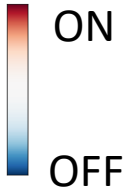


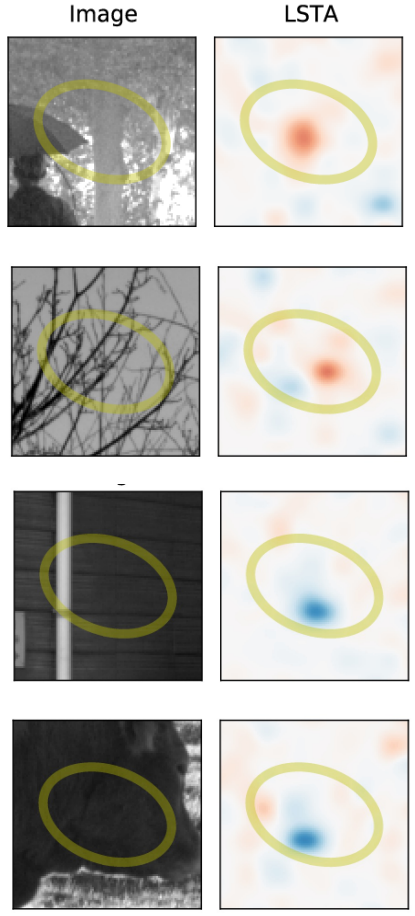
Classical ON cell



OFF

ON





ON

OFF

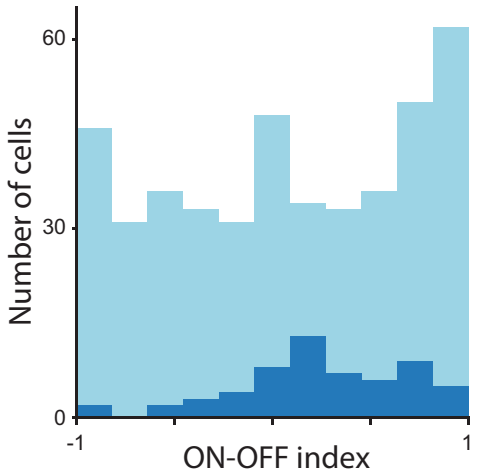
Depending on the image, the image-dependent receptive field (LSTA) can be ON or OFF.

Polarity inversion in many cell types

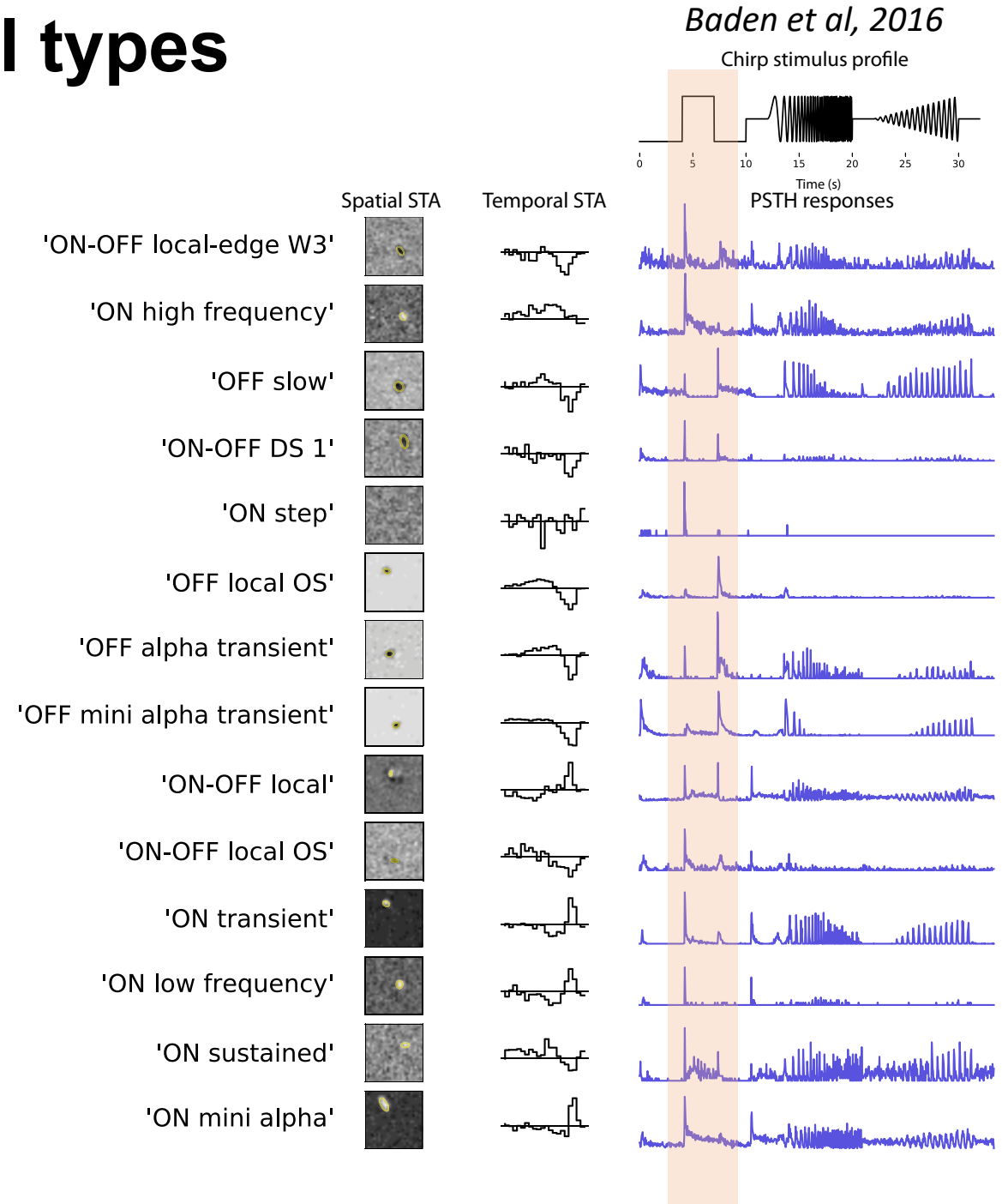
This effect is observed in many cell types.

Not just standard "ON-OFF" ganglion cells.

Large changes in the ON-OFF ratio.

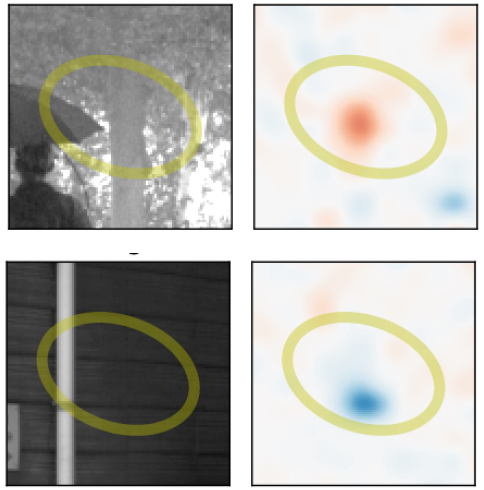


Baden et al, 2016



Intermediate conclusion 1

Polarity is context-dependent

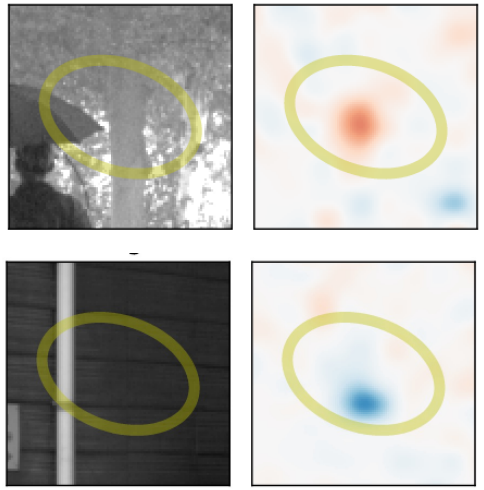


ON

OFF

Intermediate conclusion 1

Polarity is context-dependent



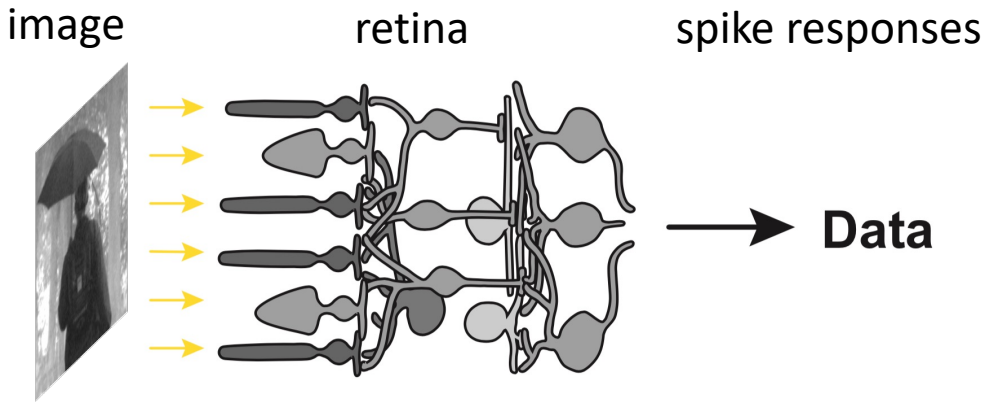
ON

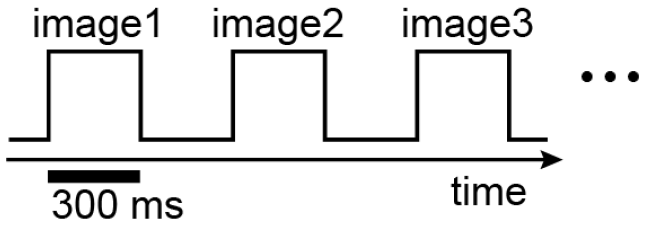
OFF

Can we find a model to reproduce these findings ?

Modeling retina responses

Experimental training protocol

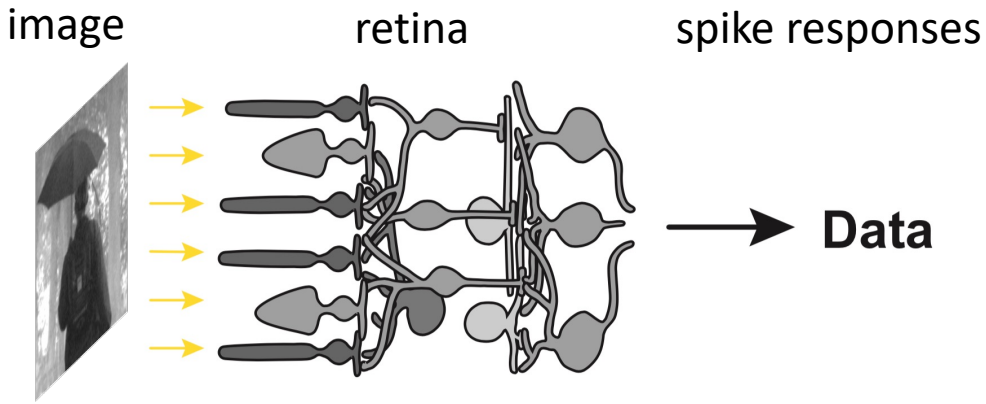


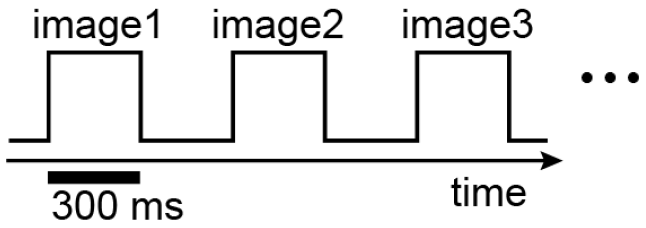




Modeling retina responses

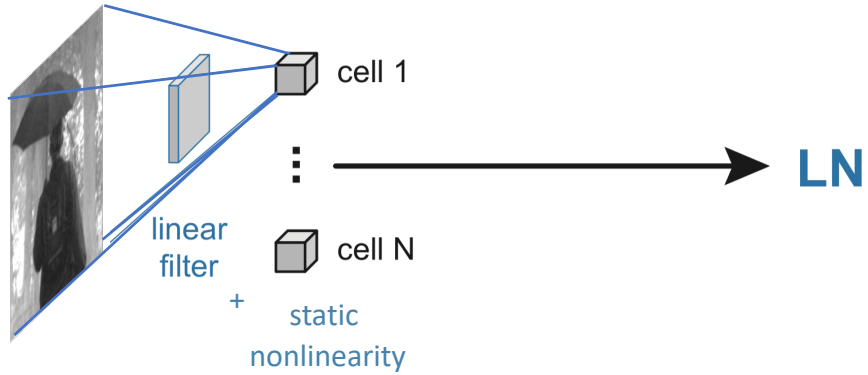
Experimental training protocol





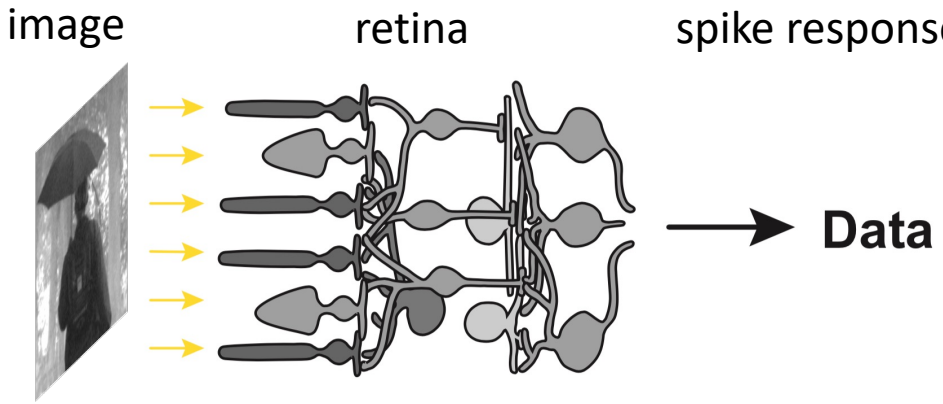


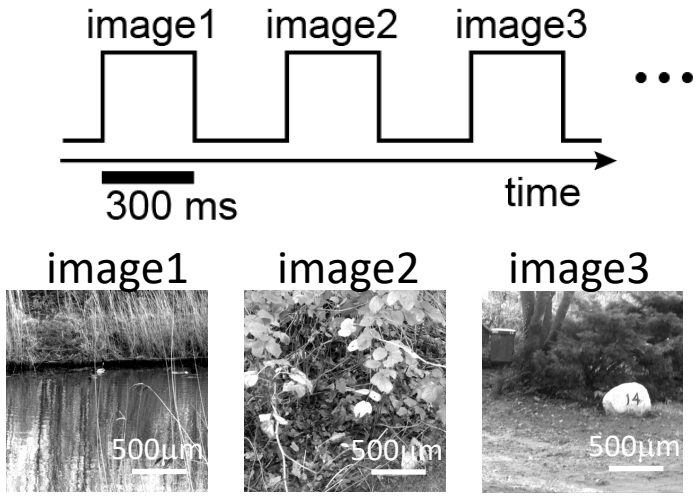
Linear Nonlinear model



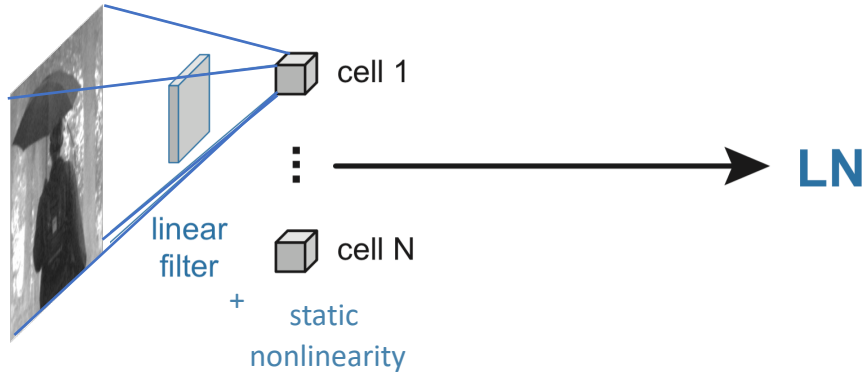
Modeling retina responses

Experimental training protocol

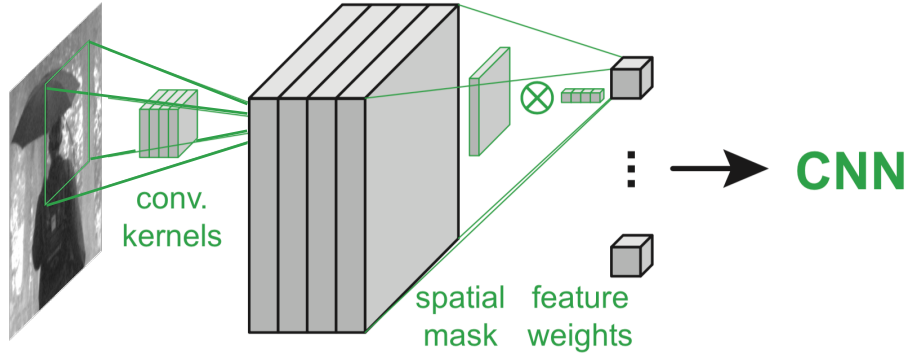




Linear Nonlinear model

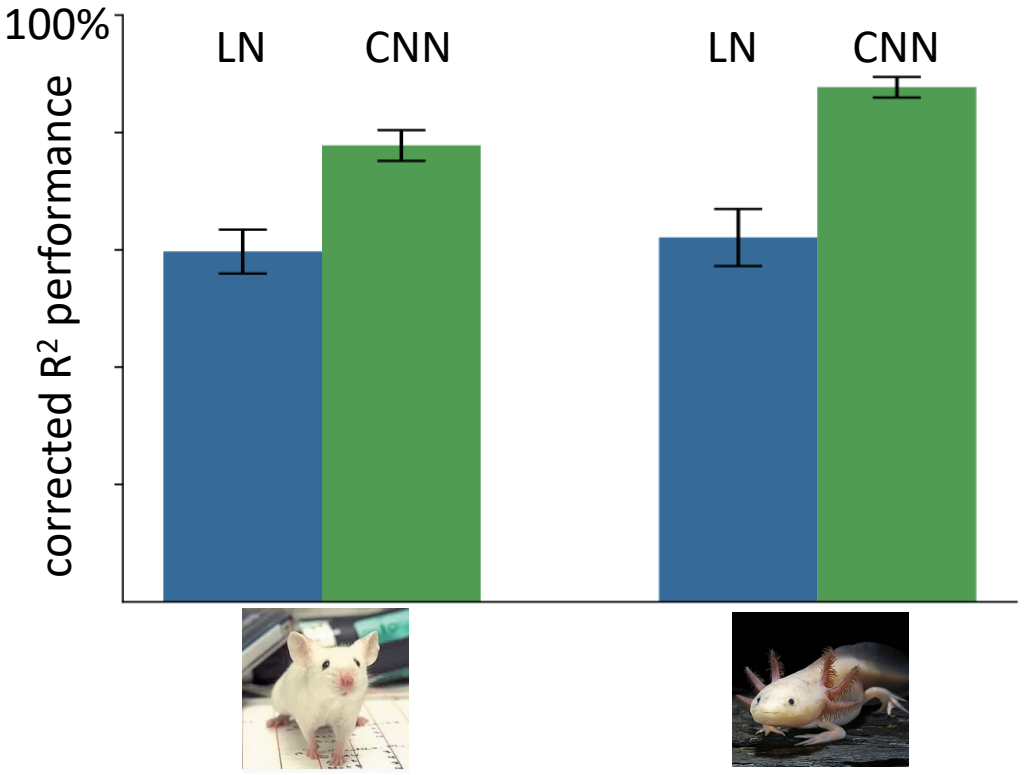


Convolutional Neural Network model

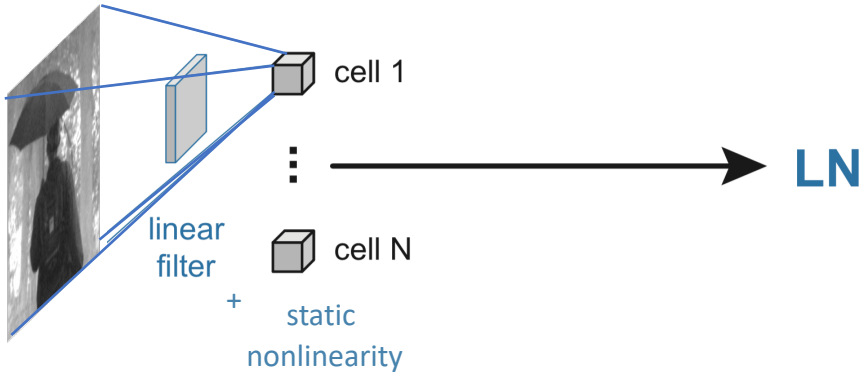


Modeling retina responsese

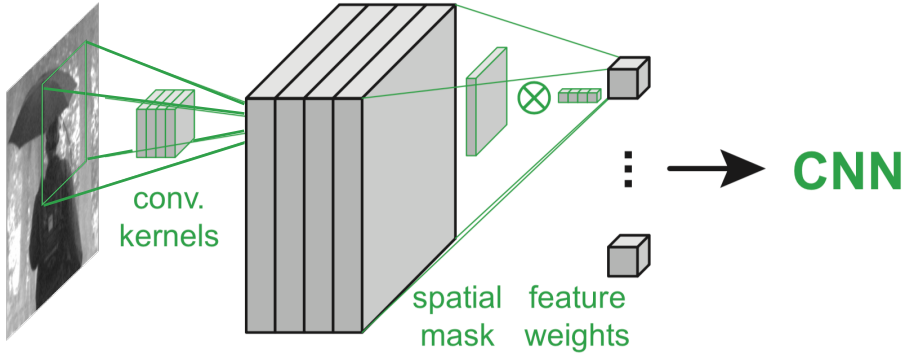
CNN performs better than LN



Linear Nonlinear model

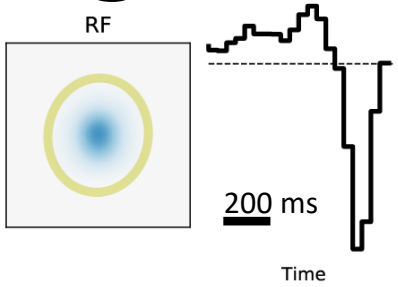


Convolutional Neural Network model

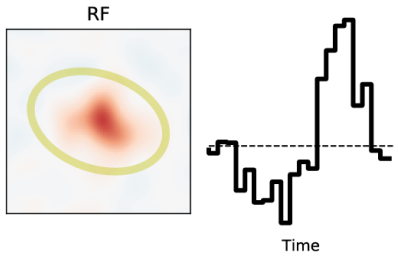


Testing different models

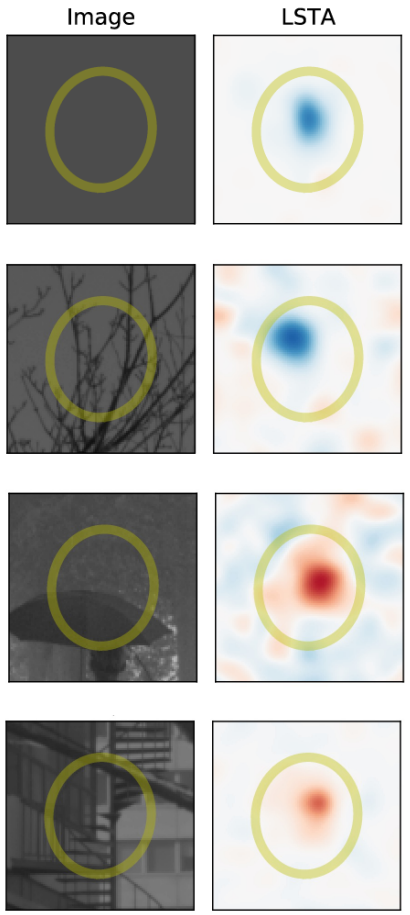


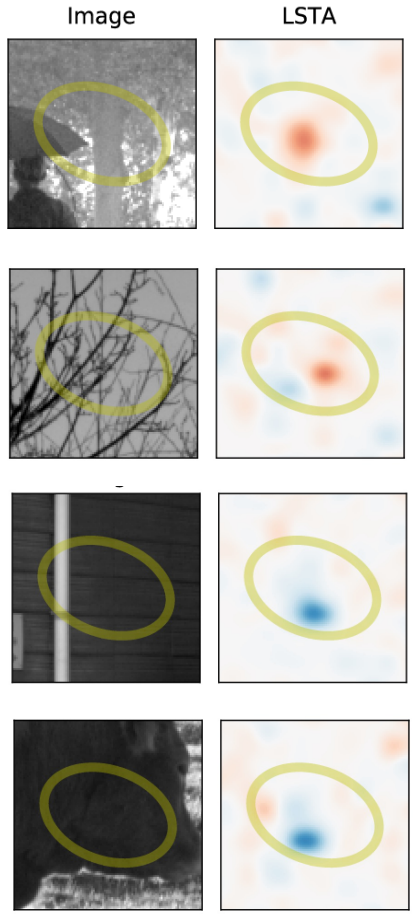


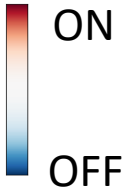




Prediction of the RF shape (not amplitude).

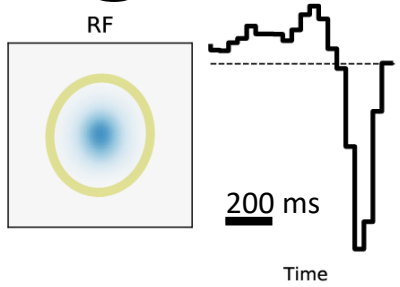




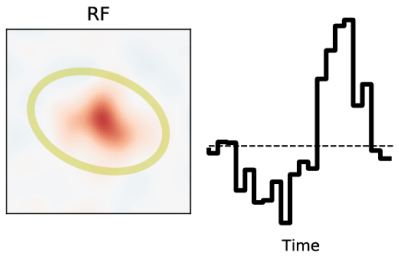


Testing different models

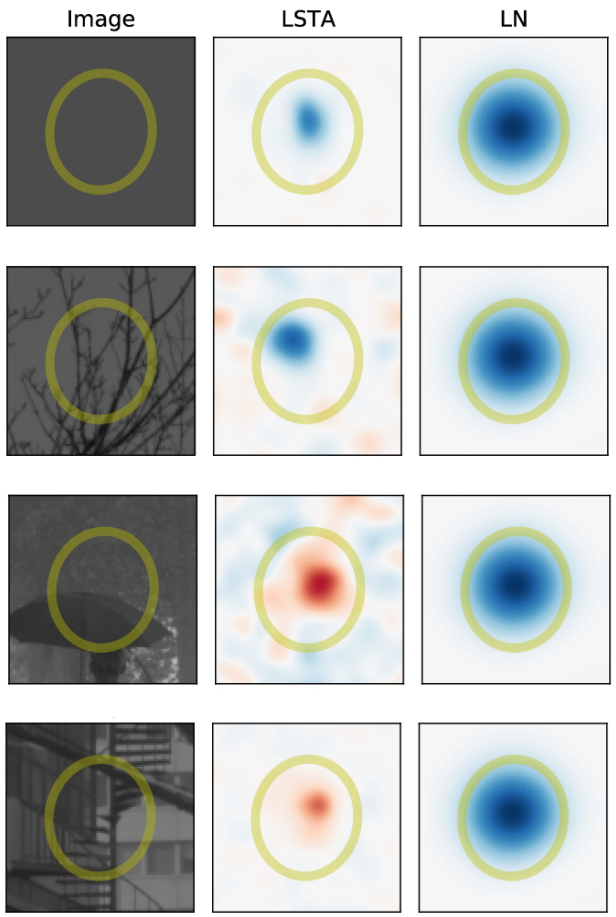


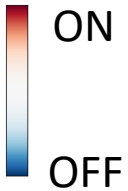


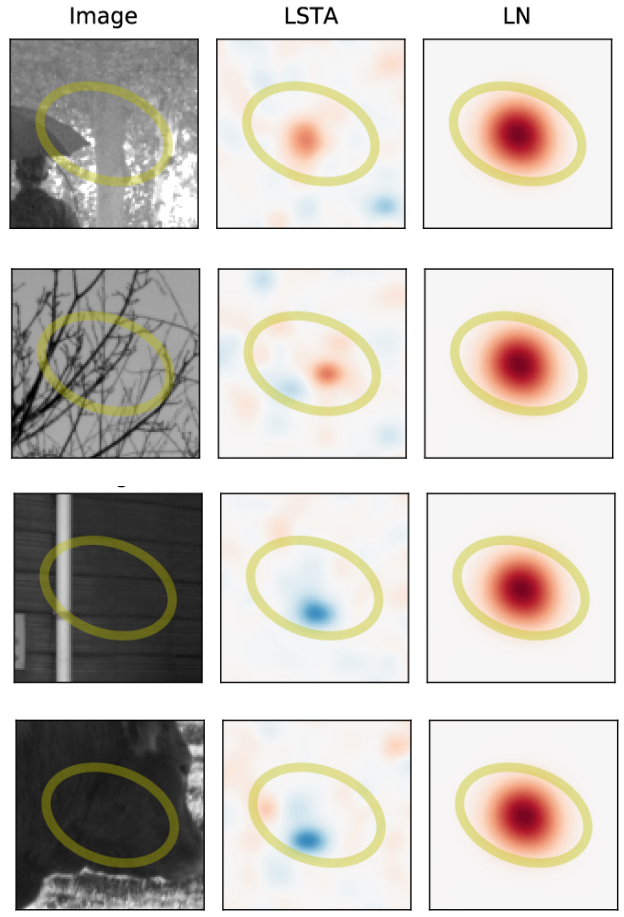




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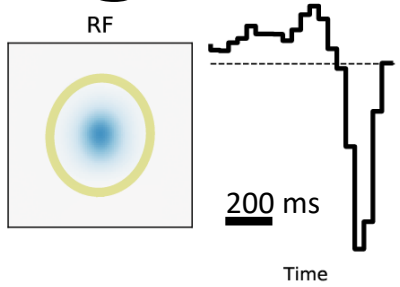




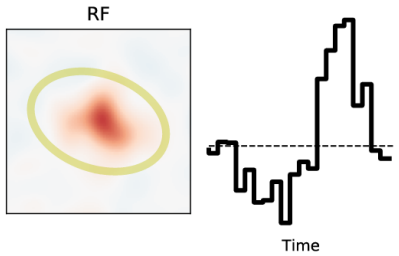
LN model cannot show polarity inversion.

Testing different models

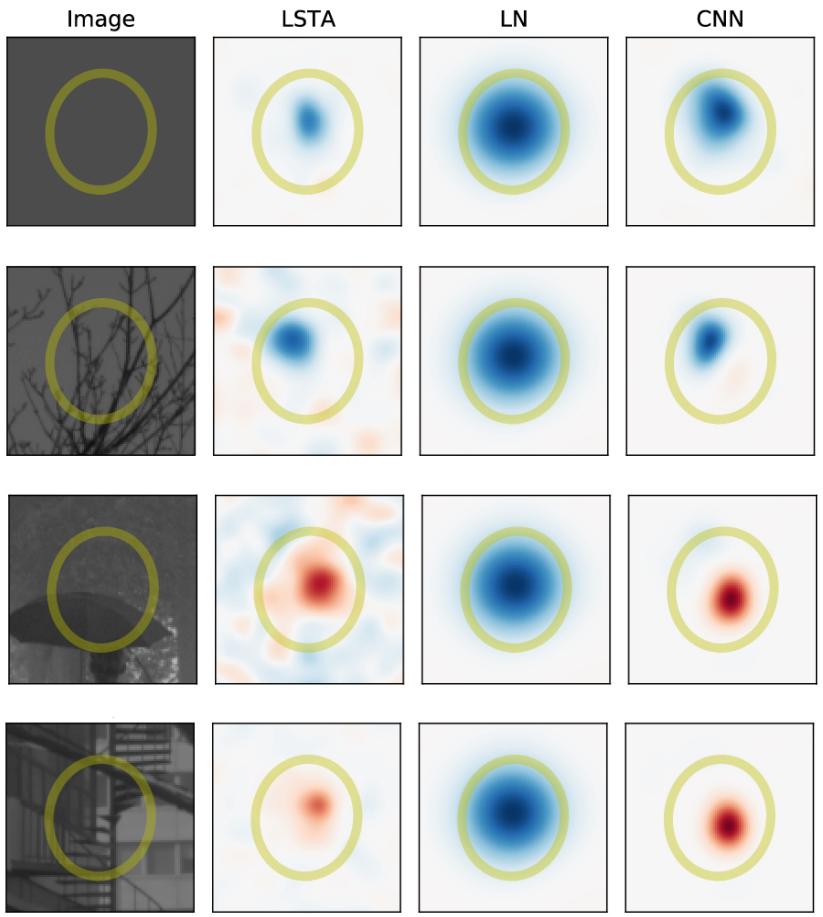


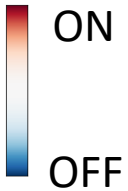


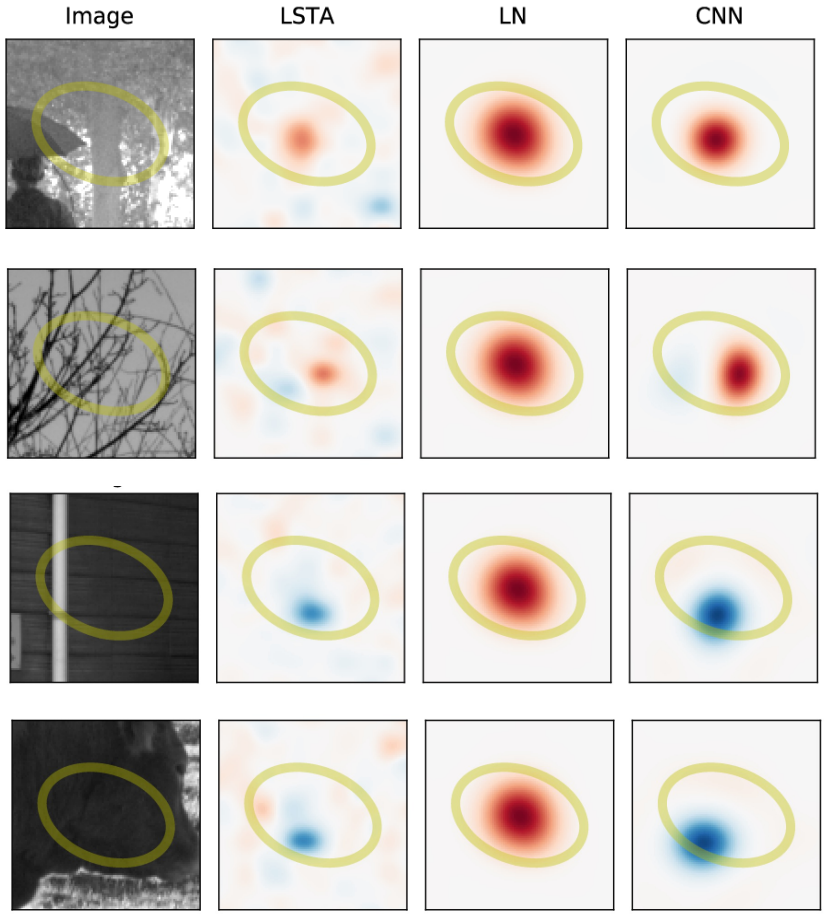




Prediction of the RF shape (not amplitude).





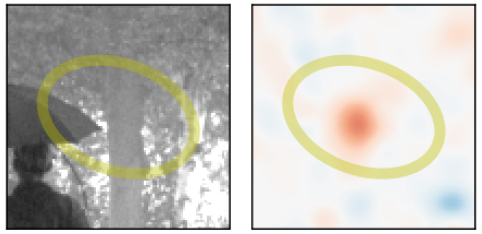


LN model cannot show polarity inversion.

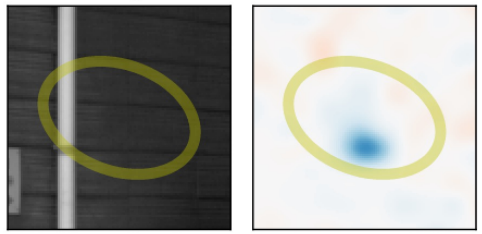
CNN predicts:
- ✓ polarity
- ✓ shape
- ✓ position

Intermediate conclusion 2

Polarity is context-dependent

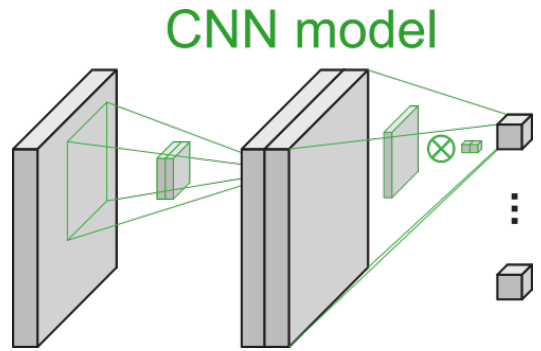


ON



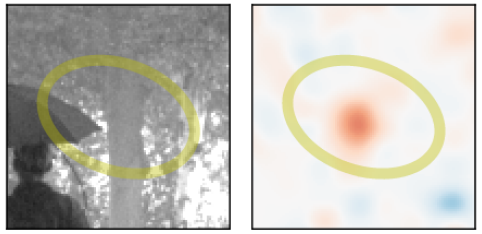
OFF

ON-OFF pathway convergence allows polarity inversion
A CNN model predicts these findings.

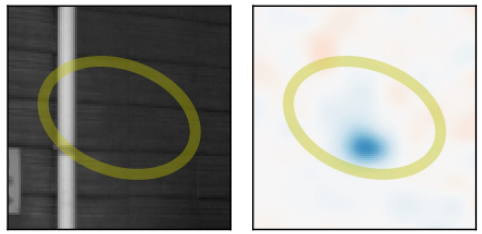


Intermediate conclusion 2

Polarity is context-dependent

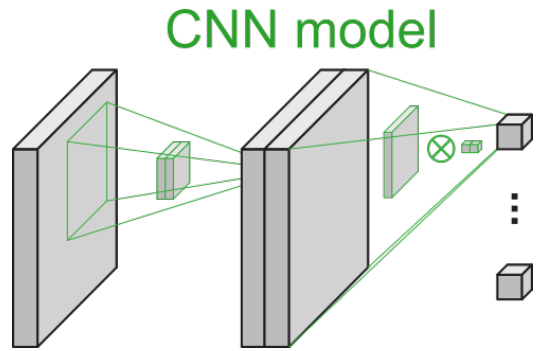


ON



OFF

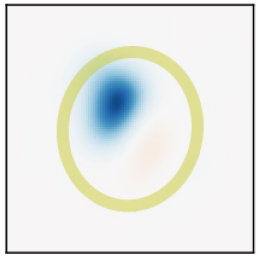
ON-OFF pathway convergence allows polarity inversion
A CNN model predicts these findings.



What is the relation between image and LSTA?



?



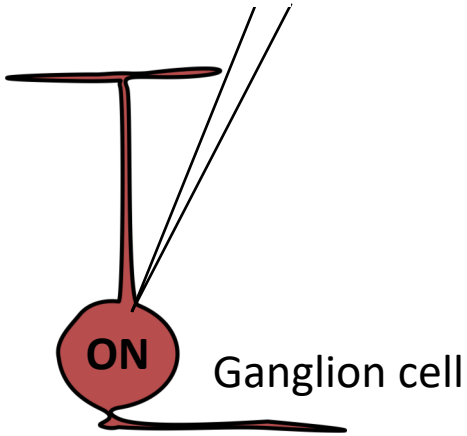
Selectivity in natural contexts





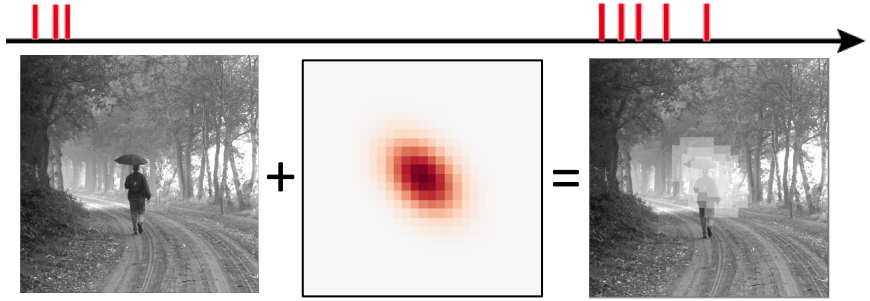


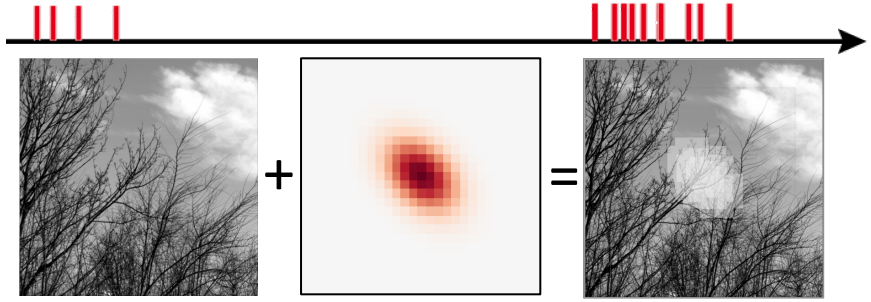


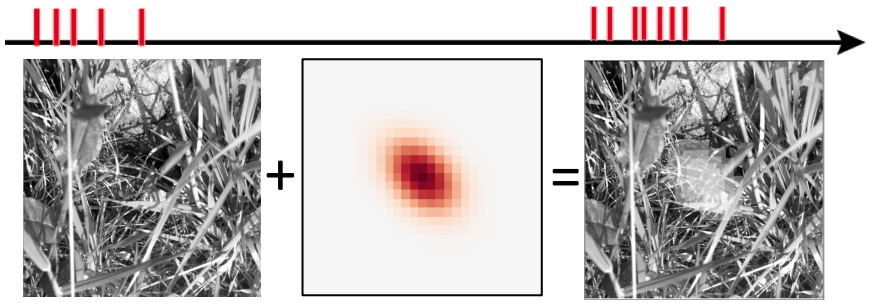


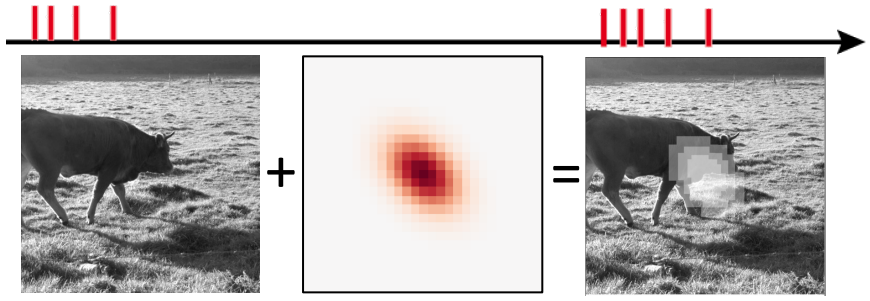
Ganglion cell

Selectivity in natural contexts

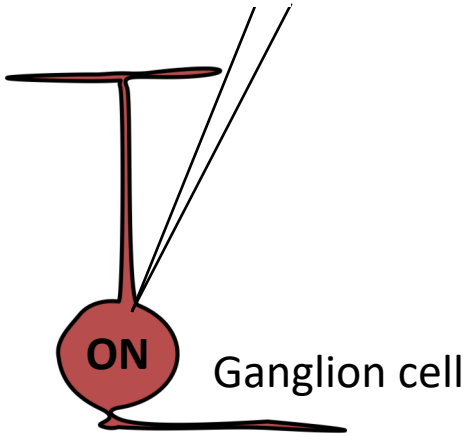






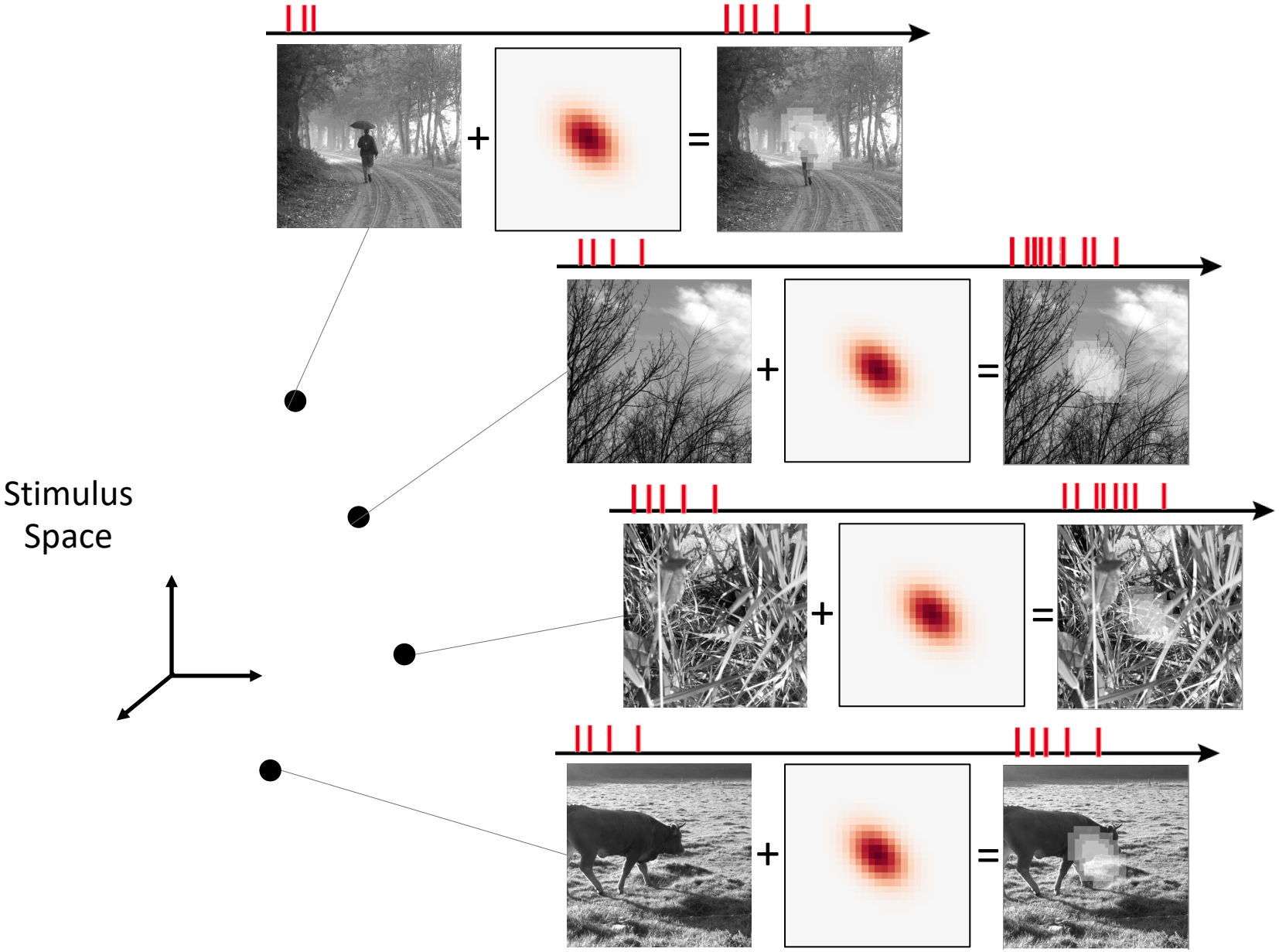


ON cell = increasing locally the luminance increases the firing rate



Ganglion cell

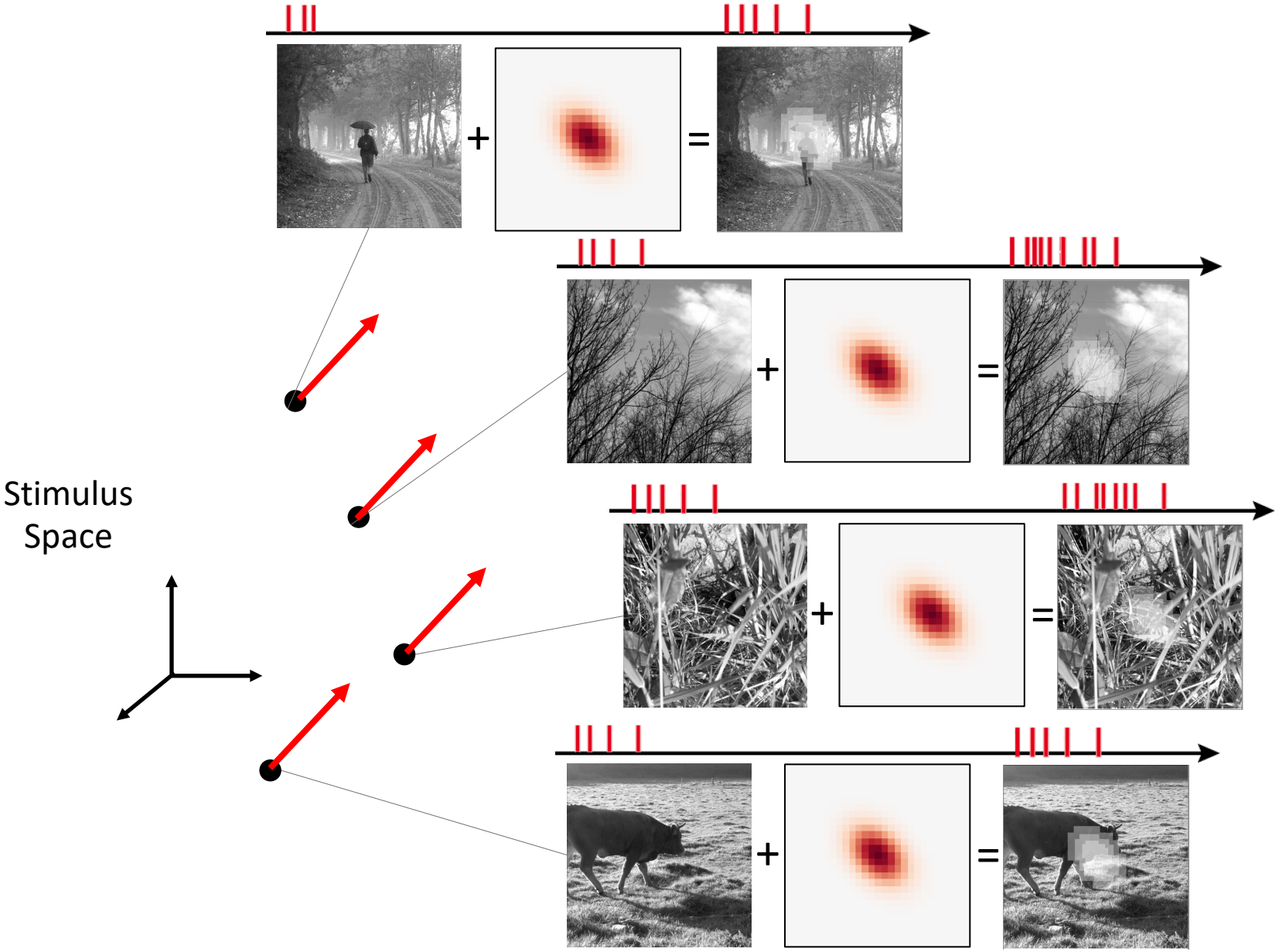
Selectivity in natural contexts



ON cell = increasing locally the luminance increases the firing rate

Image = a point in stimulus space

Selectivity in natural contexts

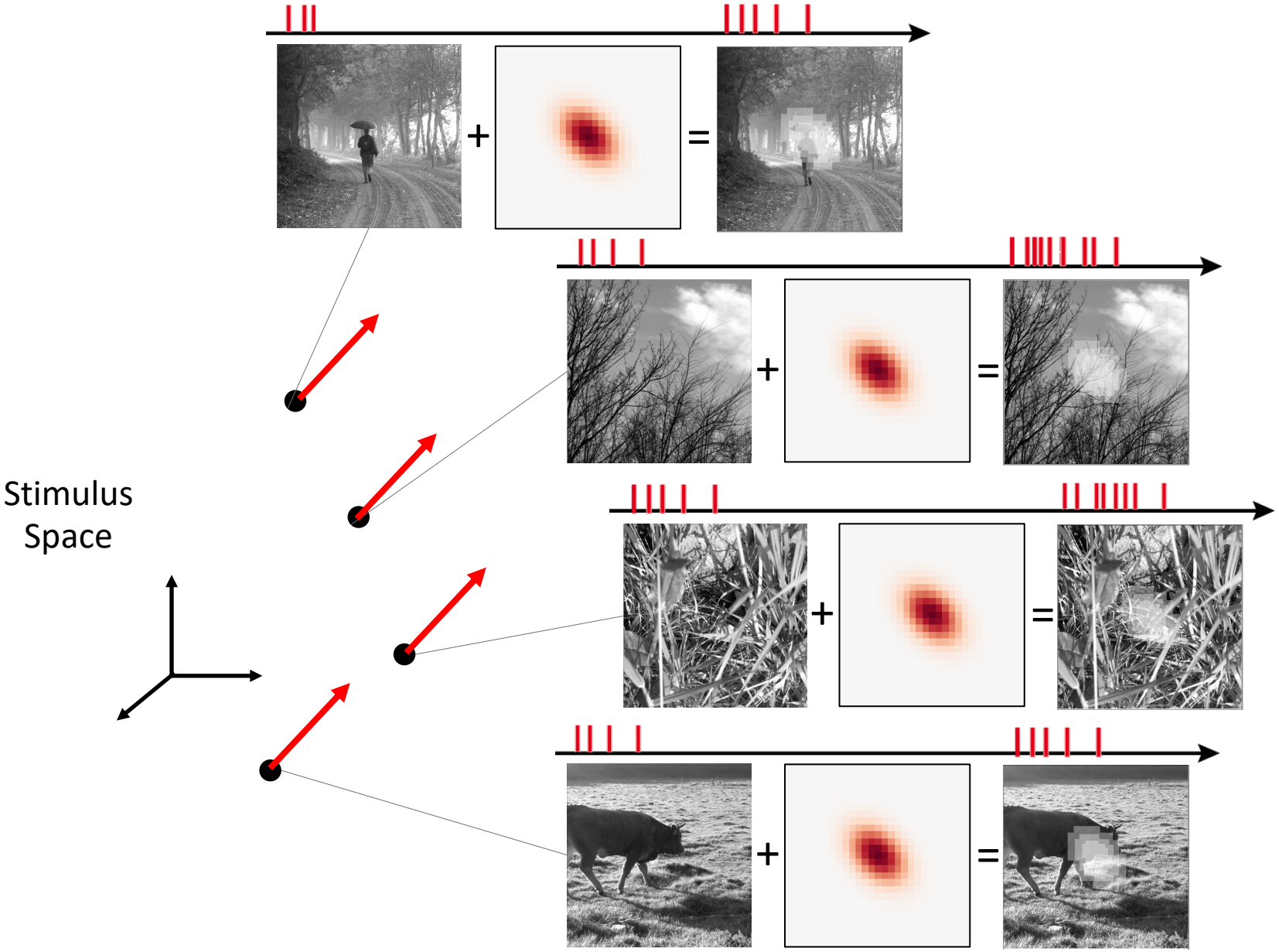


ON cell = increasing locally the luminance increases the firing rate

Image = a point in stimulus space

Arrow = Best direction in the stimulus space to increase the firing rate.

Selectivity in natural contexts



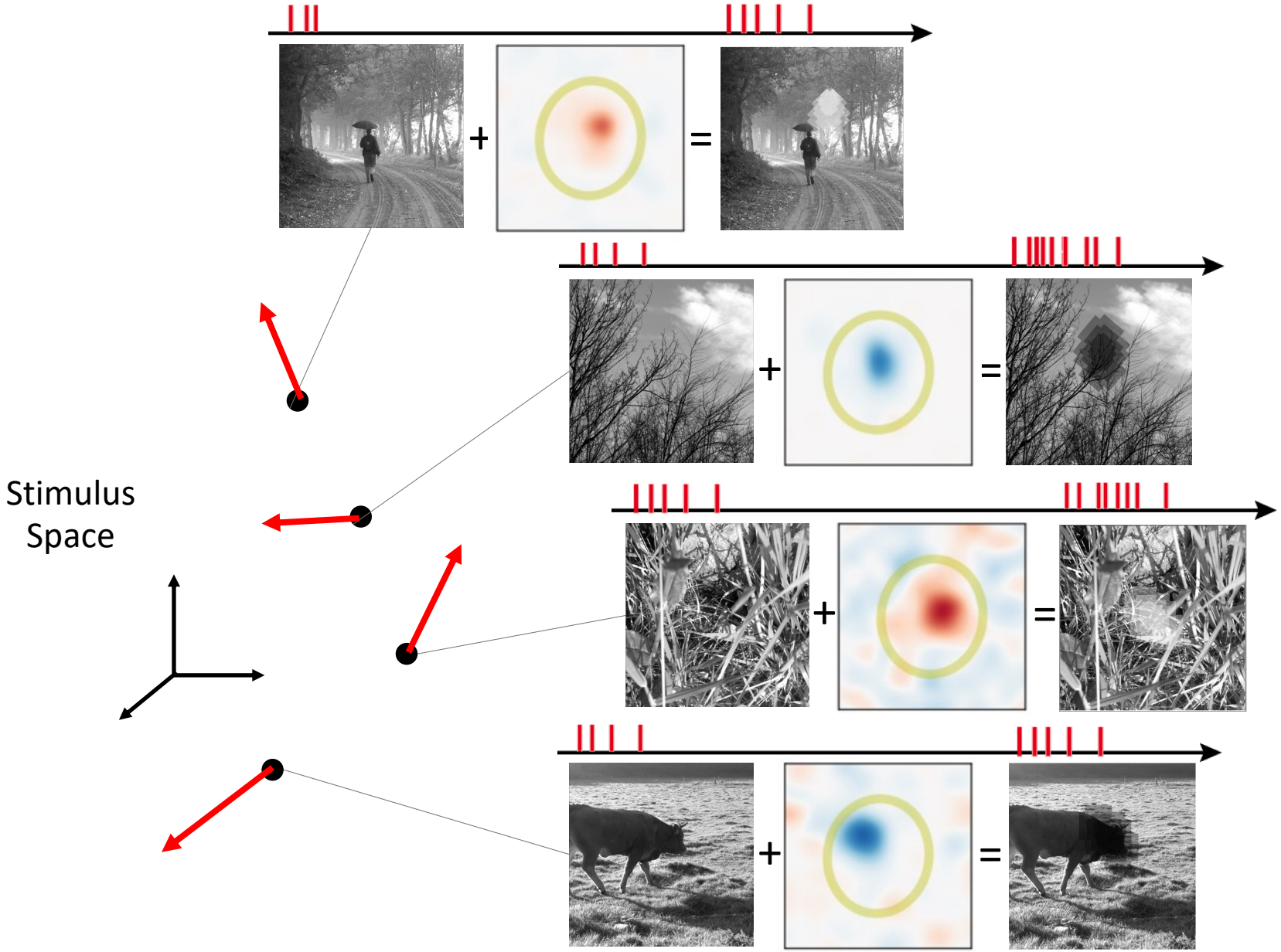
ON cell = increasing locally the luminance increases the firing rate

Image = a point in stimulus space

Arrow = Best direction in the stimulus space to increase the firing rate.

We showed ON-OFF selectivity changes with natural stimuli

Selectivity in natural contexts



ON cell = increasing locally the luminance increases the firing rate

Image = a point in stimulus space

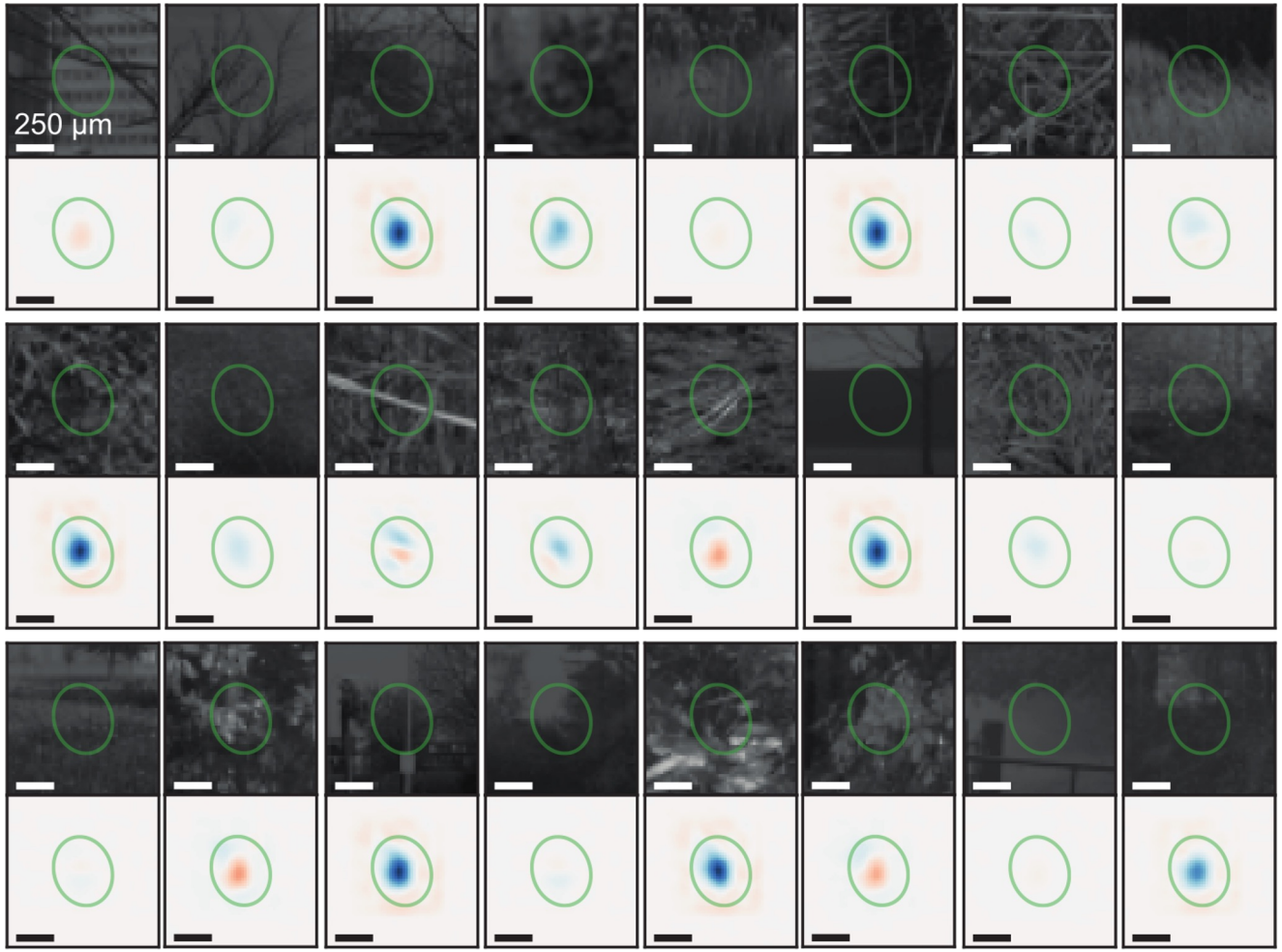
Arrow = Best direction in the stimulus space to increase the firing rate.

We showed ON-OFF selectivity changes with natural stimuli.

Finding the relevant subspace

The model generates ~4k image-dependent LSTAs

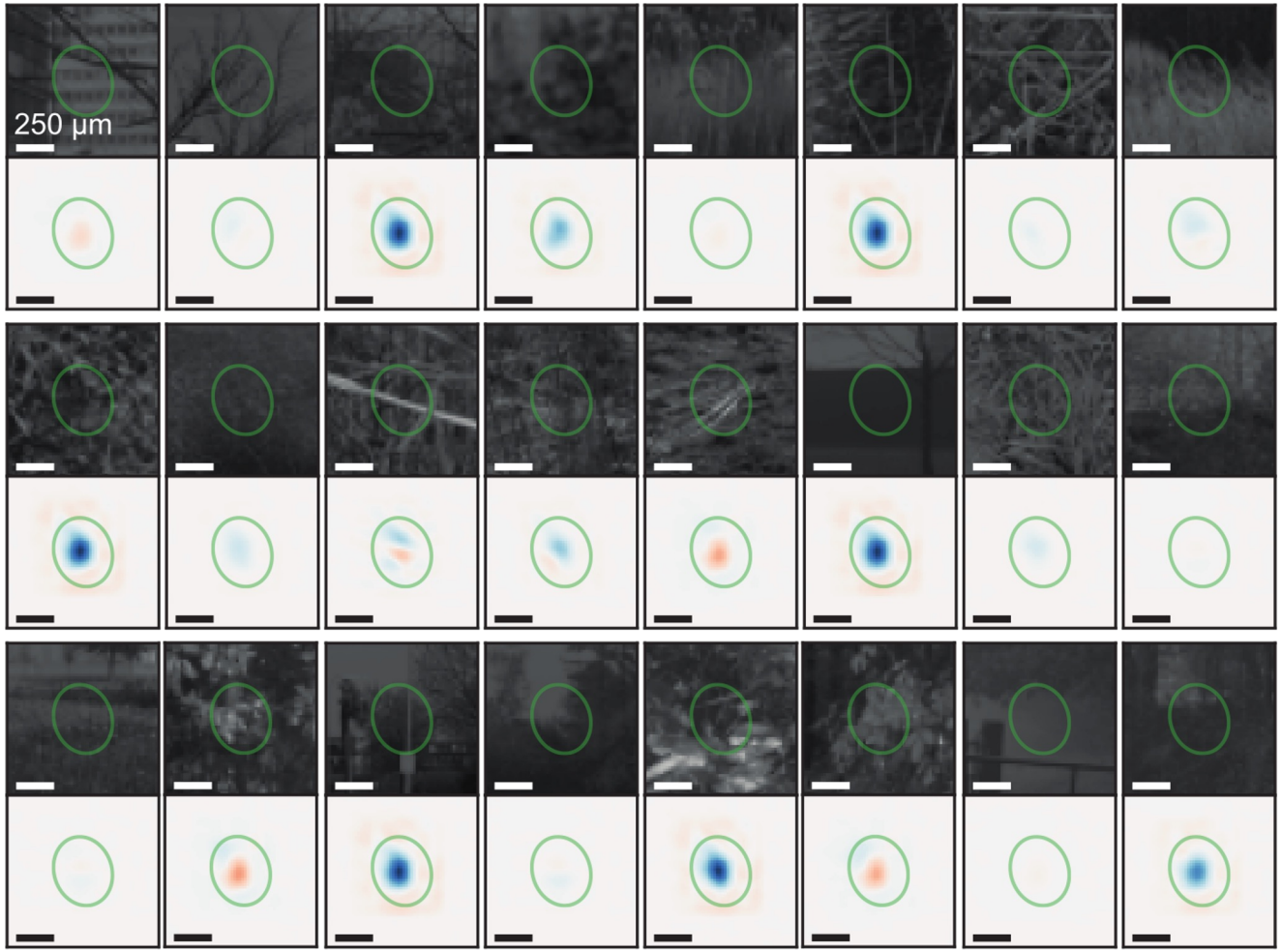
LSTA: Best direction to increase the response

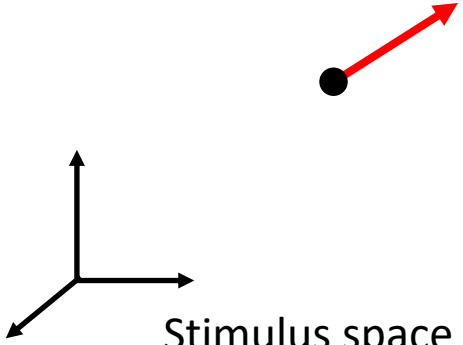


Finding the relevant subspace

The model generates ~4k image-dependent LSTAs

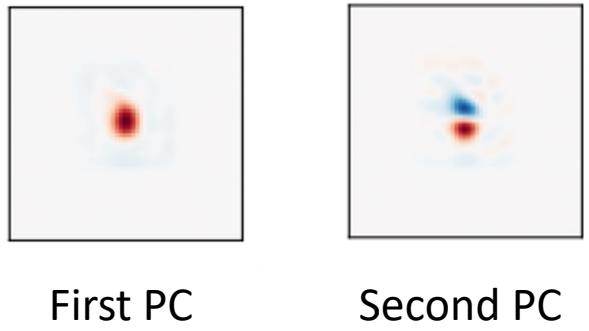
LSTA: Best direction to increase the response





2 PCAs explain ~85% of the total variance

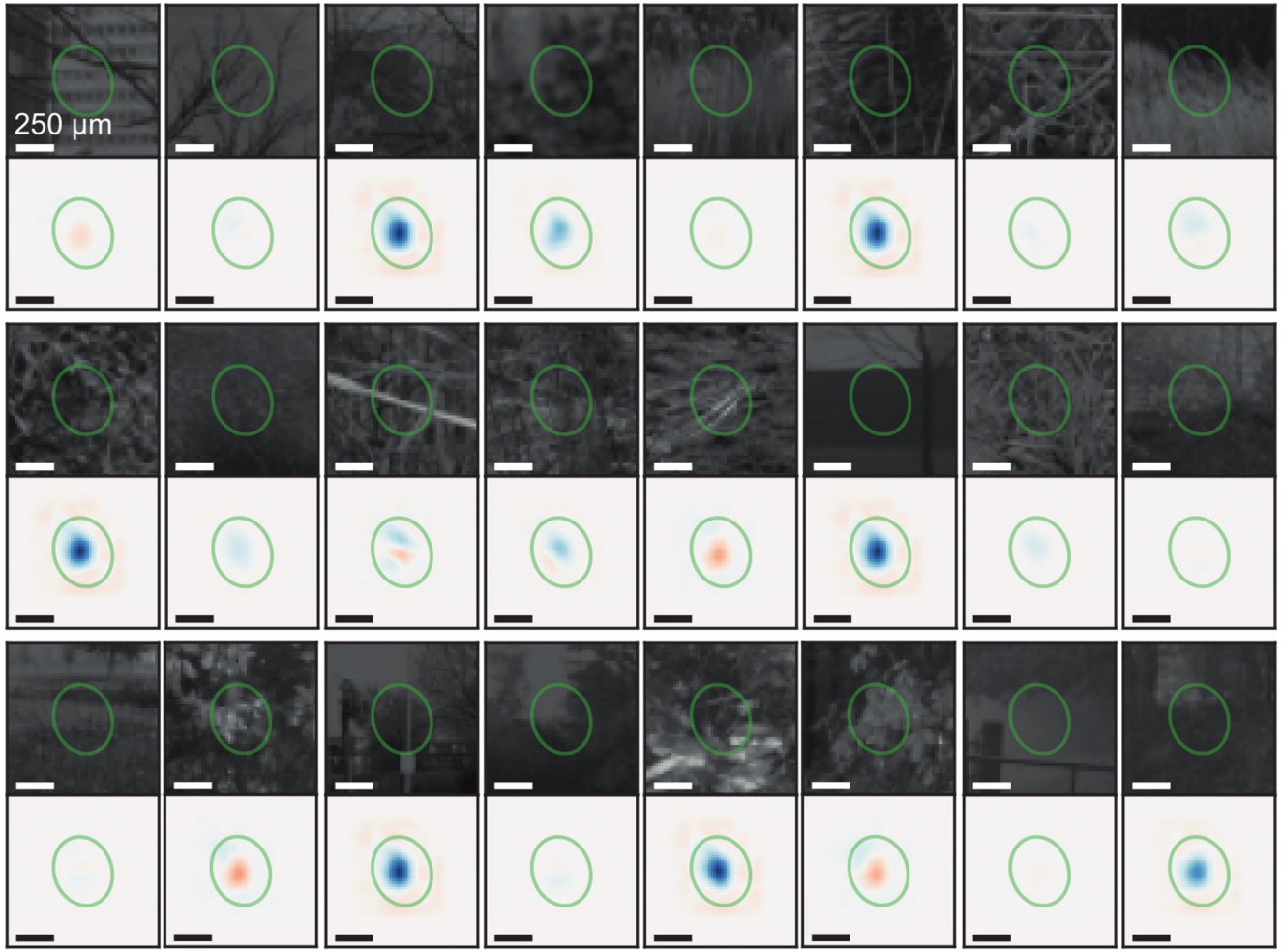
PCA

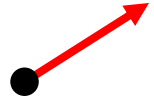


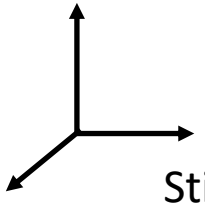
Finding the relevant subspace

The model generates ~4k image-dependent LSTAs

LSTA: Best direction to increase the response





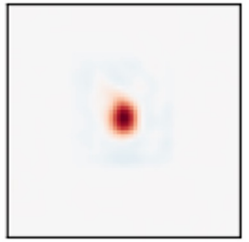


Stimulus space

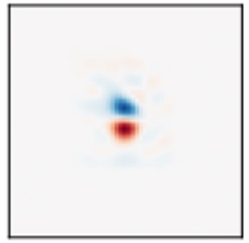
Relevant stimulus space is bidimensional

2 PCAs explain ~85% of the total variance

PCA



First PC

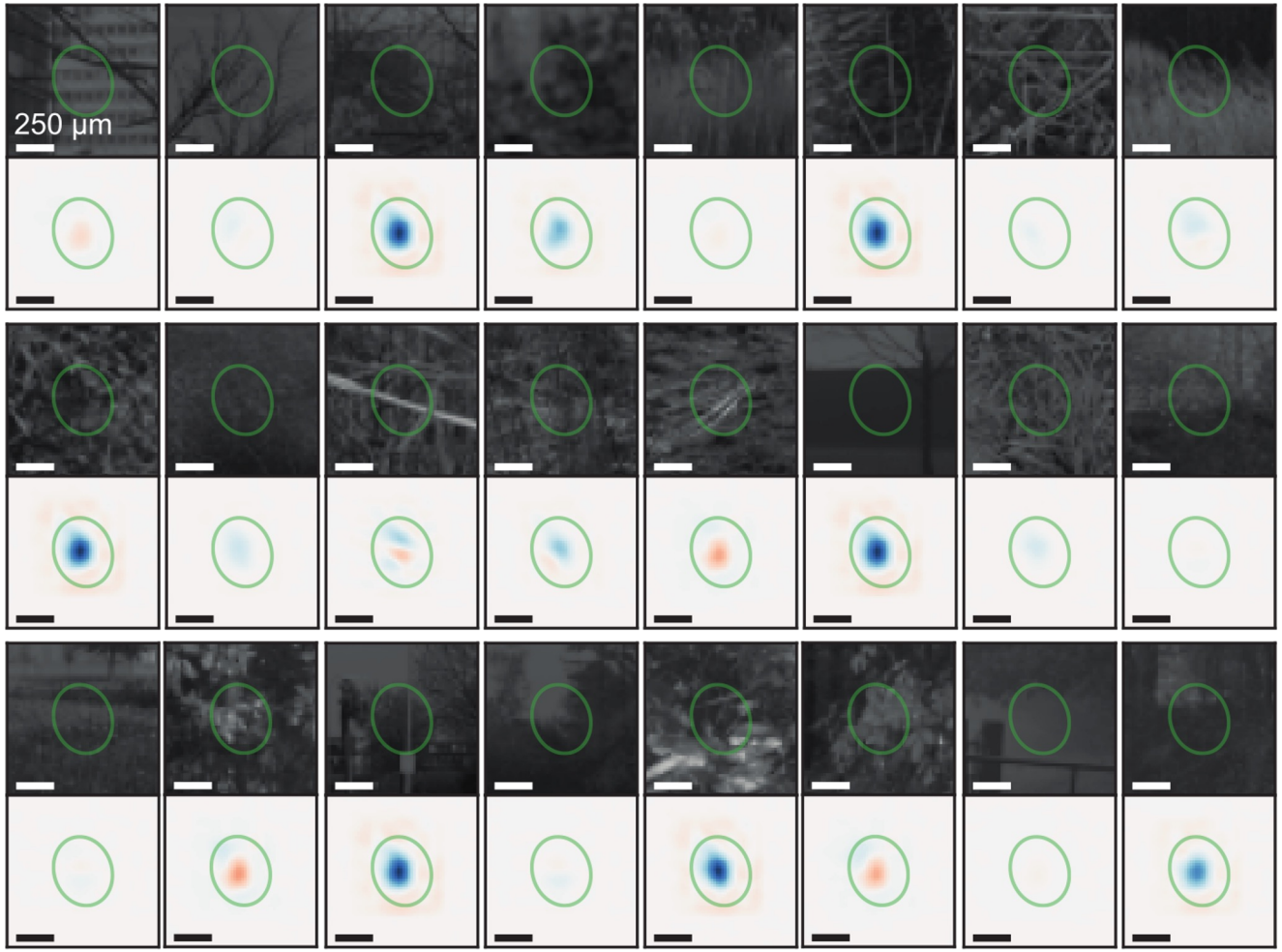


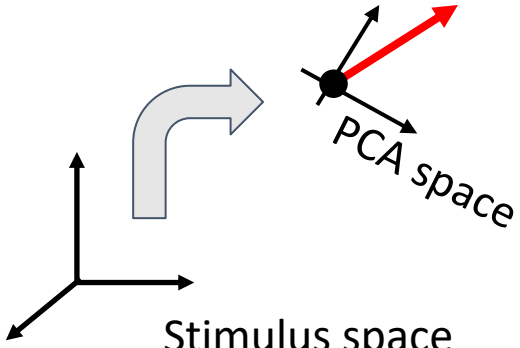
Second PC

Finding the relevant subspace

The model generates ~4k image-dependent LSTAs

LSTA: Best direction to increase the response





2 PCAs explain ~85% of the total variance

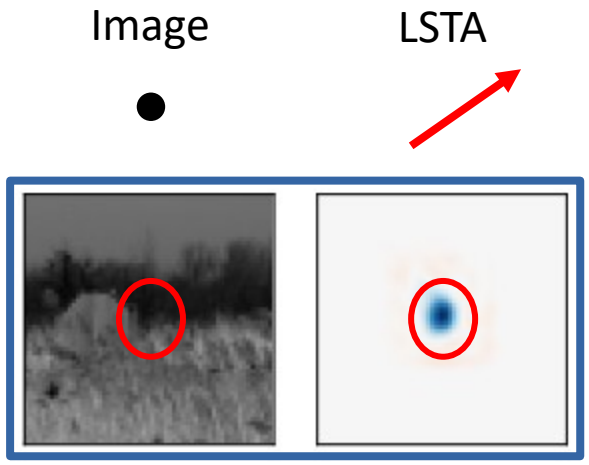
PCA

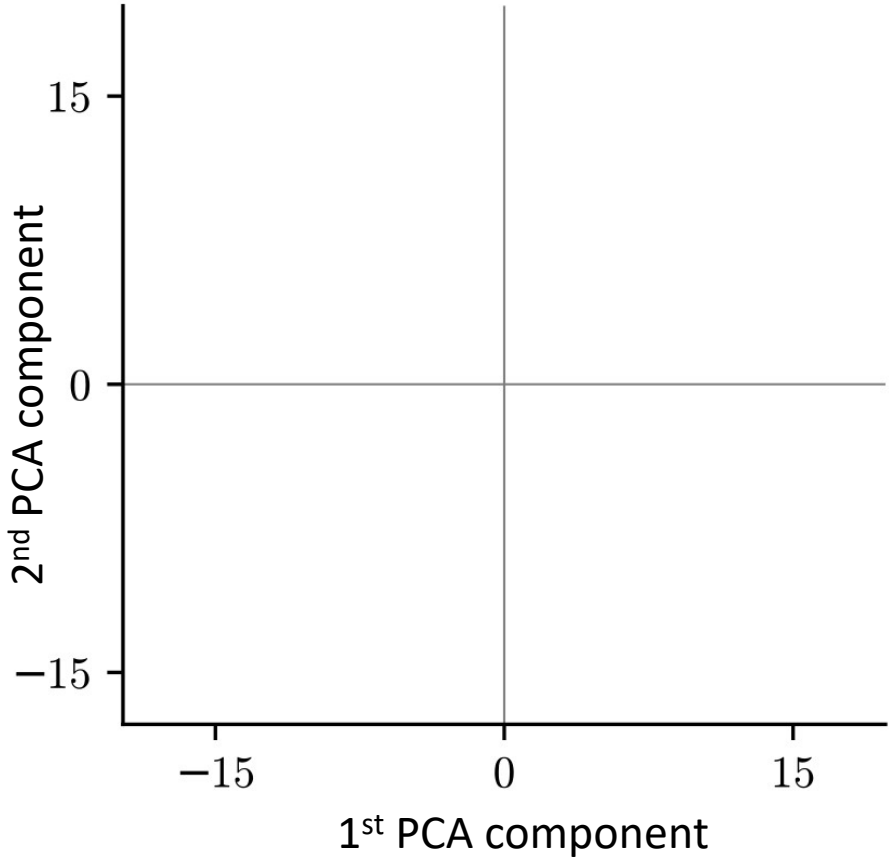


First PC

Second PC

Structure of the dependence on the image



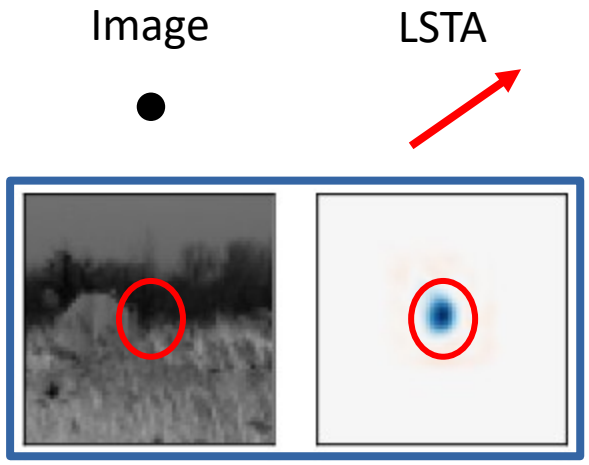


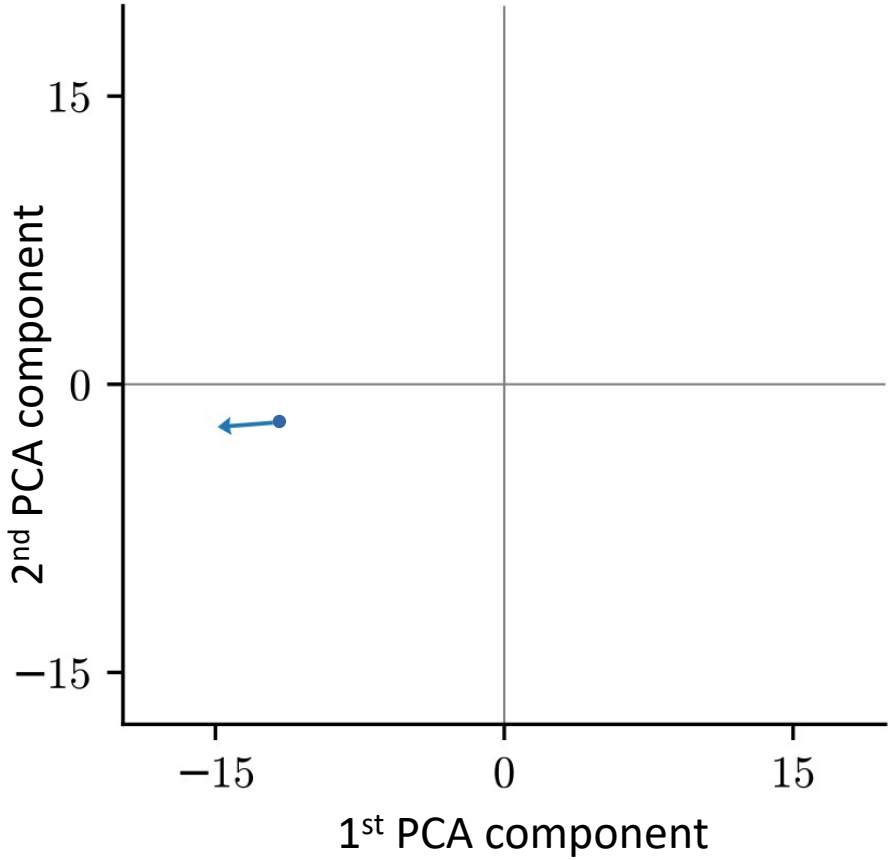
2D stimulus space representation

Starting point of the arrow:
the image in the stimulus space

Arrow: the LSTA corresponding to this image.

Structure of the dependence on the image



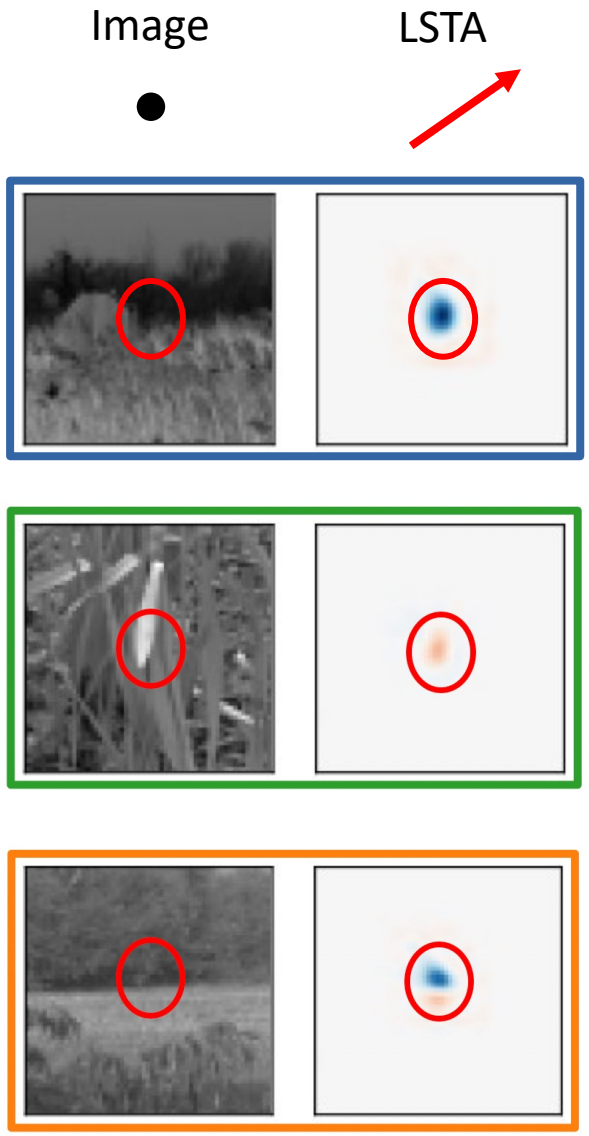


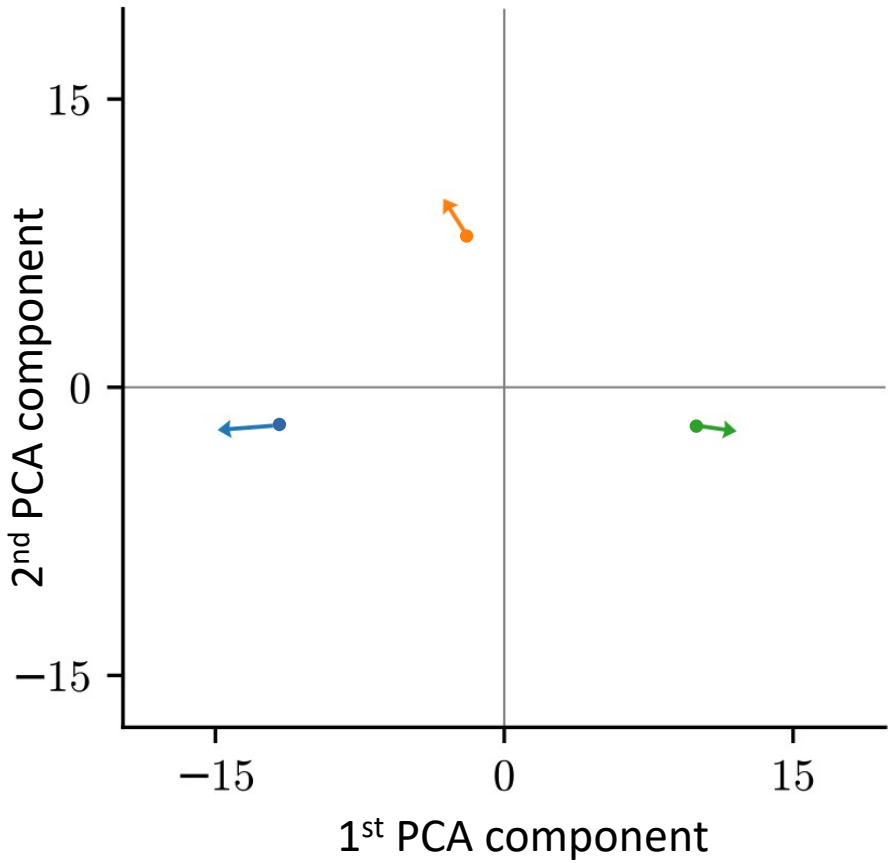
2D stimulus space representation

Starting point of the arrow:
the image in the stimulus space

Arrow: the LSTA corresponding to this image.

Structure of the dependence on the image



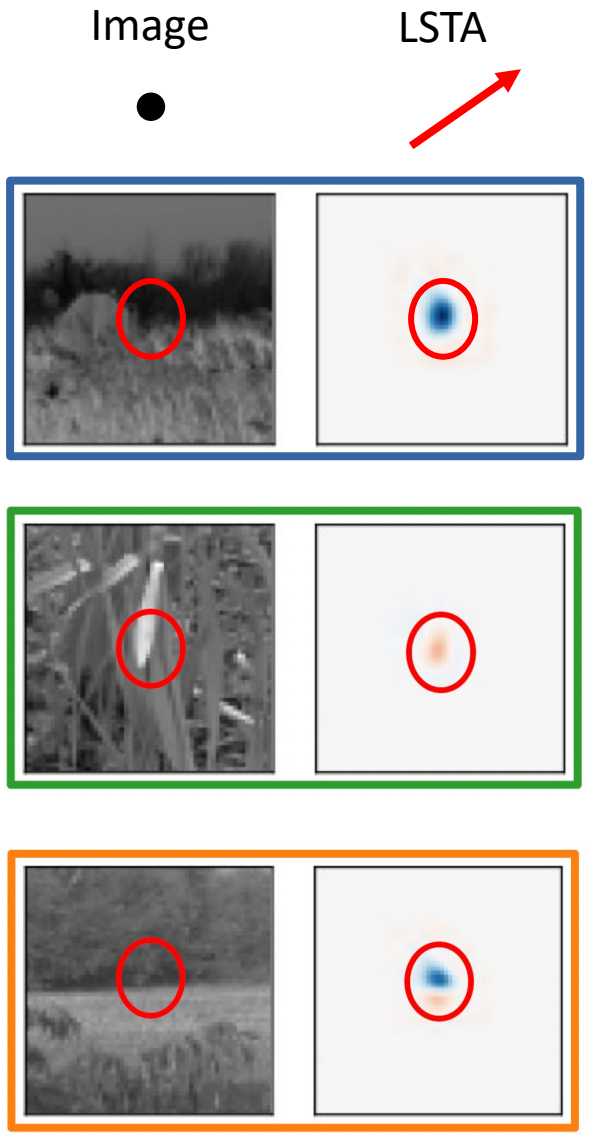


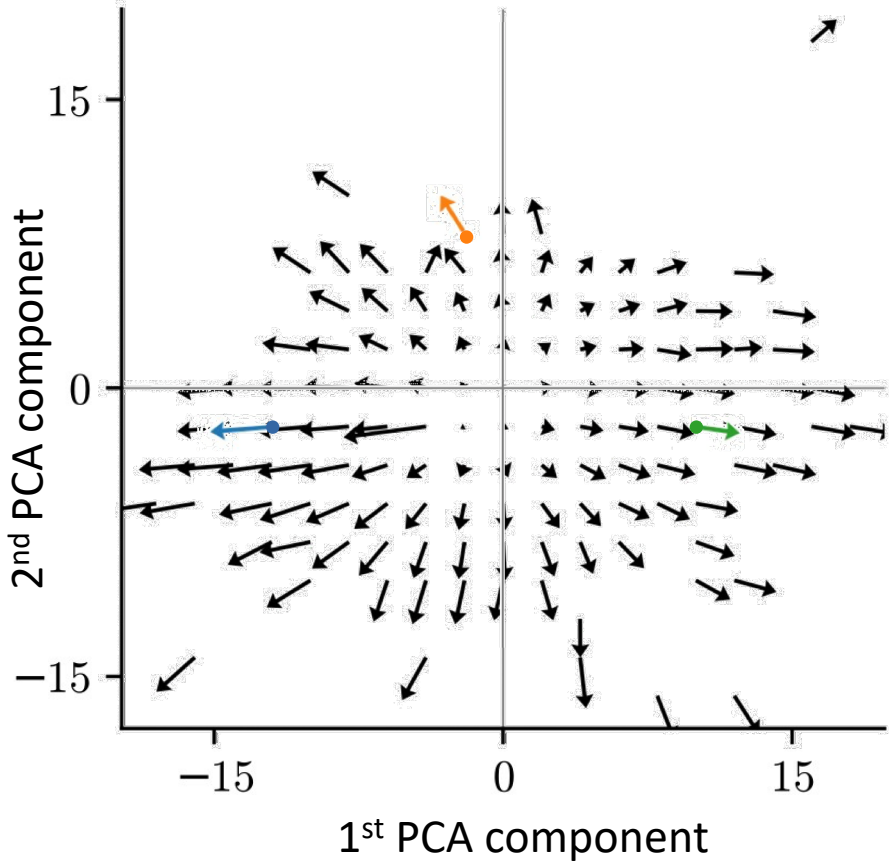
2D stimulus space representation

Starting point of the arrow:
the image in the stimulus space

Arrow: the LSTA corresponding to this image.

Structure of the dependence on the image





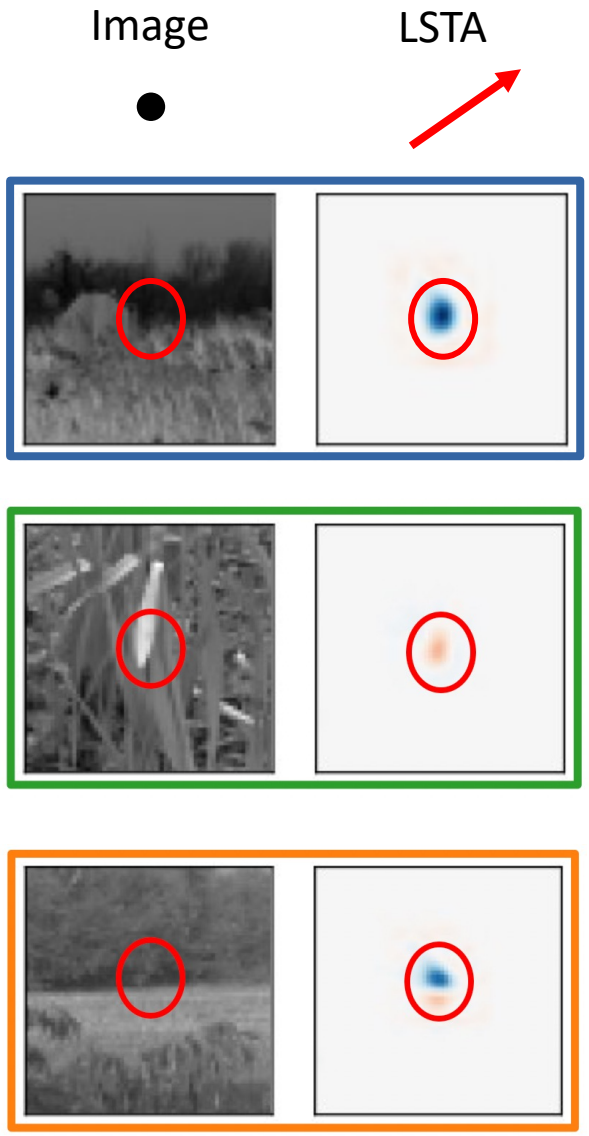
2D stimulus space representation

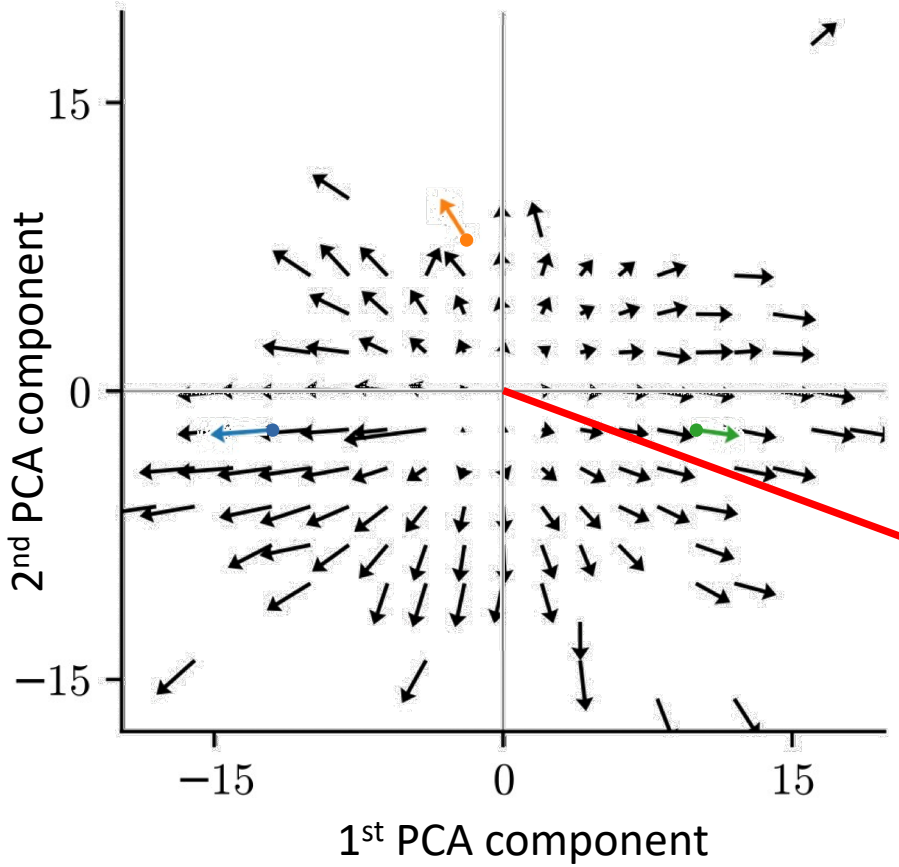
Starting point of the arrow:
the image in the stimulus space

Arrow: the LSTA corresponding to this image.

The LSTA varies consistently with the images.

Structure of the dependence on the image



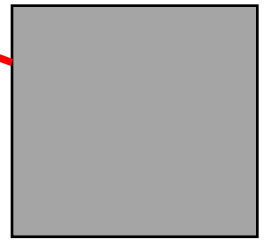


2D stimulus space representation

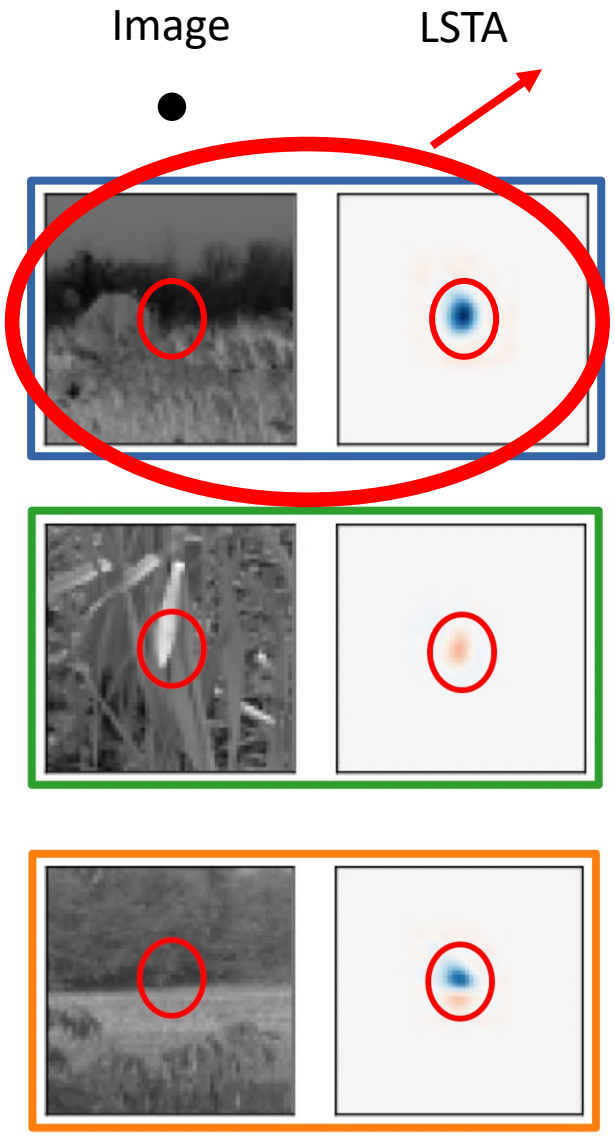
Starting point of the arrow:
the image in the stimulus space

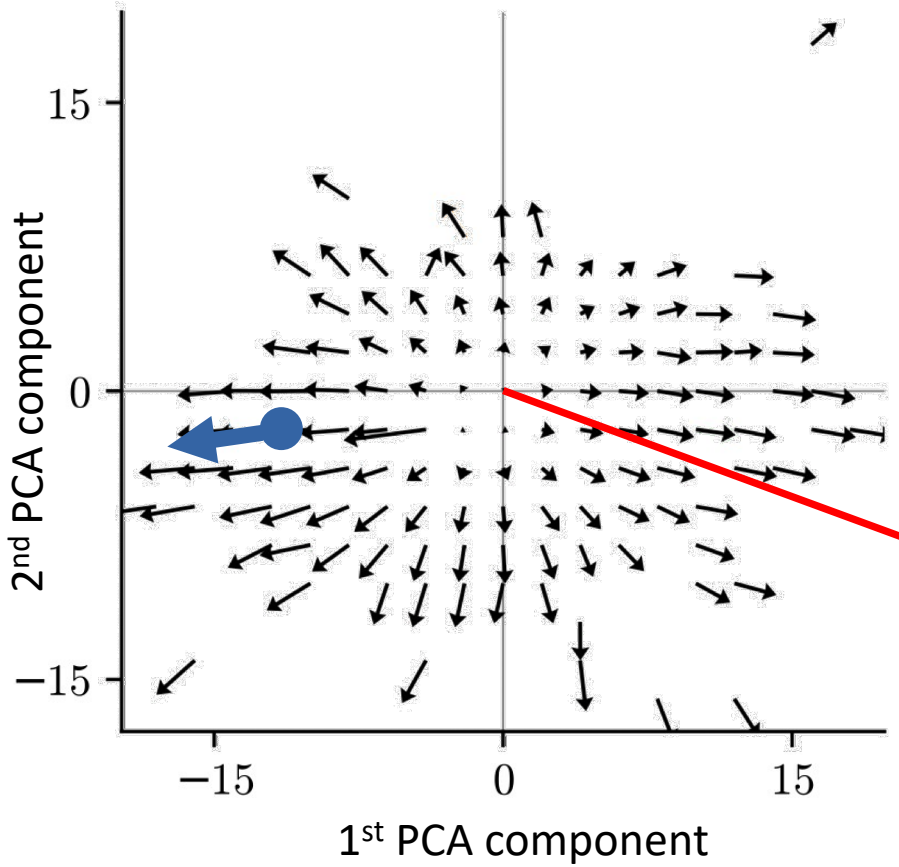
Arrow: the LSTA corresponding to this image.

The LSTA varies consistently with the images.



Structure of the dependence on the image



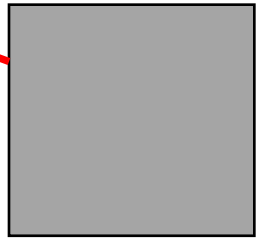


2D stimulus space representation

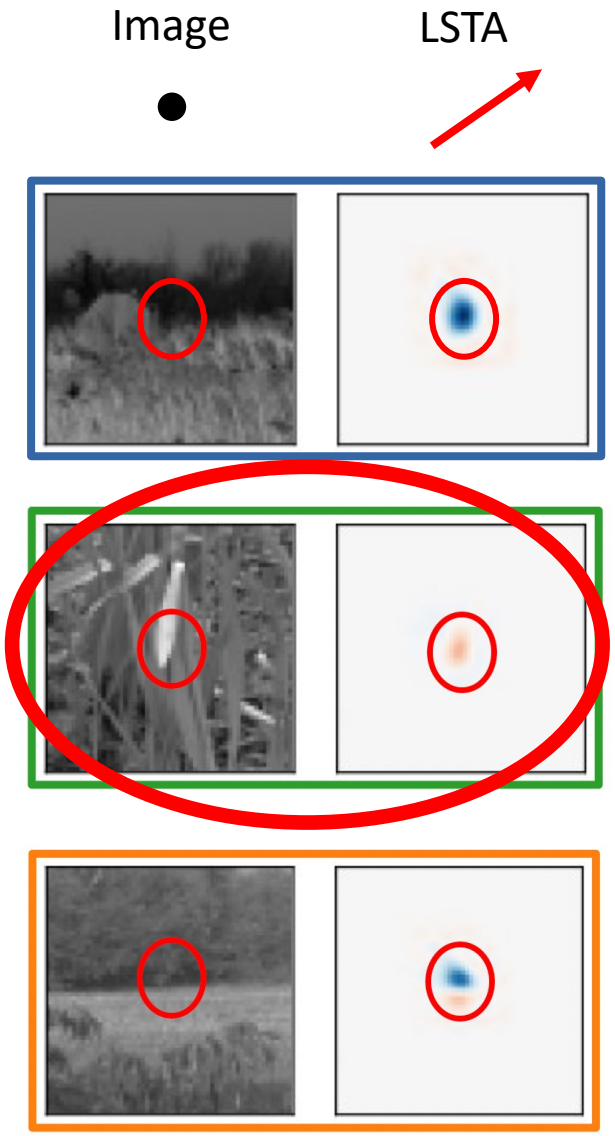
Starting point of the arrow:
the image in the stimulus space

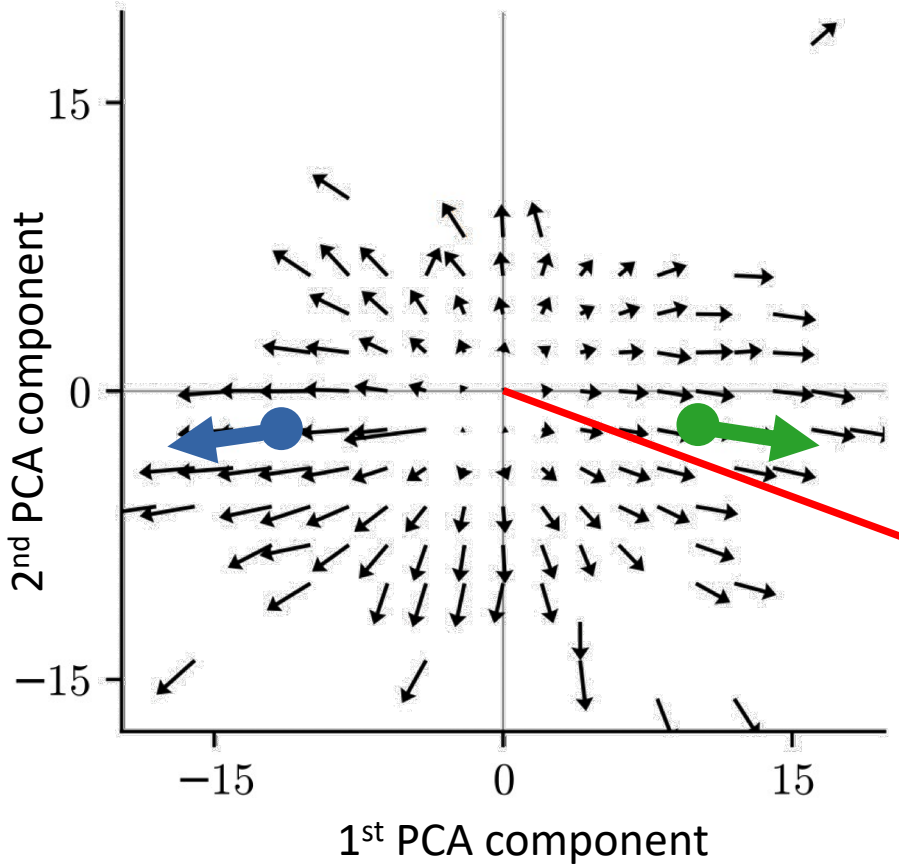
Arrow: the LSTA corresponding to this image.

The LSTA varies consistently with the images.



Structure of the dependence on the image



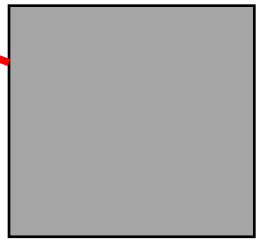


2D stimulus space representation

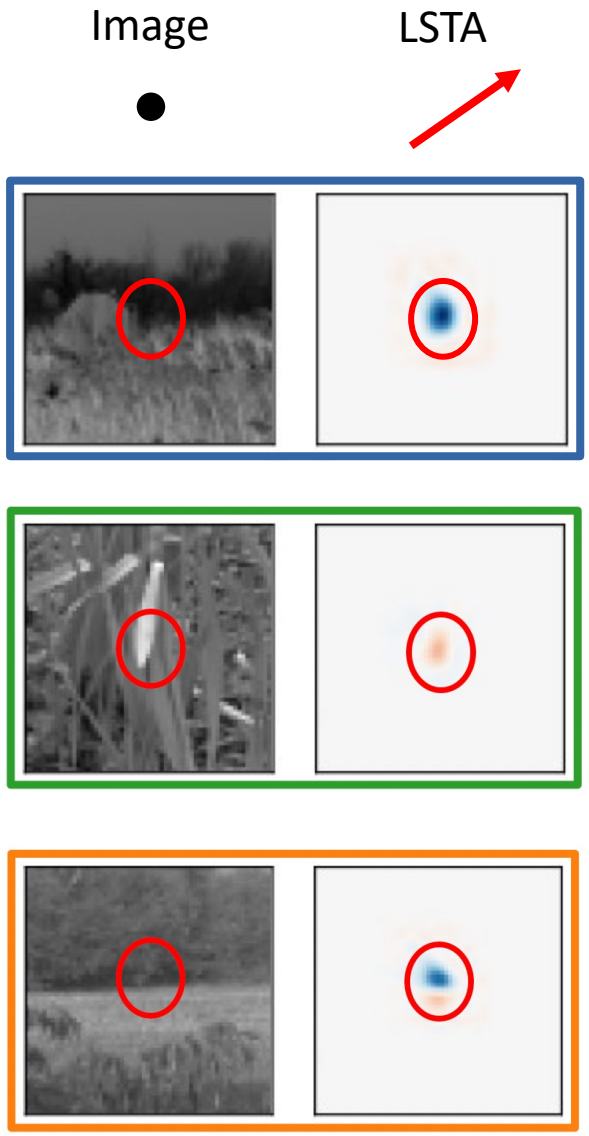
Starting point of the arrow:
the image in the stimulus space

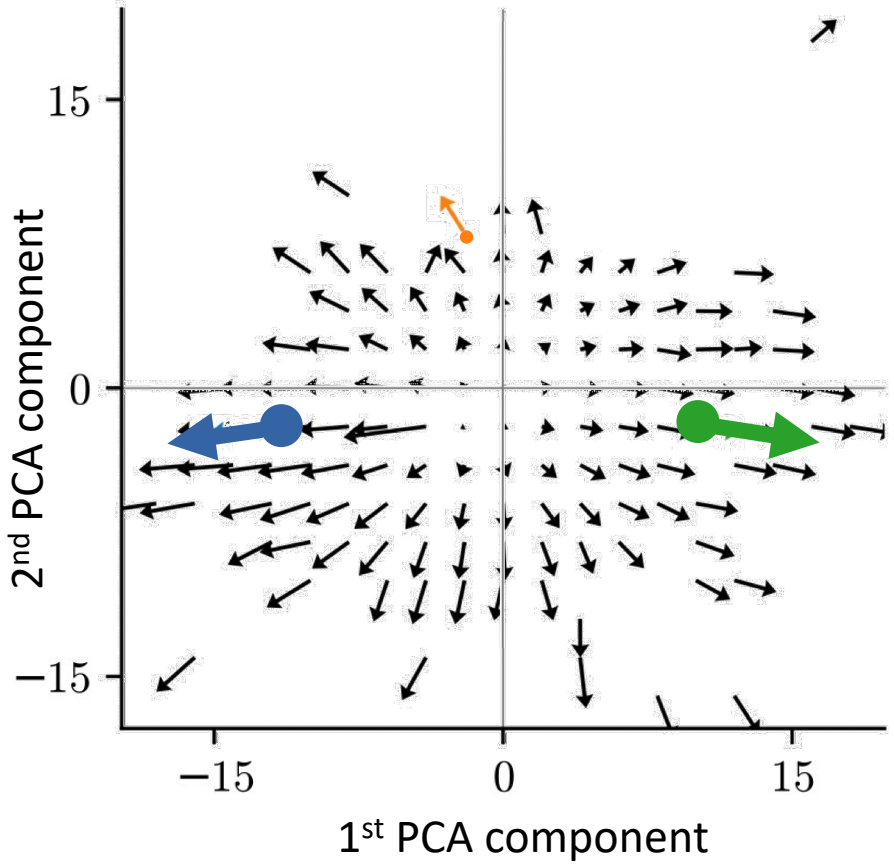
Arrow: the LSTA corresponding to this image.

The LSTA varies consistently with the images.



Structure of the dependence on the image





2D stimulus space representation

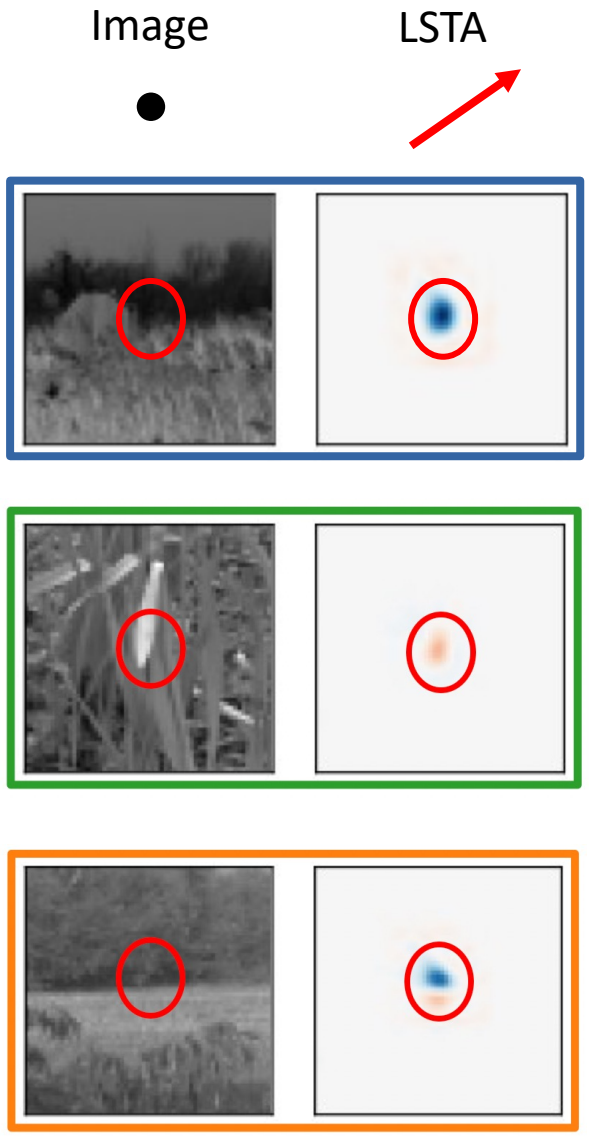
Starting point of the arrow:
the image in the stimulus space

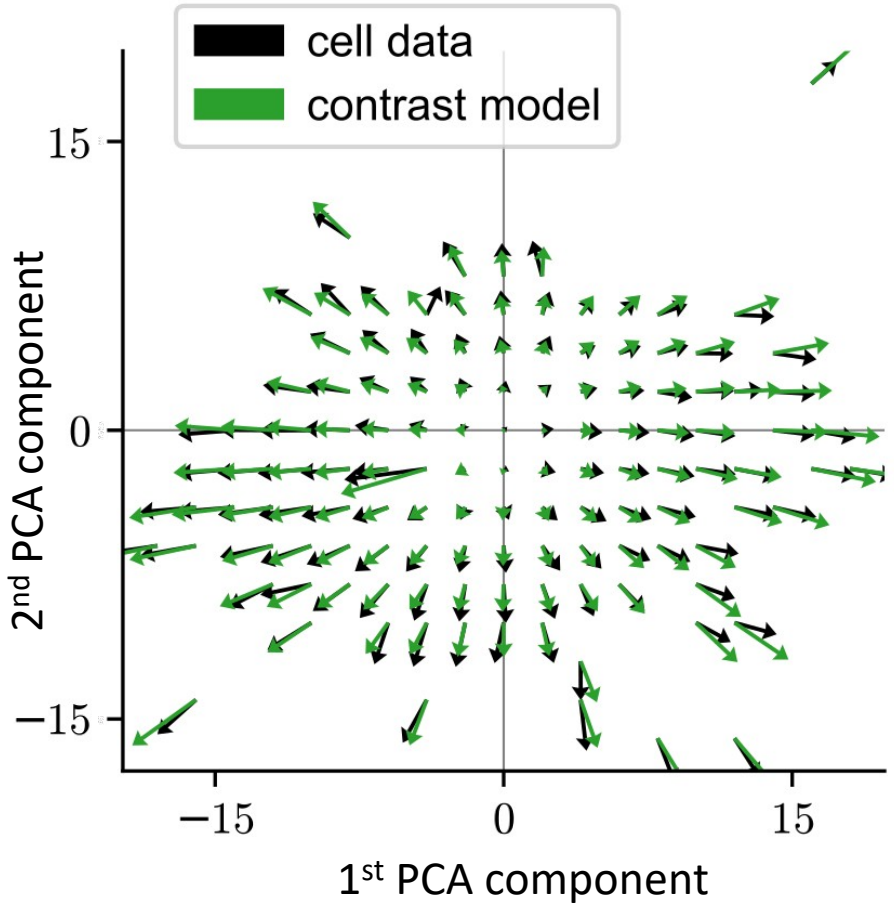
Arrow: the LSTA corresponding to this image.

The LSTA varies consistently with the images.

Hypothesis: the response is proportional to a local contrast.

Structure of the dependence on the image





2D stimulus space representation

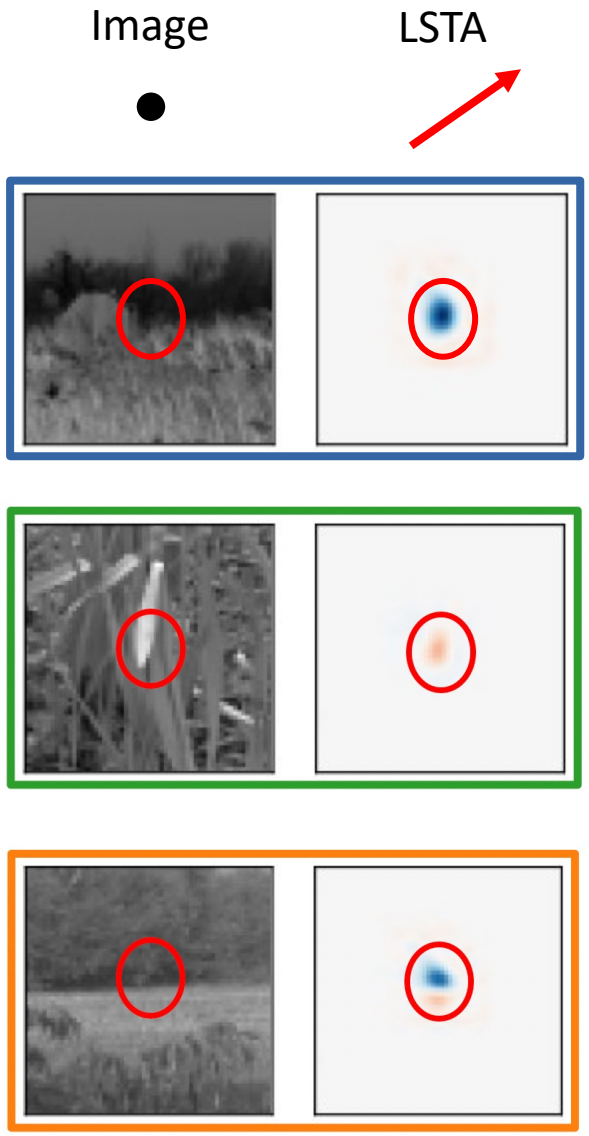
Starting point of the arrow:
the image in the stimulus space

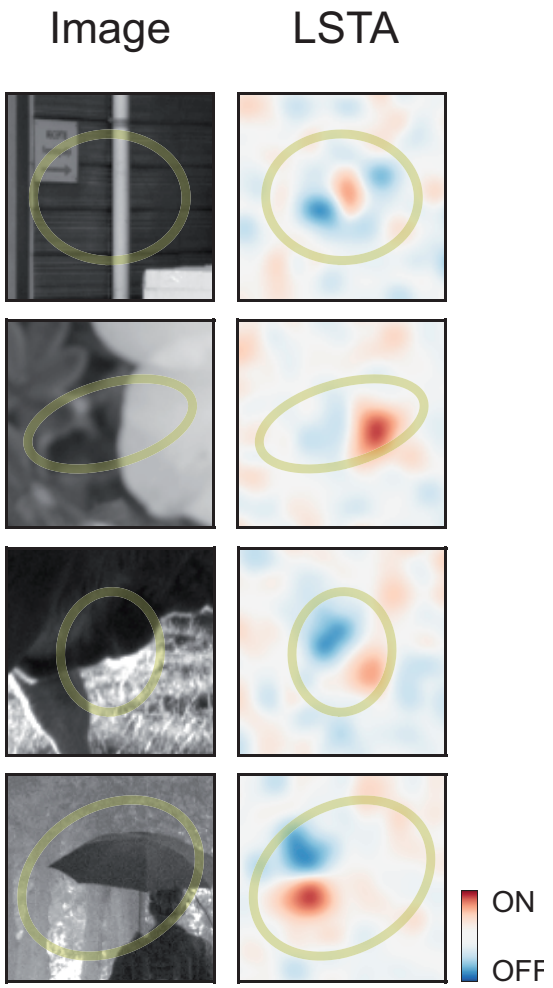
Arrow: the LSTA corresponding to this image.

The LSTA varies consistently with the images.

Hypothesis: the response is proportional to a local contrast.

Structure of the dependence on the image





Starting point of the arrow:
the image in the stimulus space

Arrow: the LSTA corresponding to this image.

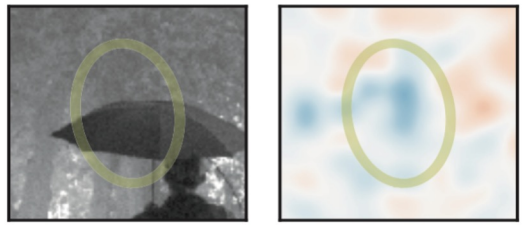
The LSTA varies consistently with the images.

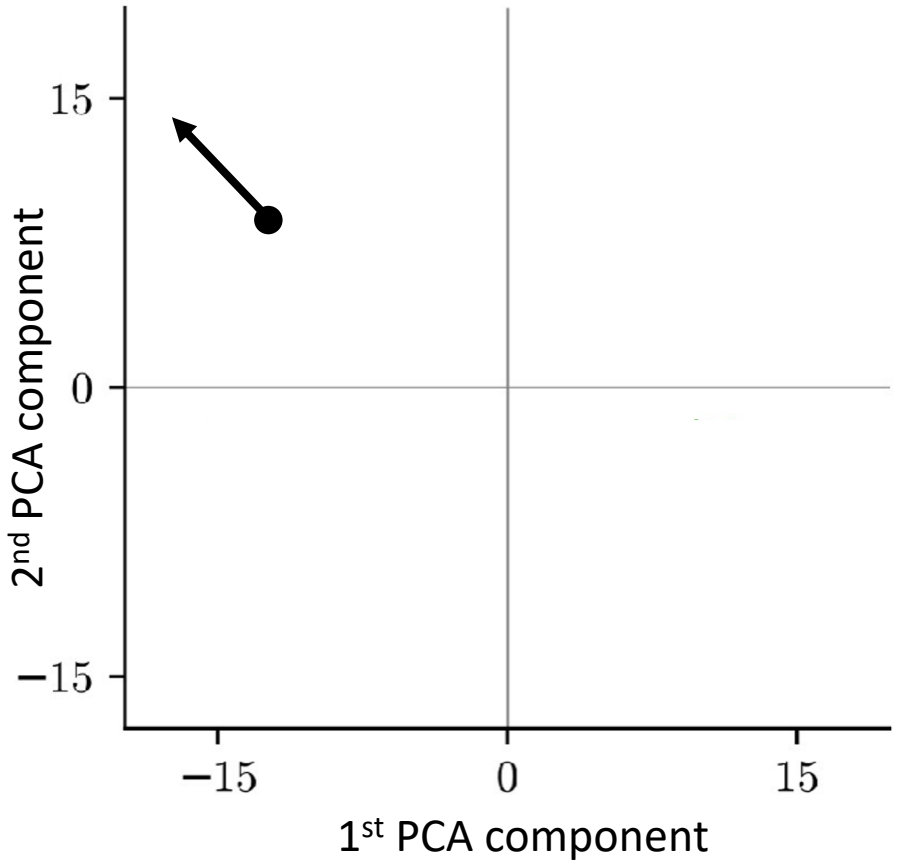
Hypothesis: the response is proportional to a local contrast.

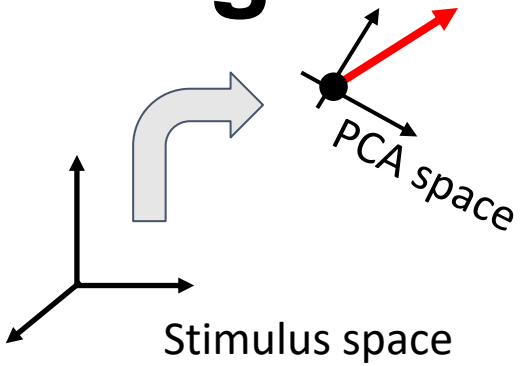
Structure of the dependence on the image

Image

LSTA





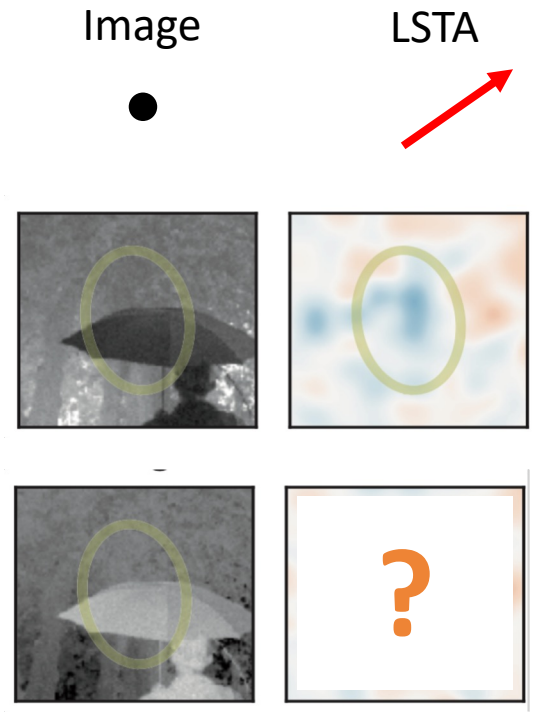


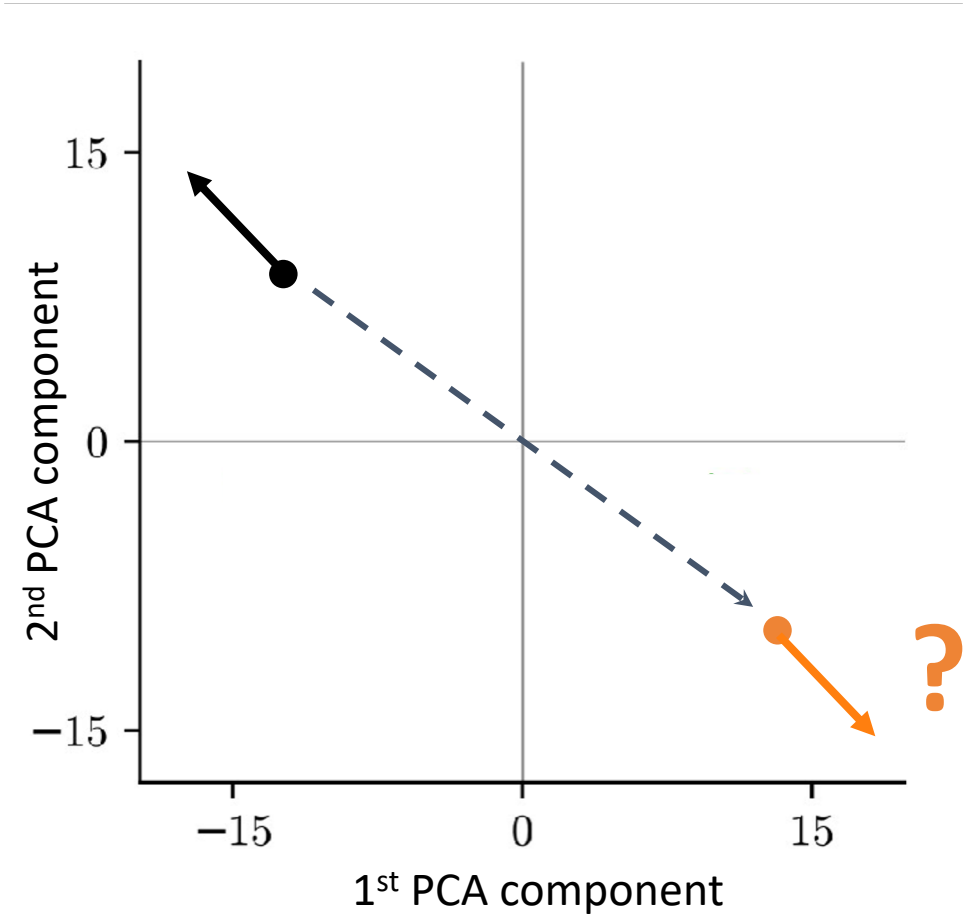
The LSTA varies consistently with the images.

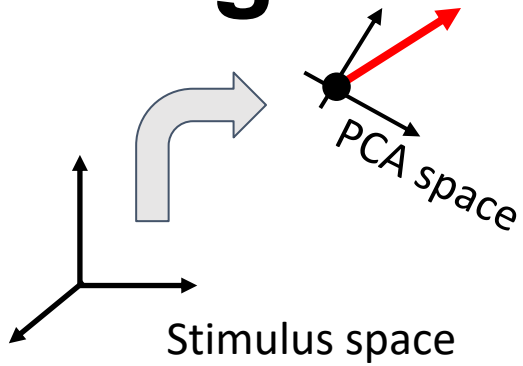
Hypothesis:
the response is proportional to a local contrast.

Can we test the hyphotesis by inverting the image's gray-scale?

Structure of the dependence on the image





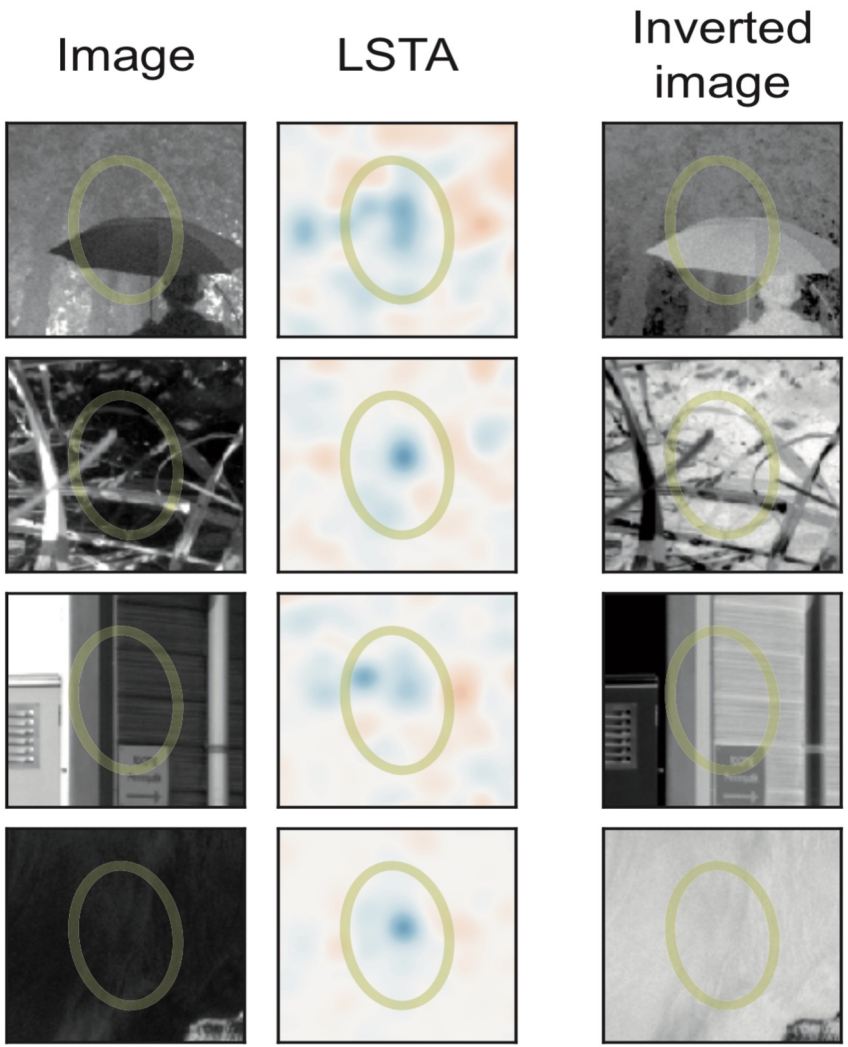


The LSTA varies consistently with the images.

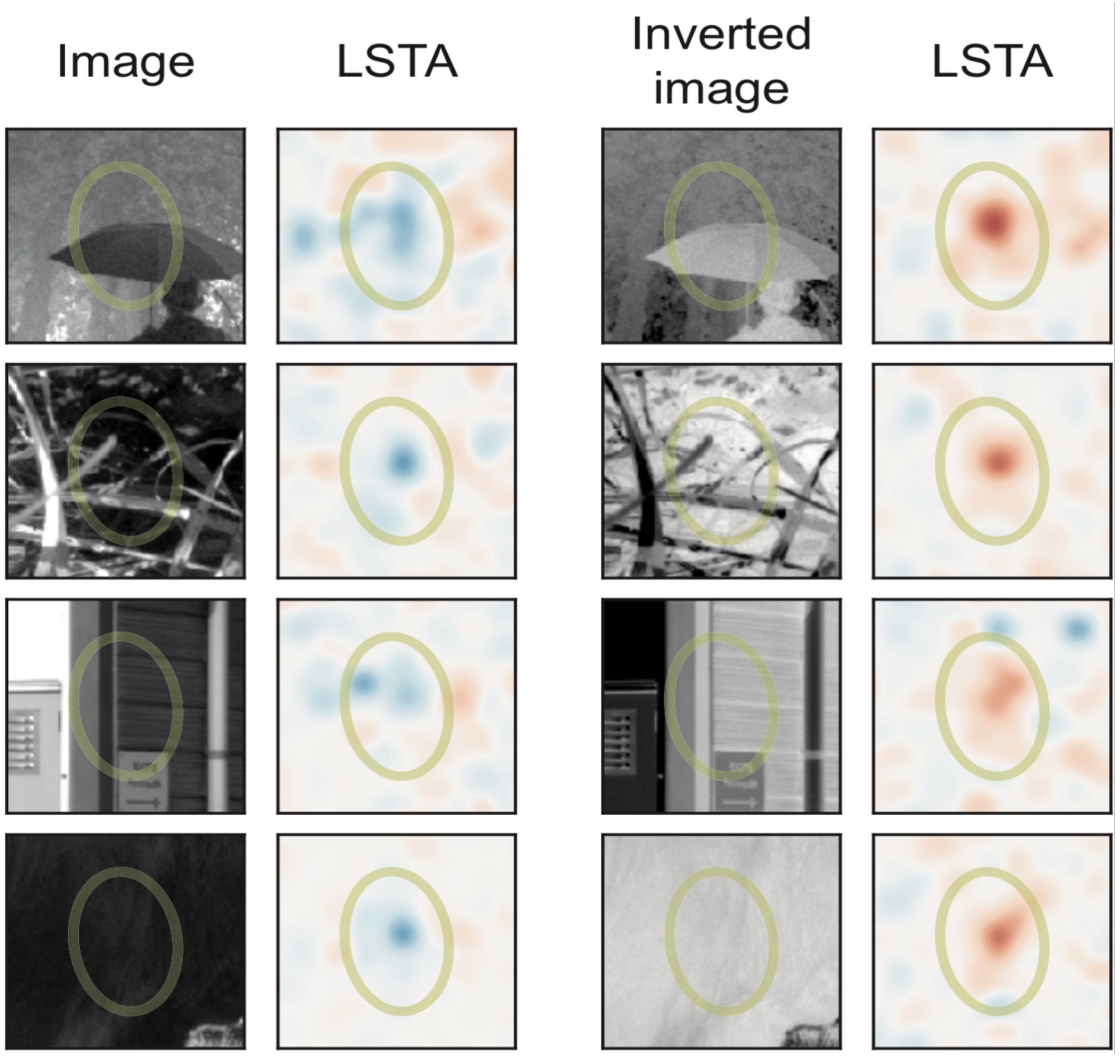
Hypothesis:
the response is proportional to a local contrast.

Can we test the hypothesis by inverting the image's gray-scale?

Inverting the ‘bright-dark’ images



Inverting the ‘bright-dark’ images



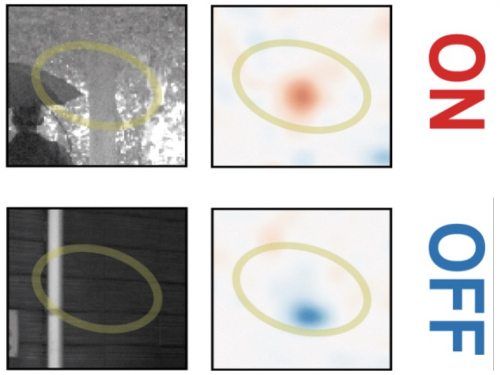
Example cell:

OFF LSTAs for the images

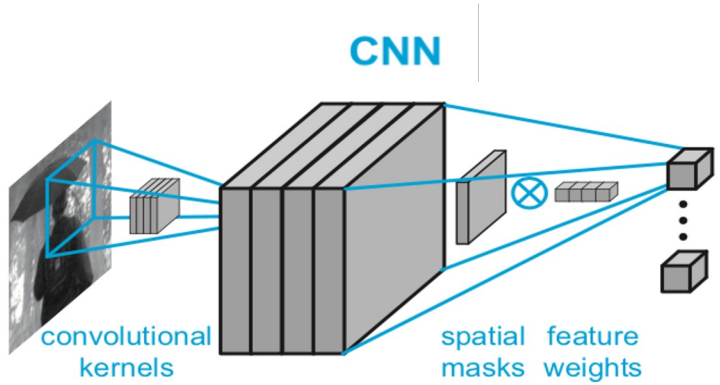
ON for the inverted counterparts.

Conclusions

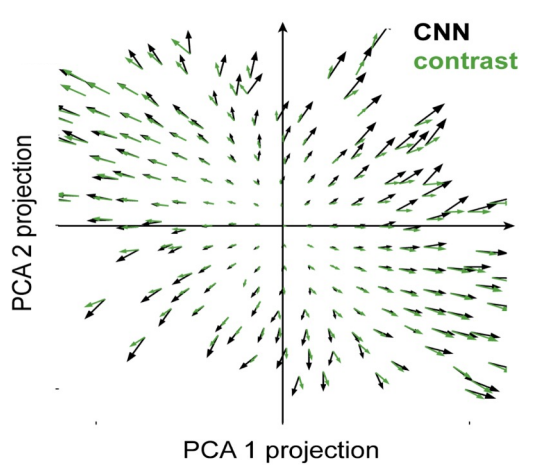
Polarity is context-dependent



ON-OFF pathway convergence allows polarity inversion
A CNN model predicts these findings.

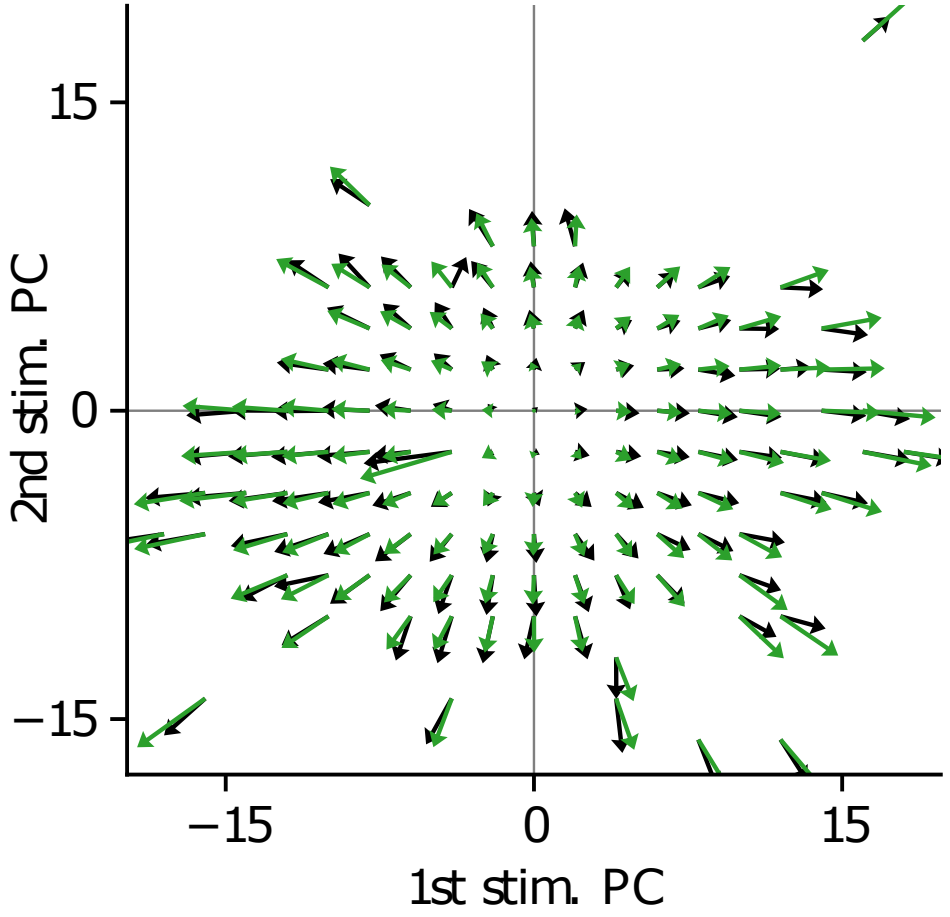


Polarity dependence on the reference image reveals coding of contrast

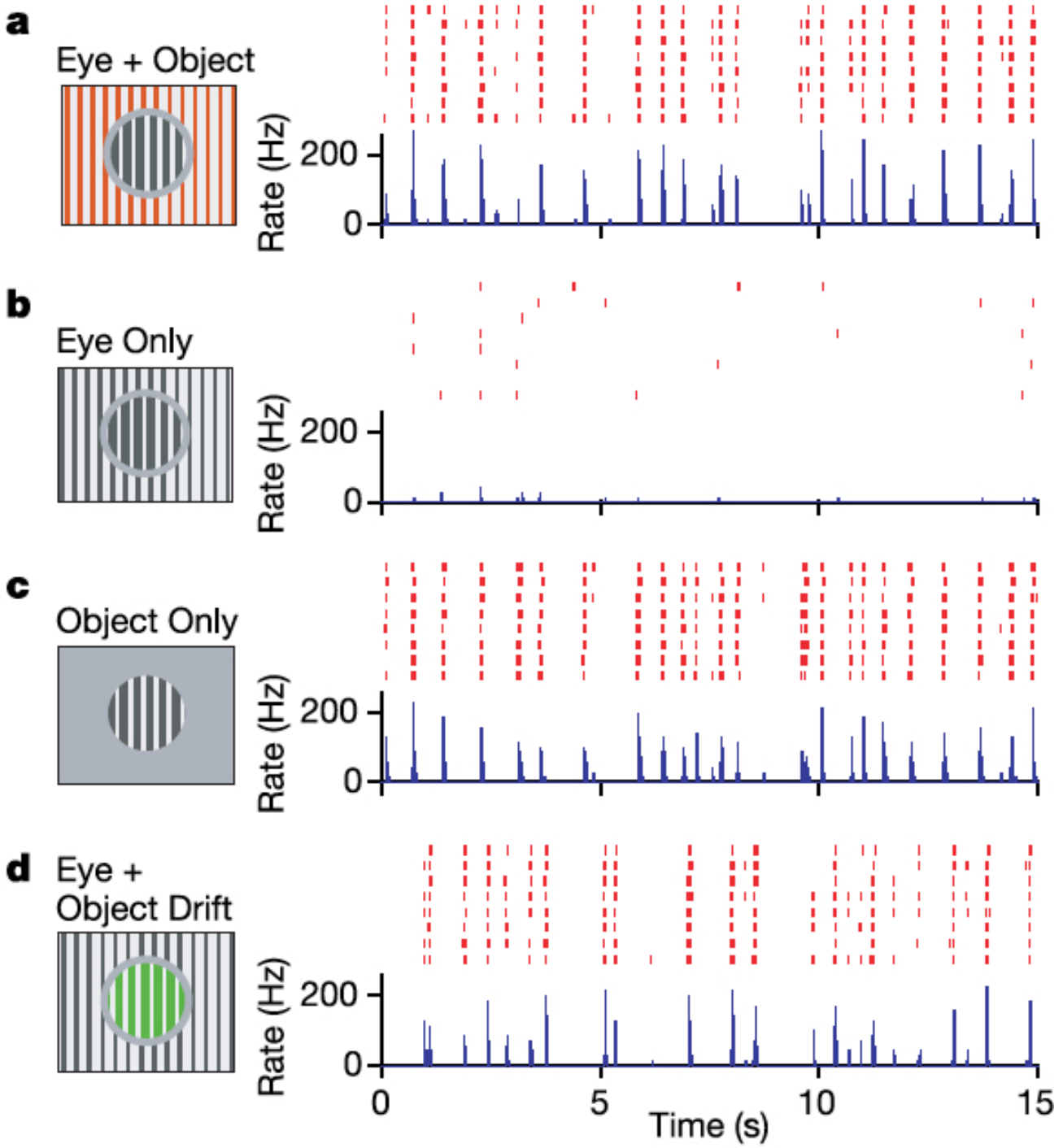


Perspectives

- A way to test models ? More constraints than average responses.
- Mixed selectivity = selectivity to a more abstract feature ?
- Possible extensions to other sensory structures ?
- The interest of doing back and forth between models and experiments.

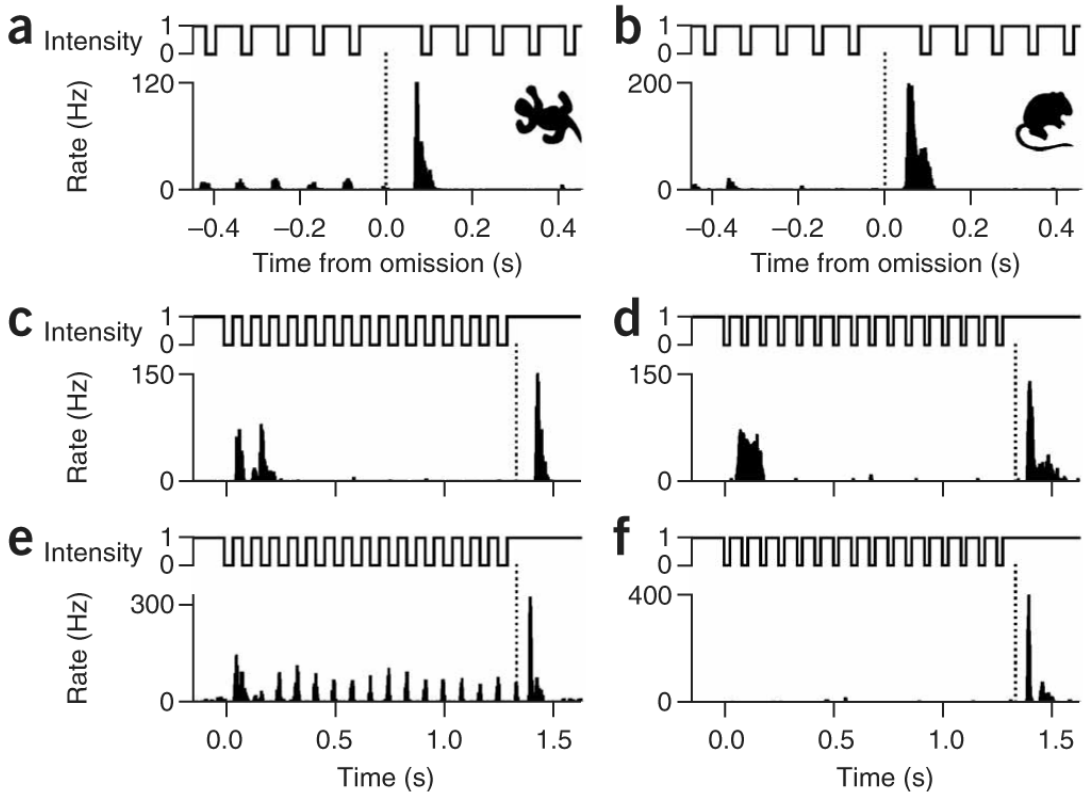


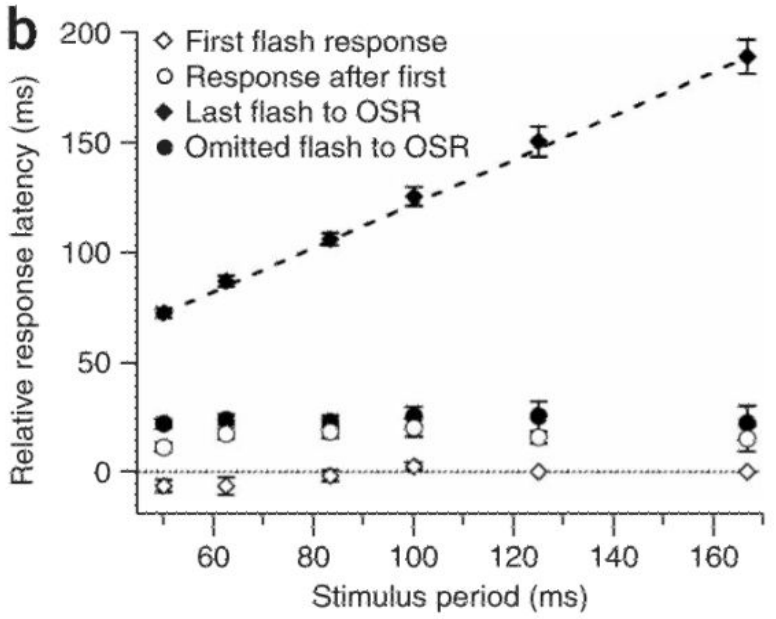
Object-Motion Selective ganglion cells



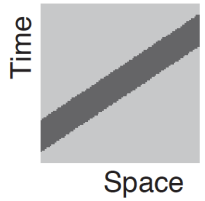
Olveckzy et al, 2003

Omitted Stimulus Response

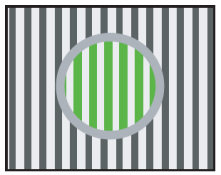




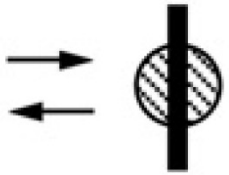
A zoo of non-linearities



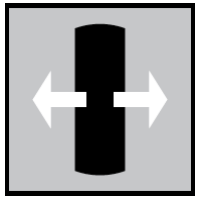
Motion anticipation: Berry et al, 1999



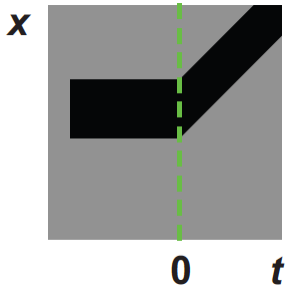
Global motion: Olveckzy et al, 2003



Motion reversal: Schwartz et al, 2007



Approaching motion: Munch et al, 2009



Start motion: Chen et al, 2013

Acknowledgements

The Vision Institute

Matias Goldin

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Matthew Chalk

Thomas Buffet

Déborah Varro

Gabriel Mahuas

Ecole Normale

Thierry Mora

Gottingen University

Alex Ecker

Positions available !

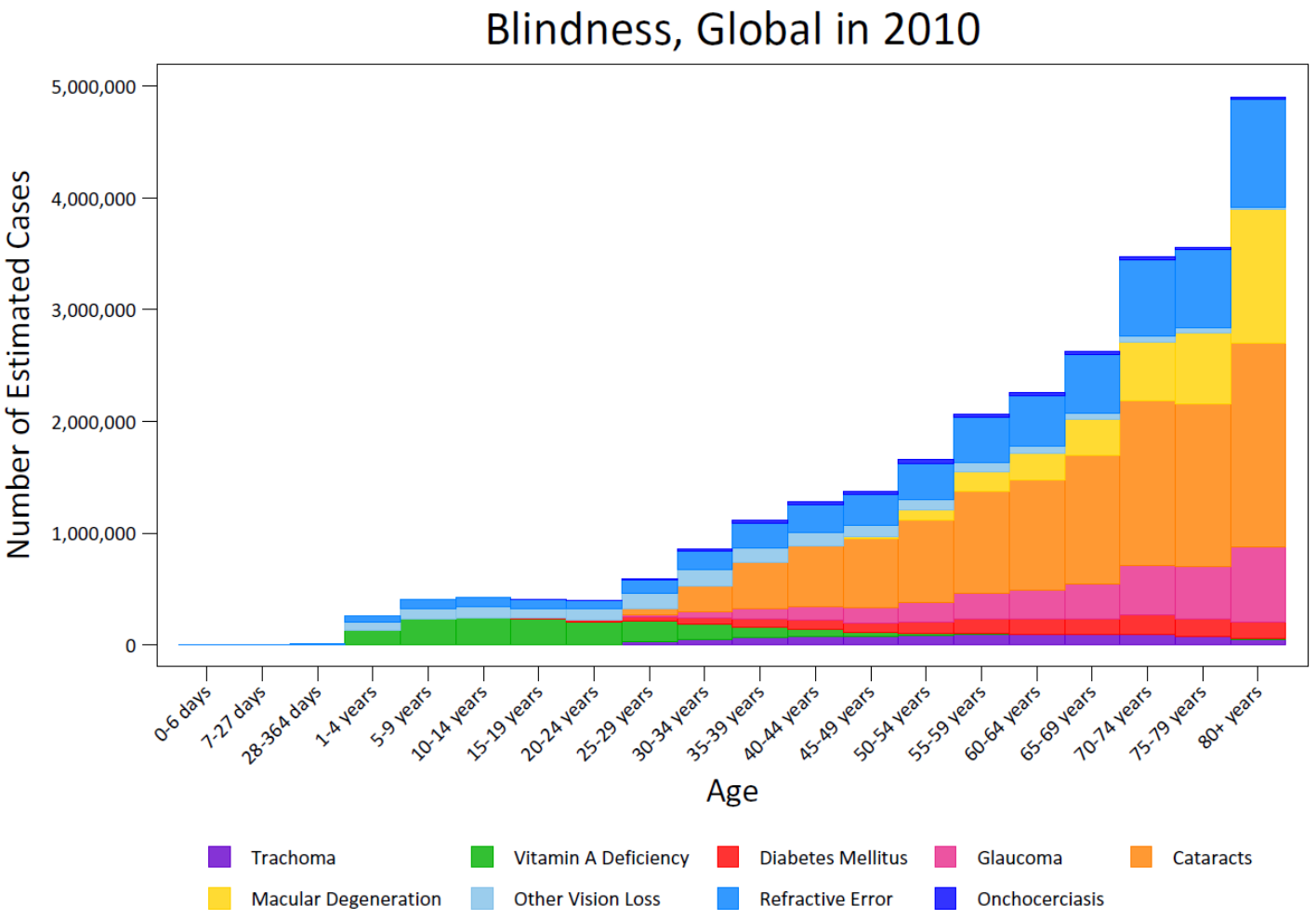




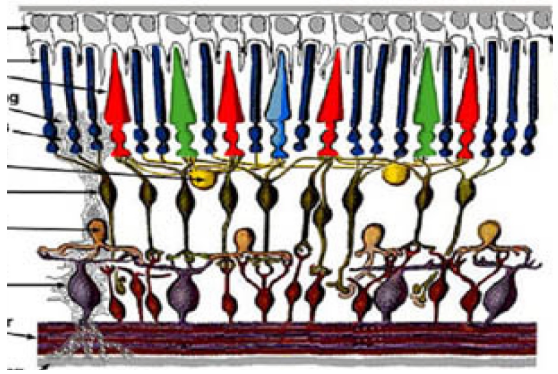
Visual restoration in blind patients

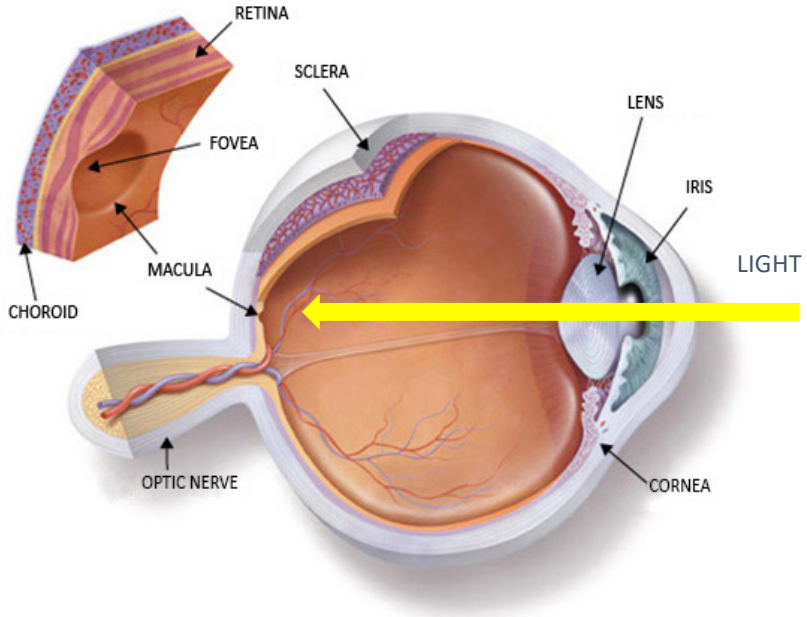
FORESIGHT
SORBONNE UNIVERSITÉ
CRÉATEURS DE FUTURS DEPUIS 1257
Inserm
cnrs
QUINZE-VINGTS
CENTRE HOSPITALIER NATIONAL D'OPHTALMOLOGIE
fondation VOIR & ENTENDRE
INSTITUT CARNOT
Voir et Entendre

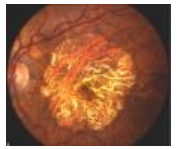
Vision loss is among the most feared health issues humans face



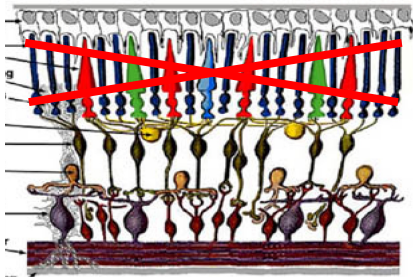
Causes of Retinal diseases





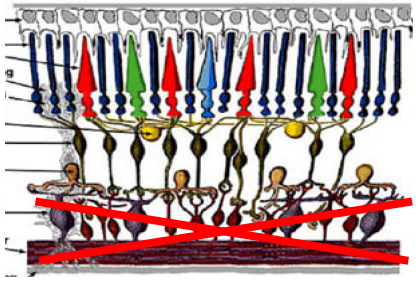


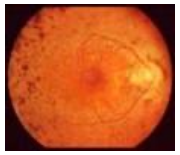
Age-related Macular degeneration
(30 M patients)





Diabetic retinopathy
(20 M patients)



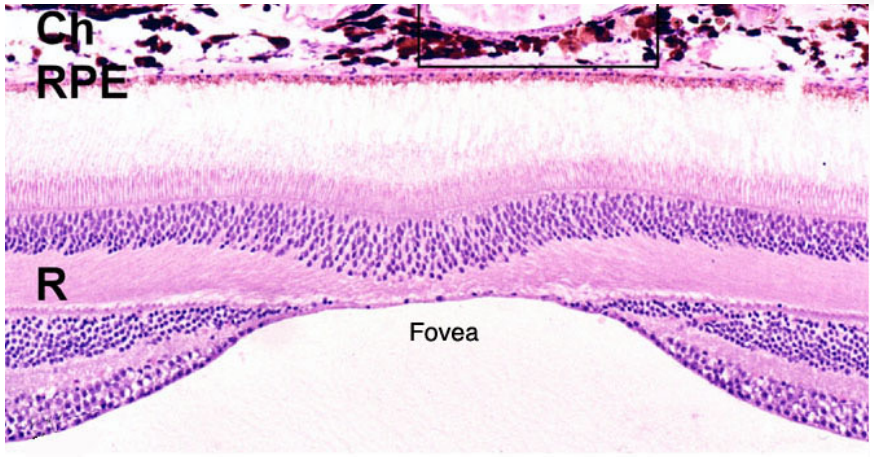


Glaucoma
(6 M patients)



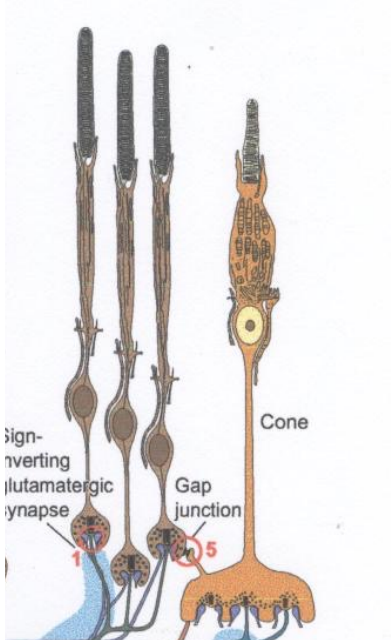
Orphan diseases
- Retinal dystrophies
- USHER
- LHON, Stargardt, (…)

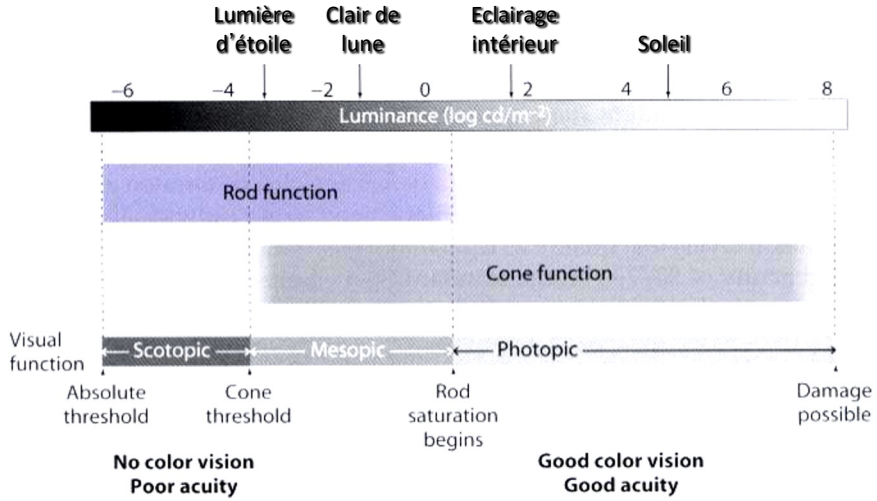
(2 M patients)

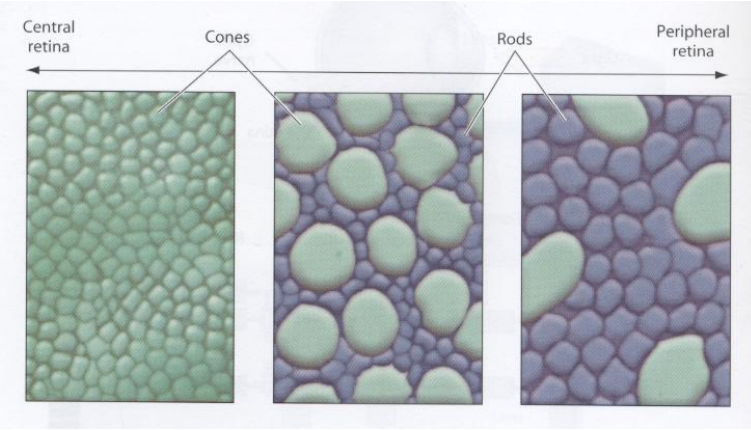


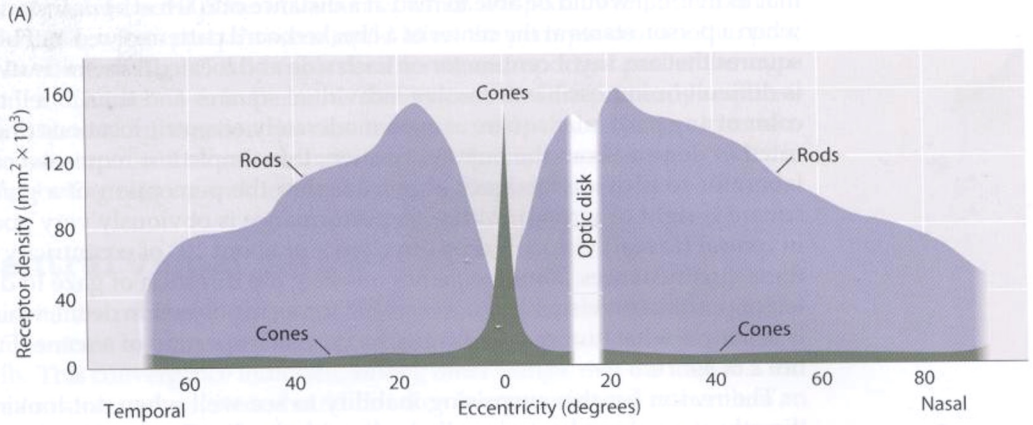
Over 50 M patients in EU and US and 700 M worldwide suffer from low vision
Cost of visual impairment in EU : 500+ billions €

Rod and cone photoreceptors

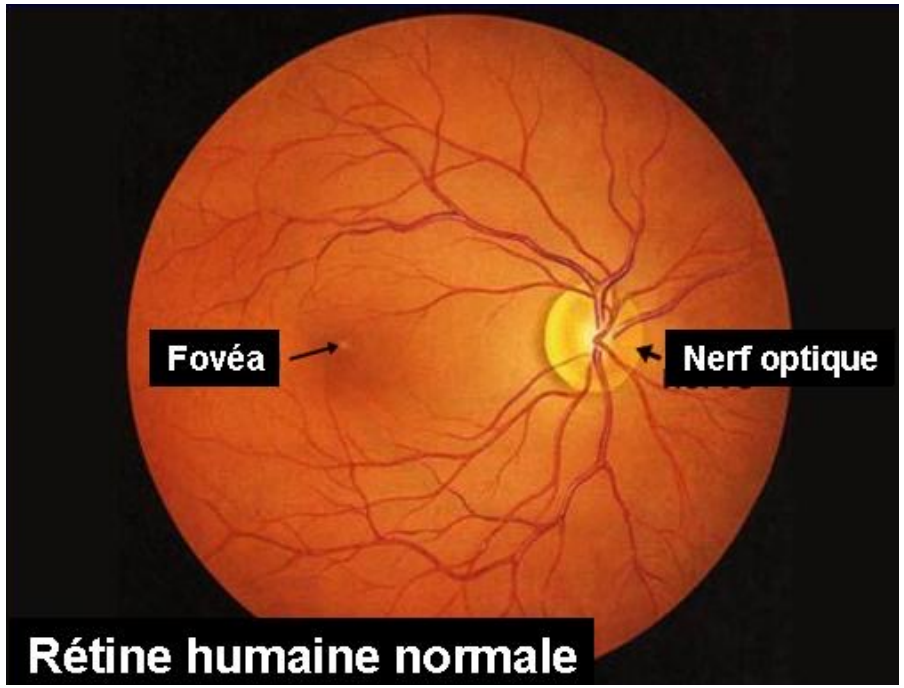


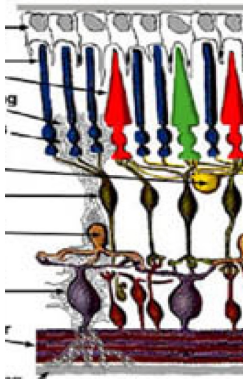


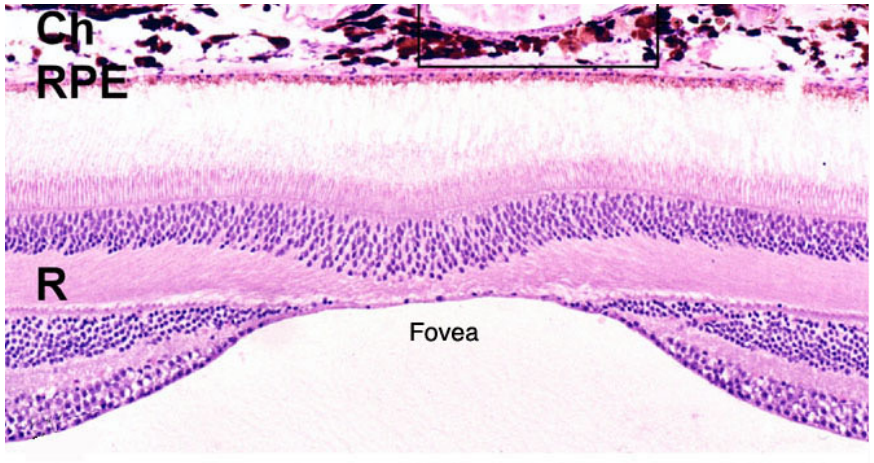


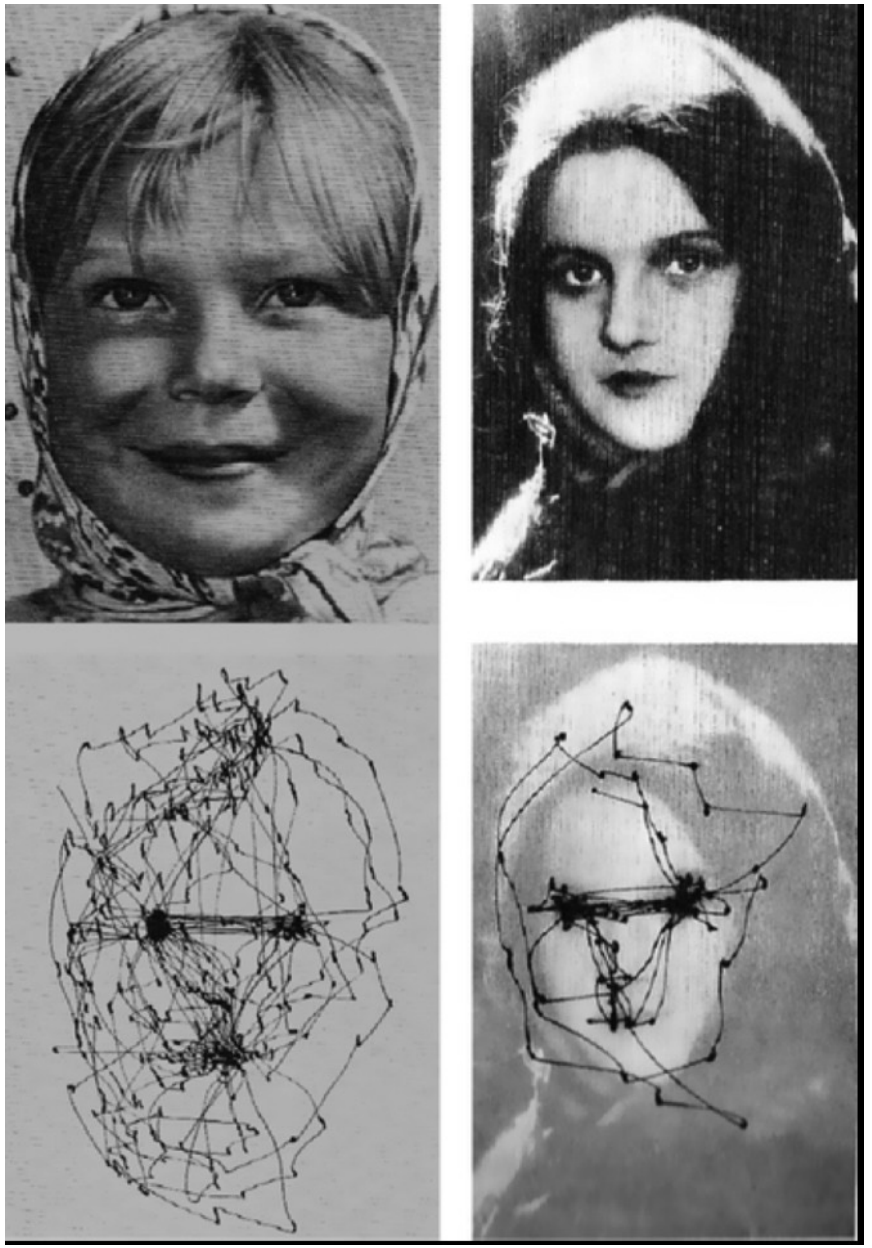


Macula: High central visual acuity



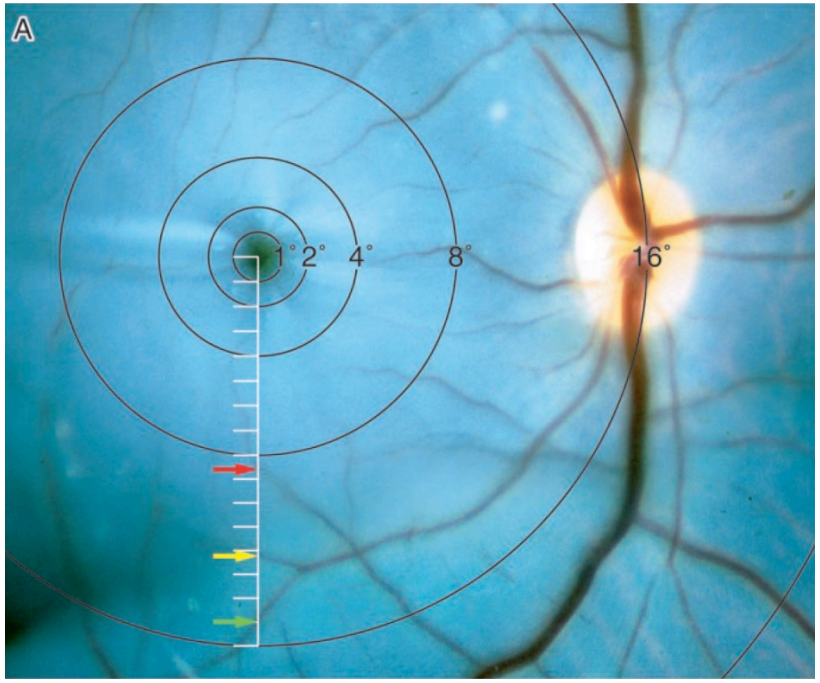


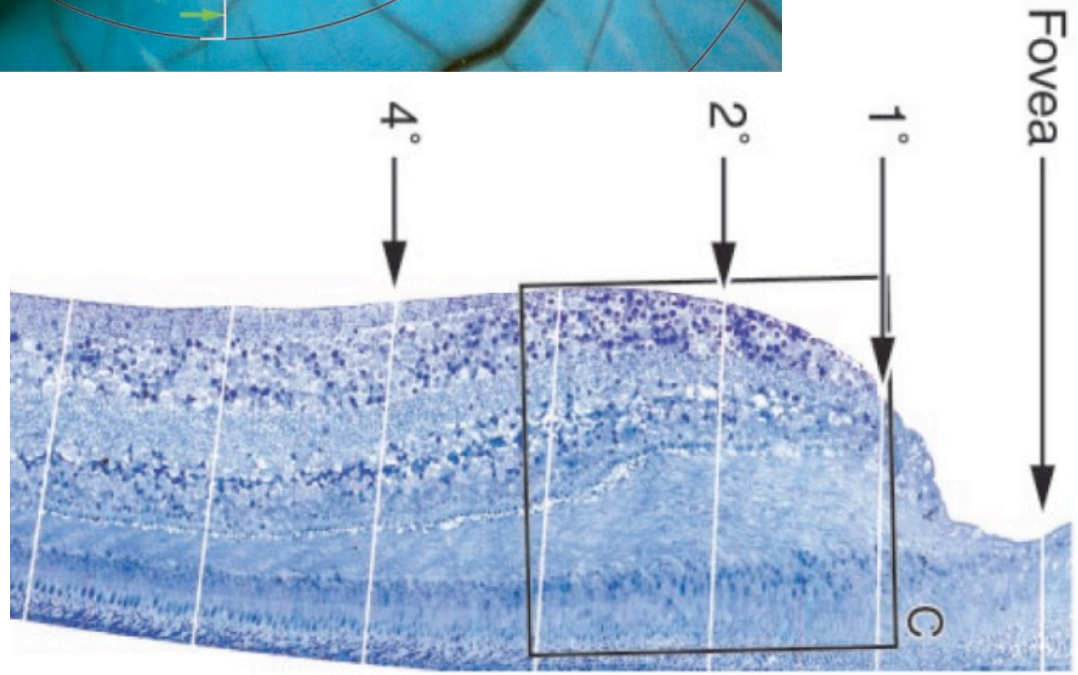


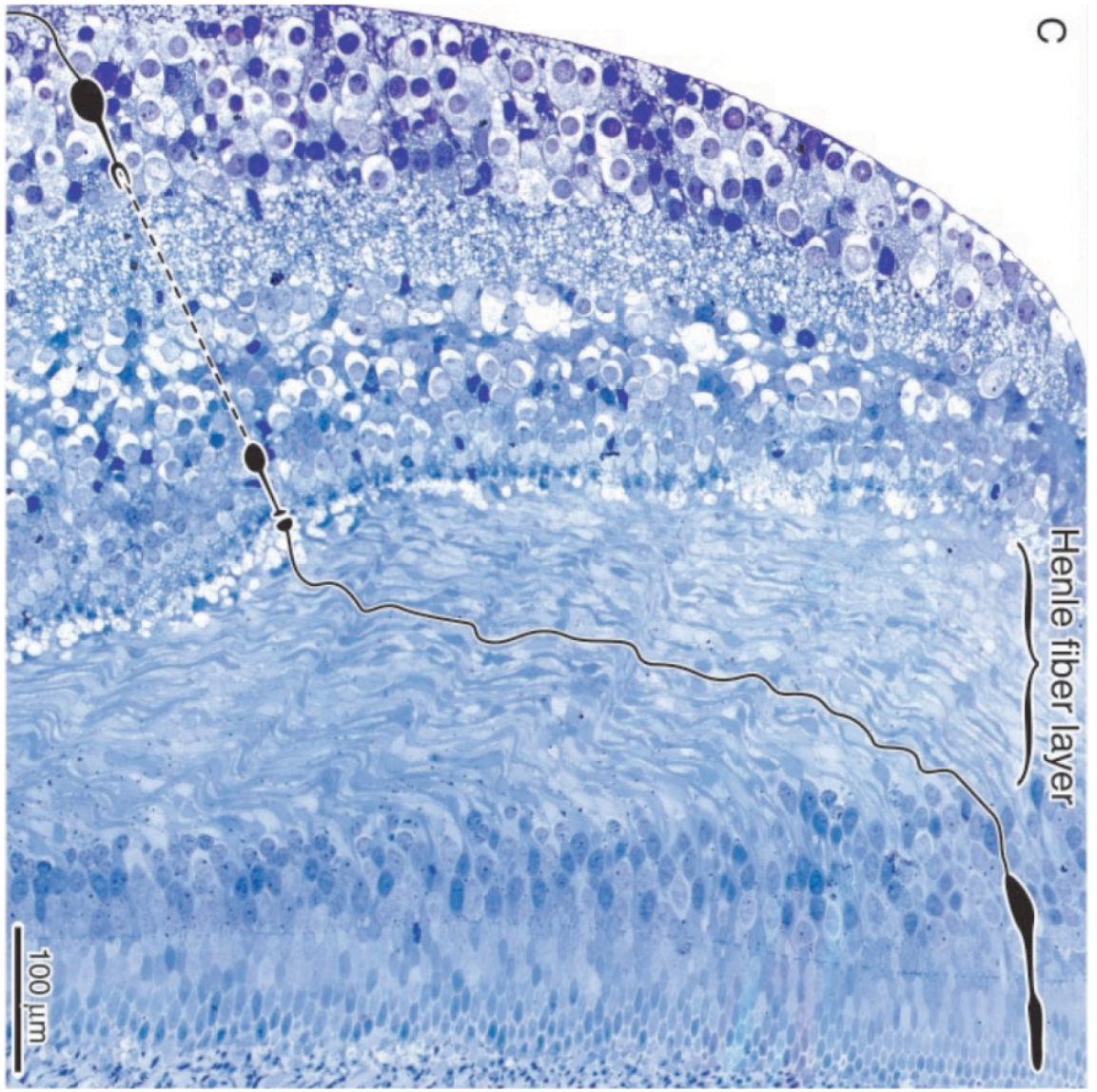


Yarbus 1959

Macula: lateral displacement of retinal ganglion cells



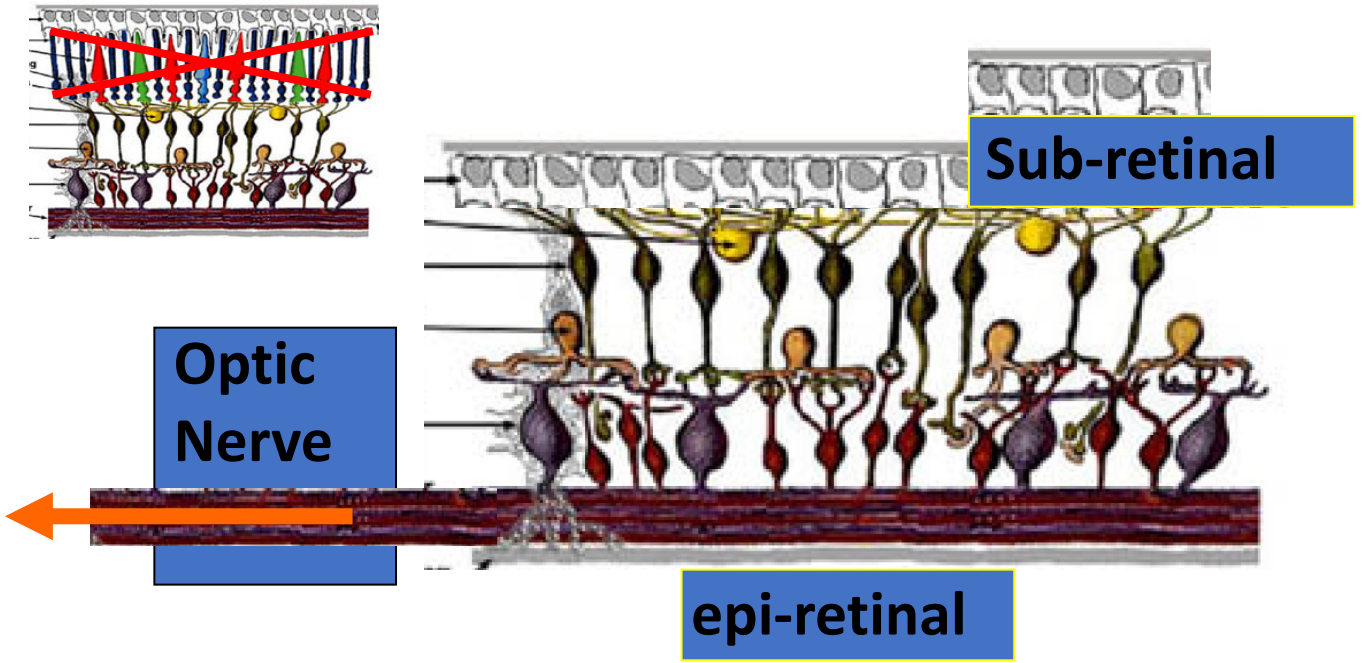




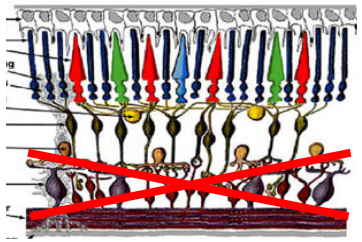
Adams and Horton 2003

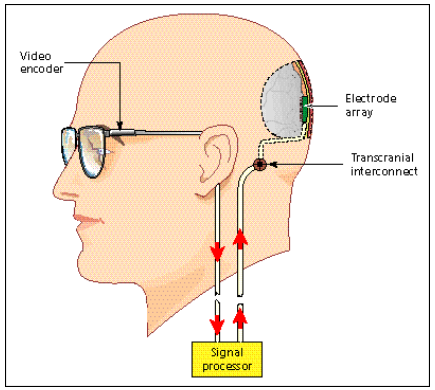
Concept of visual restoration:
Stimulation of residual neurones in the visual system

Macular degeneration
Inherited dystrophies: RP



Glaucoma
Diabetes

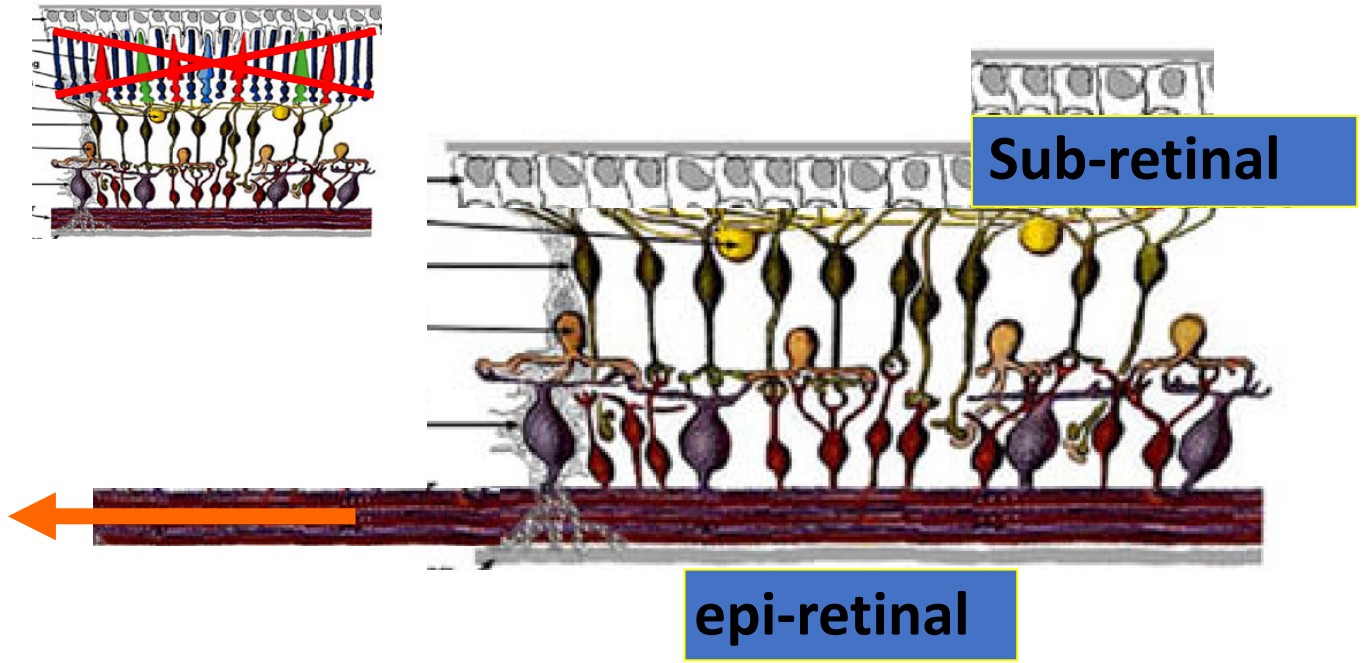




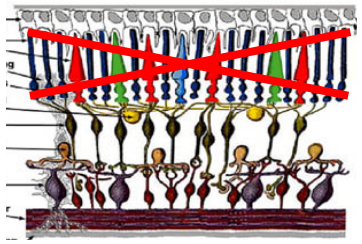
Cortical activation

Concept of visual restoration:
Stimulation of residual neurones in the visual system

Macular degeneration
Inherited dystrophies: RP



Restoring vision following photoreceptor degeneration



- Age-related macular degeneration

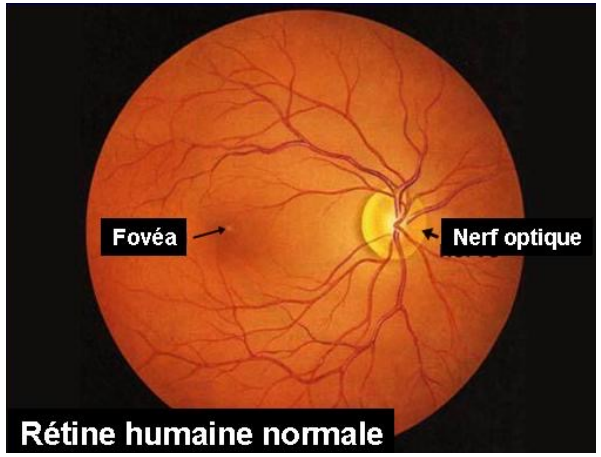
- Retinitis pigmentosa
  1/4000 birth

ARMD

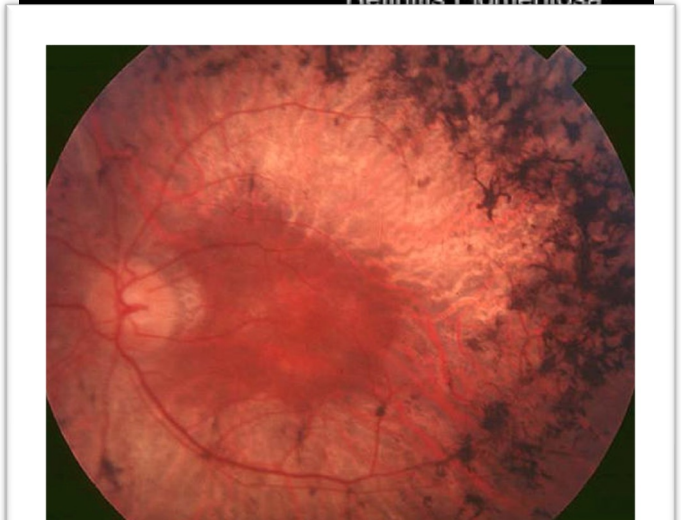


RP









2nd sight: the Argus II retinal prosthesis



Micro-processeur

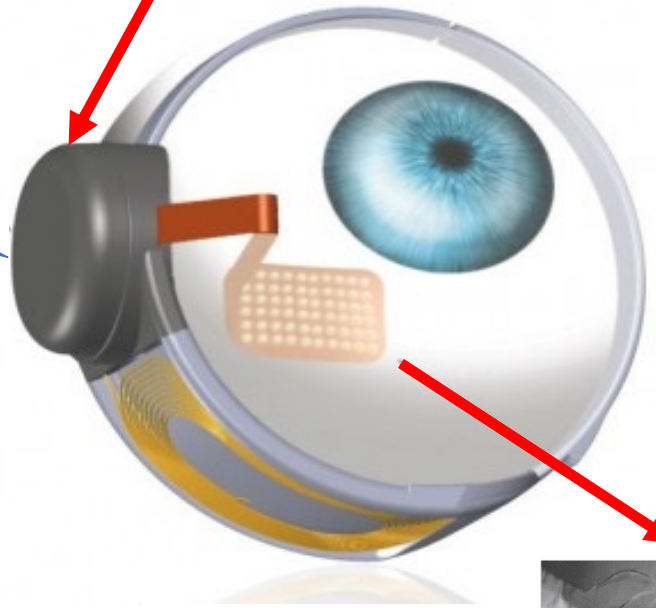
Emitter

Caméra

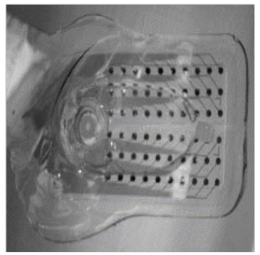


RF Link

Receptor

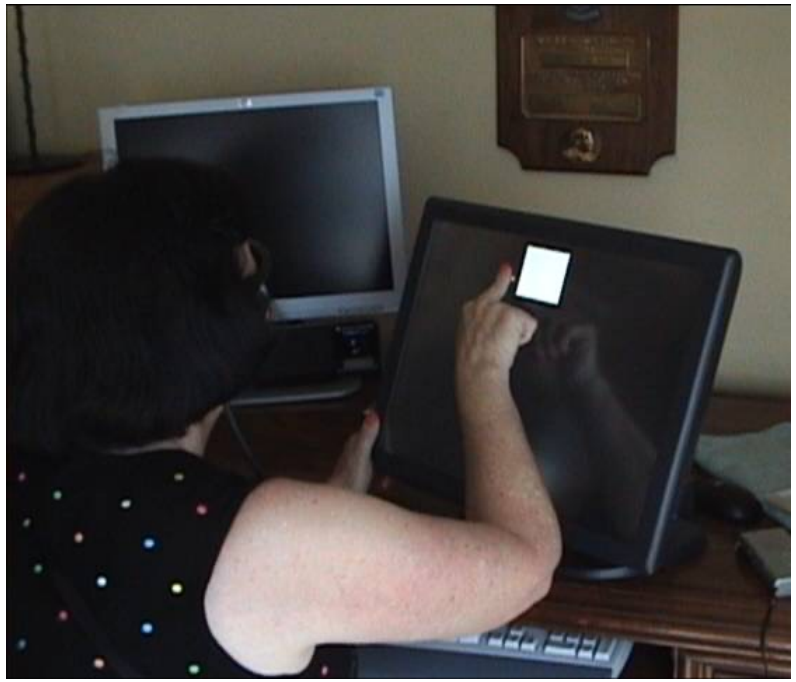


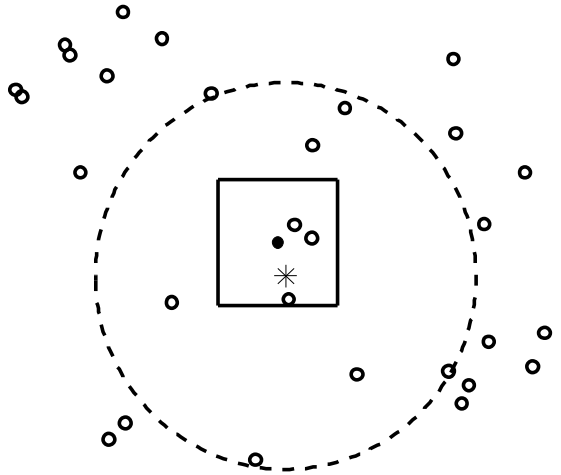
Implant



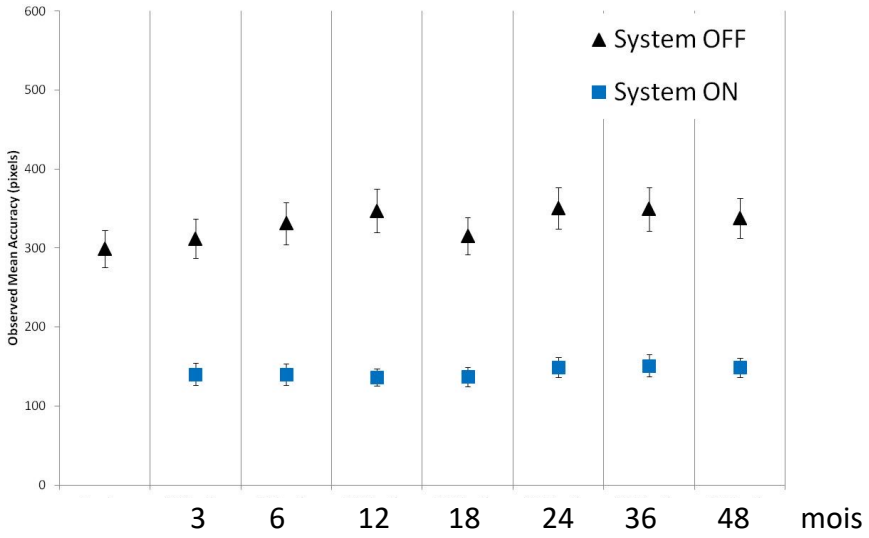
Electrode array

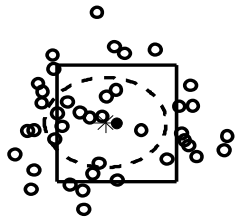
Square test localization





System OFF





System ON

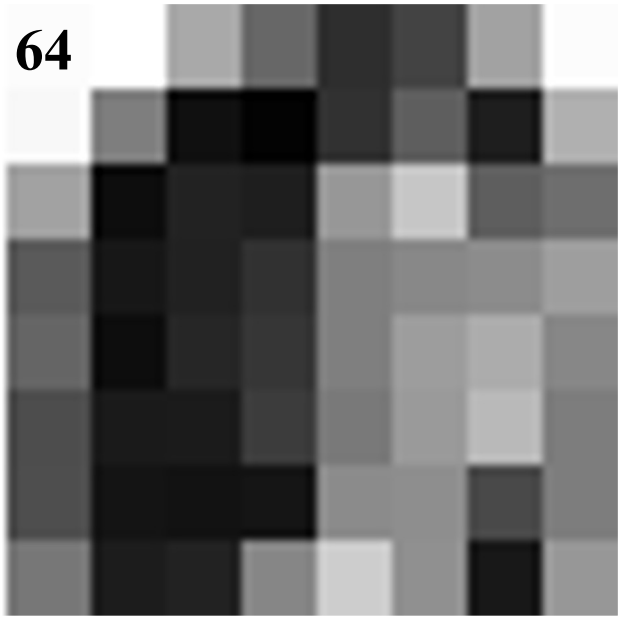
Données de USC-001

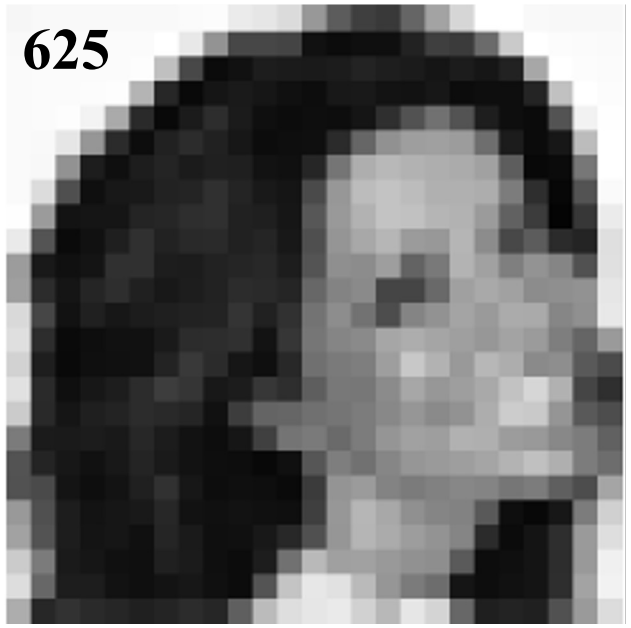
Prothèse rétinienne

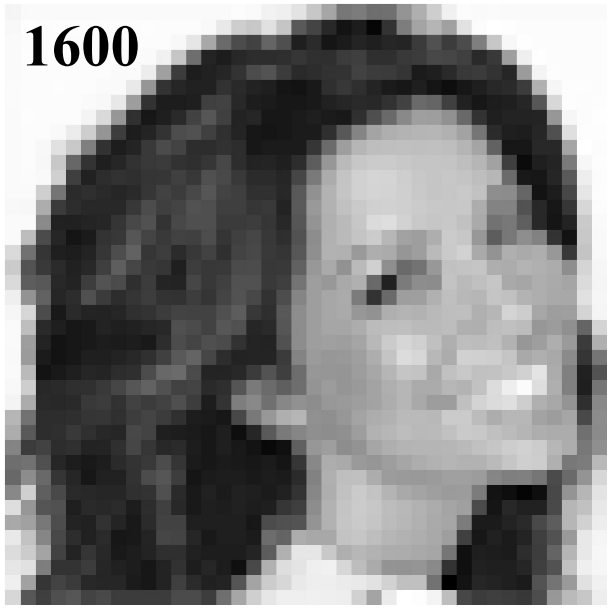


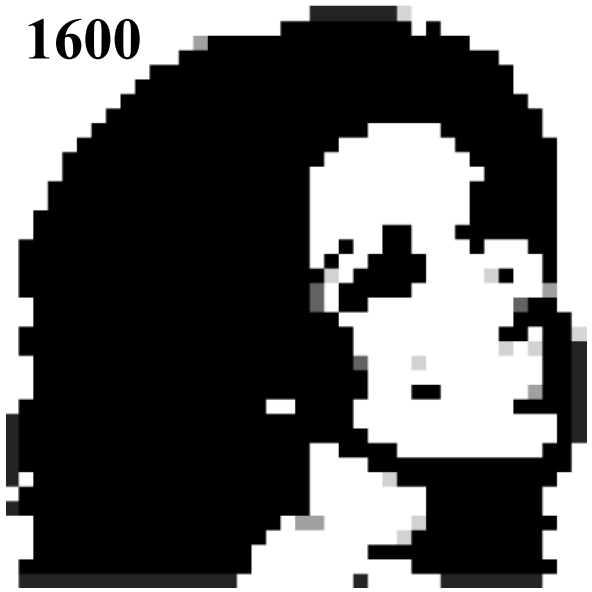
Vision and pixels



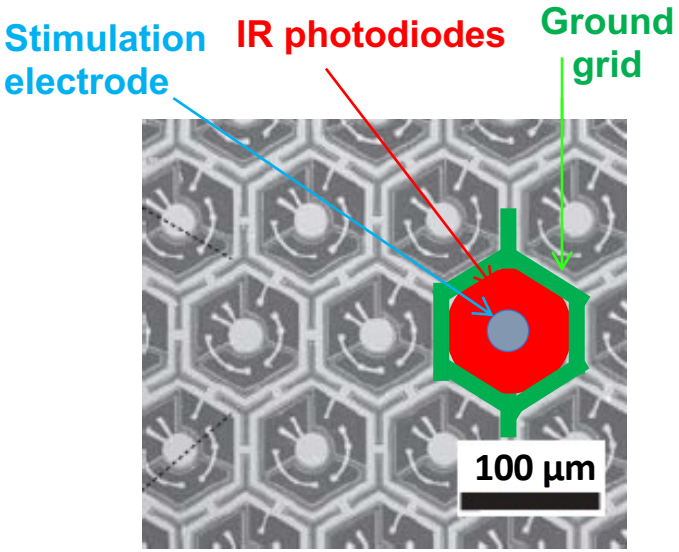


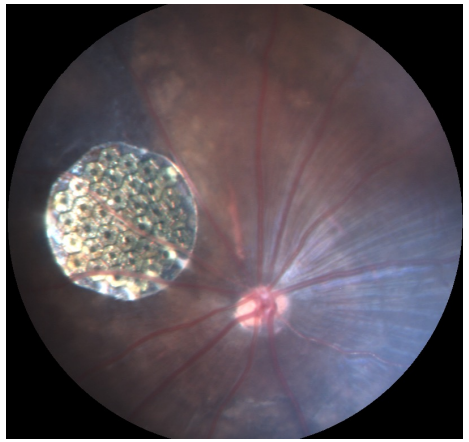


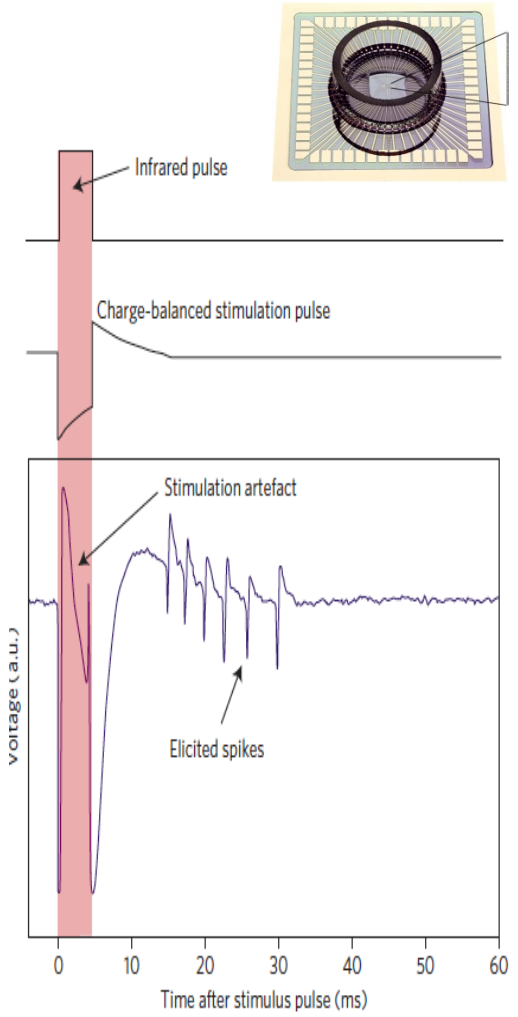


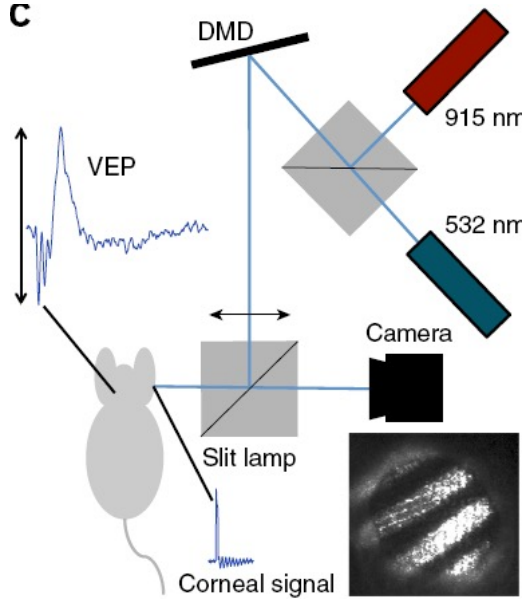


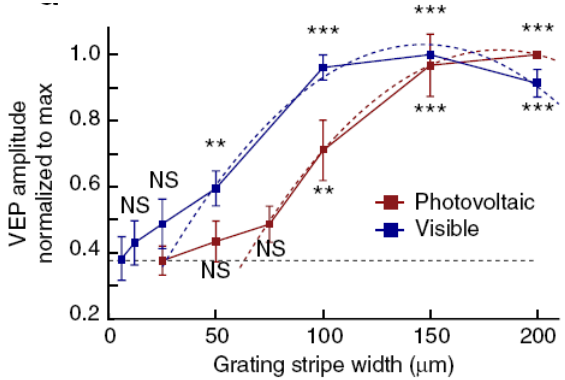
A wireless implant sensitive to InfraRed stimulation With a ground grid (Stanford U)







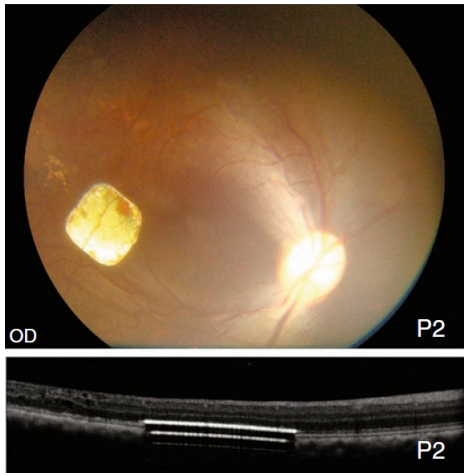


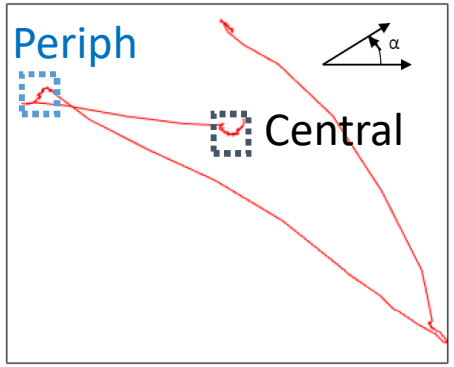


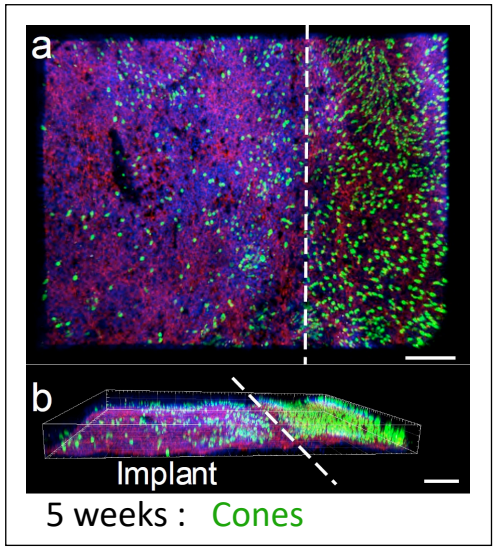
(Mathieson …. Palanker, Nature photonics 2012, Lorach …. Palanker, Nature Medicine 2015)

Preclinical validation of implants: Behavioral study

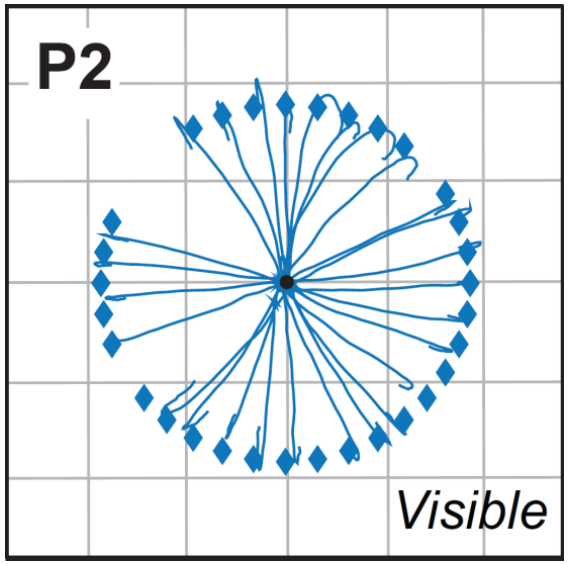




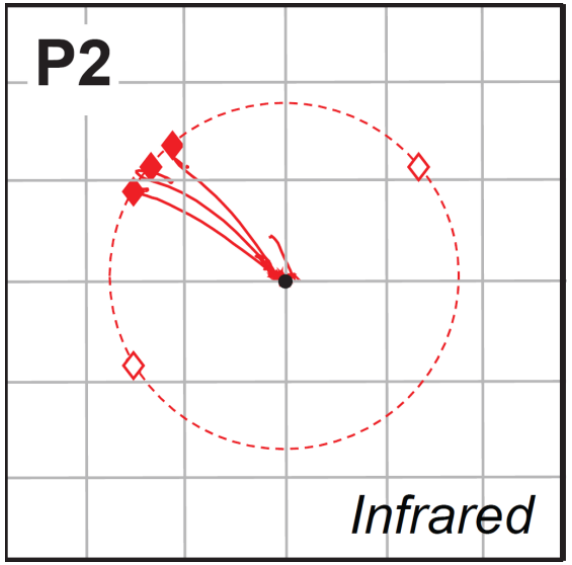




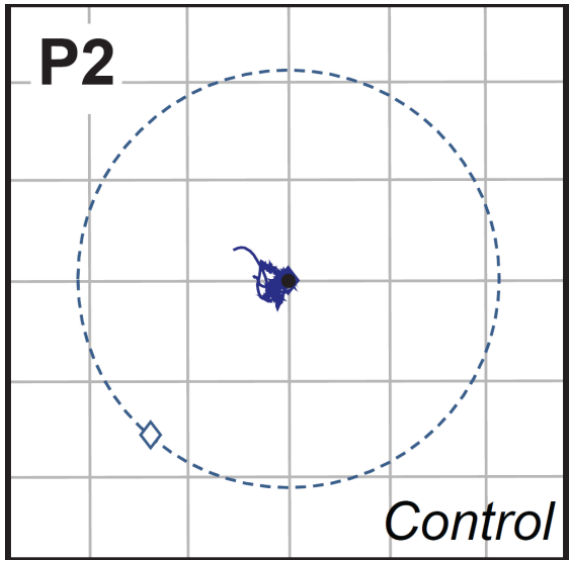
Visible



InfraRed



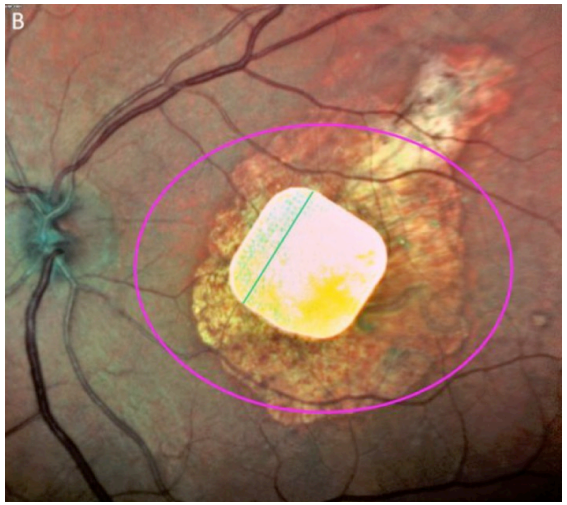
Controls



(**Prevot et al., Nature Biomed. Eng. 2020**)

Clinical trial:
Age-related macular degeneration





Visual acuity: 20/460 - 20/565

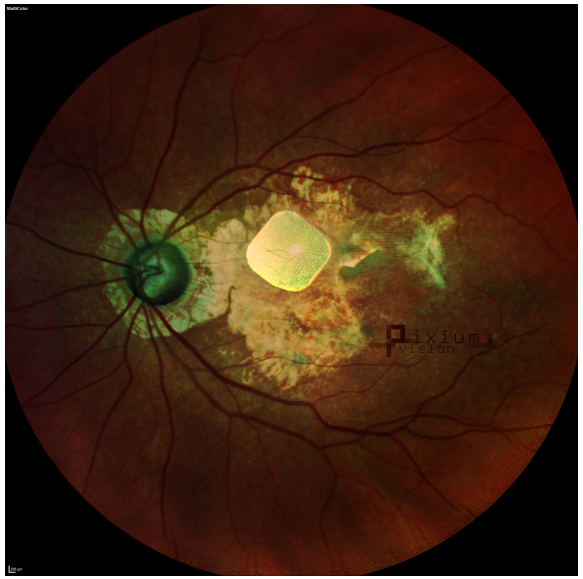
(**Palanker et al., Ophthalmology 2020**)

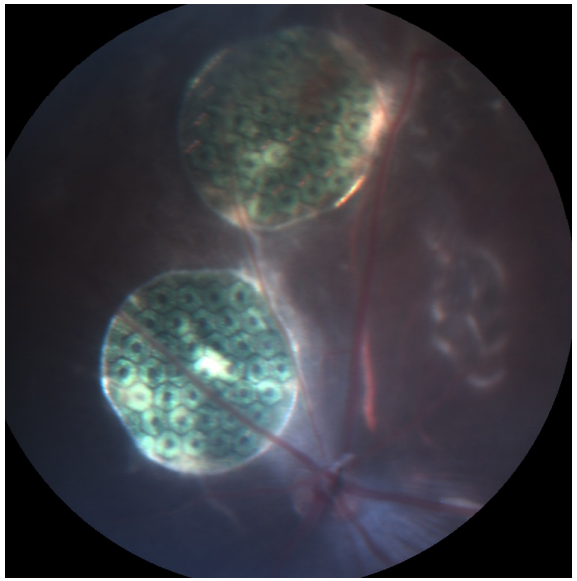
Fusion of prosthetic and natural vision

(**Palanker et al., Research Square 2021**)

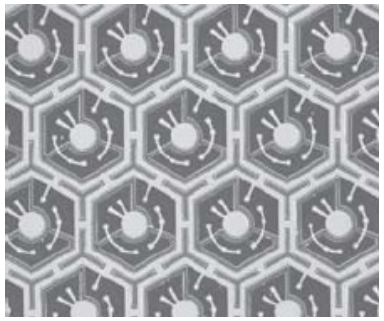


Multichip and reducing further the pixel size?



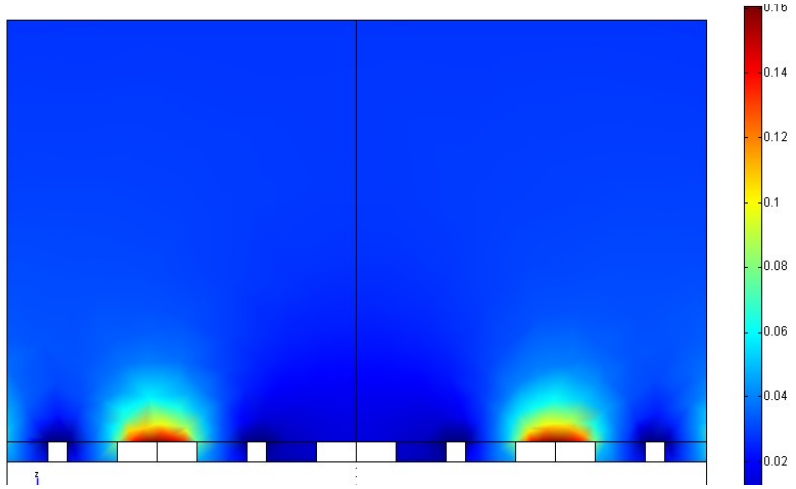


100µm



70µm

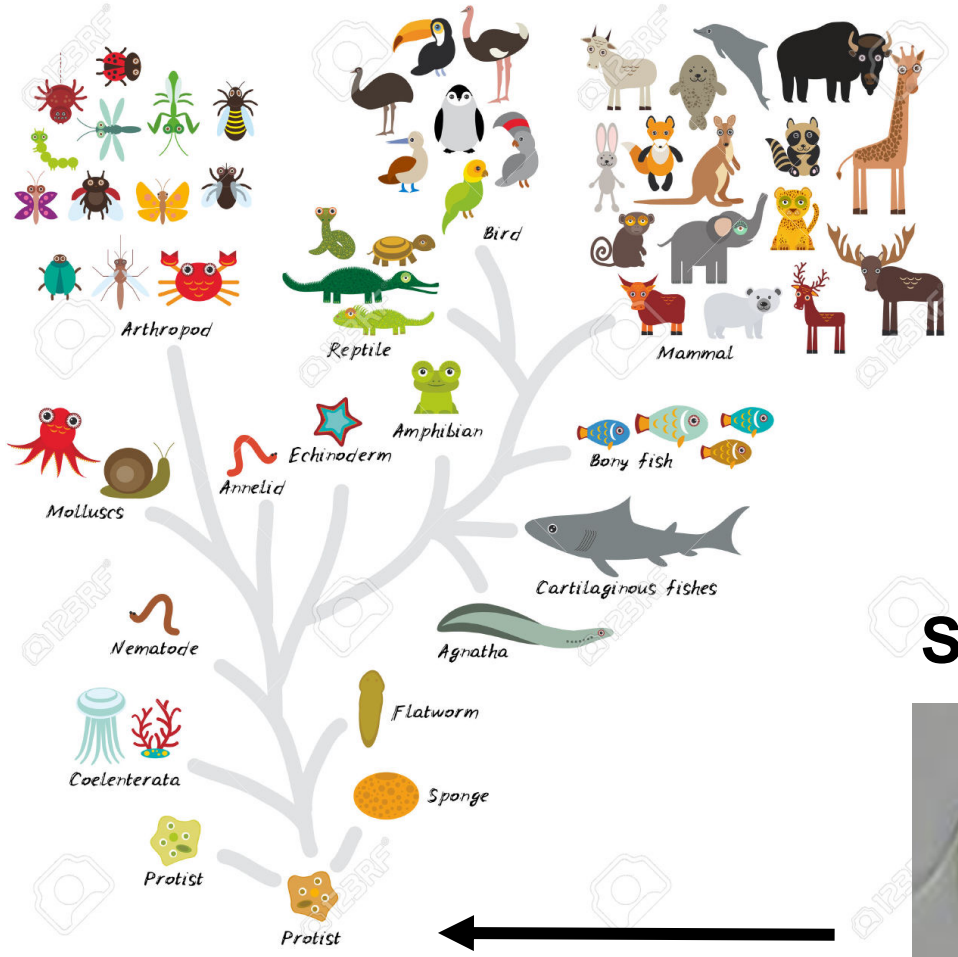




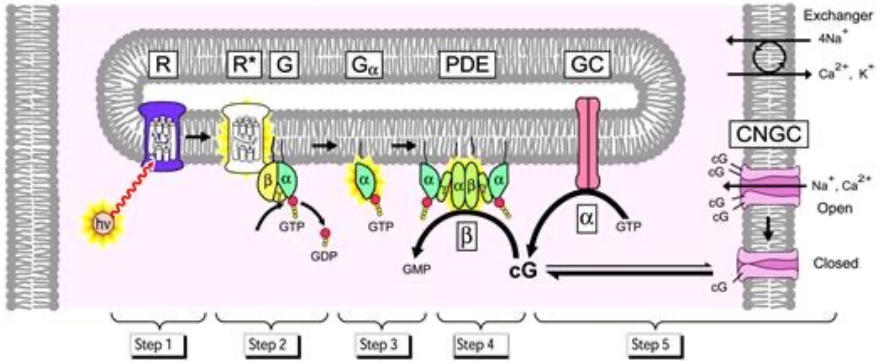
From Daniel Palanker

Optogenetic Therapy

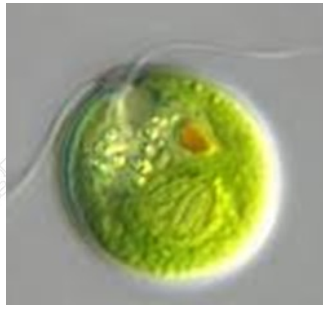
Visual systems during evolution

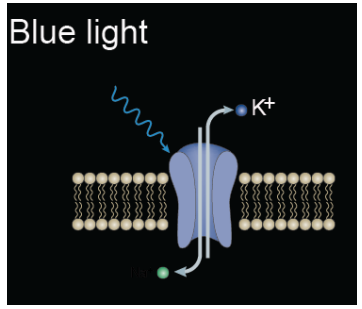


Vertebrates



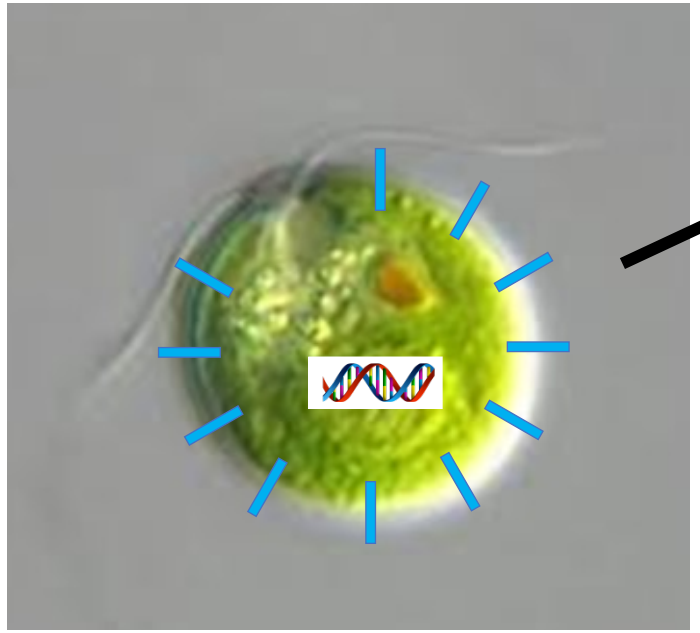
Single cell algae

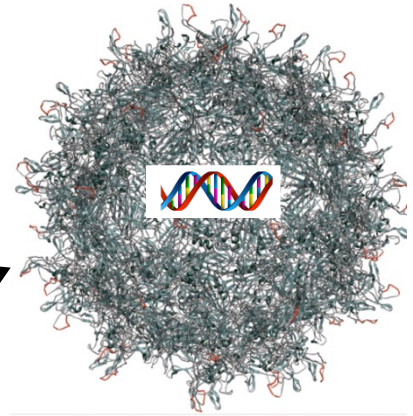


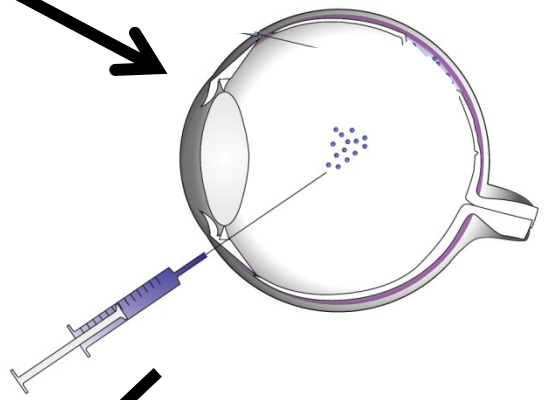


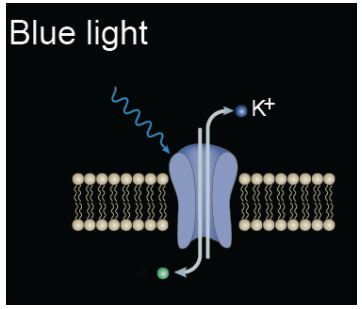
Optogenetic therapy

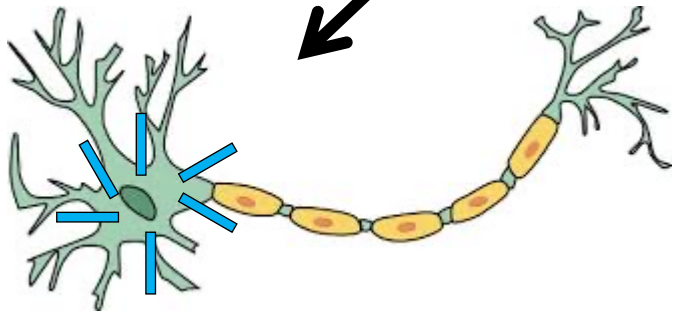
Photosensitive algae





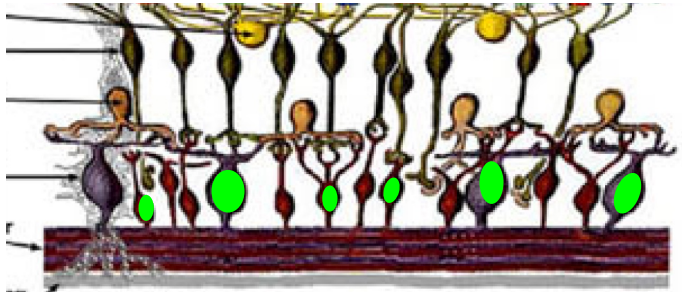


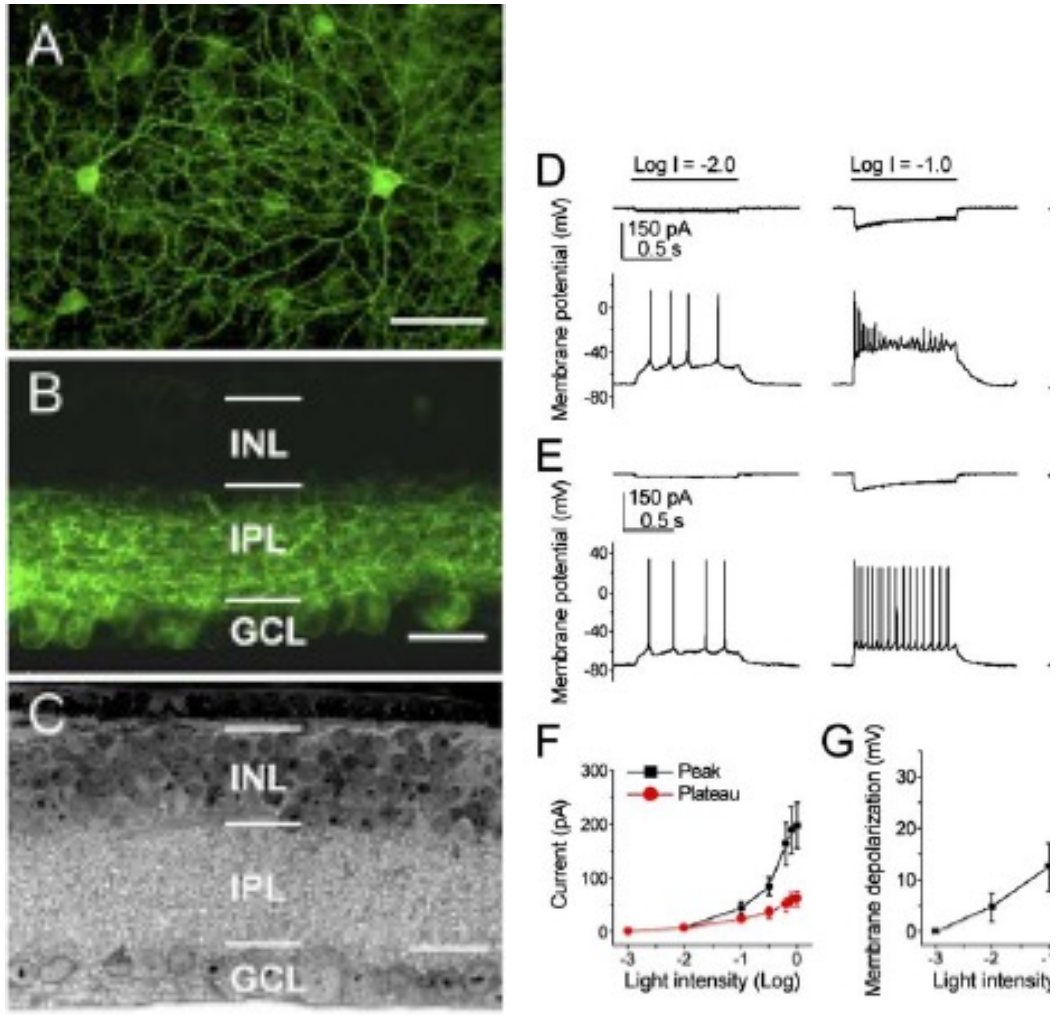




Targeting retinal ganglion cells

Bi et al. Neuron 2006, 50:23-33

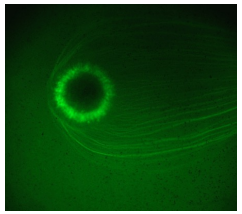


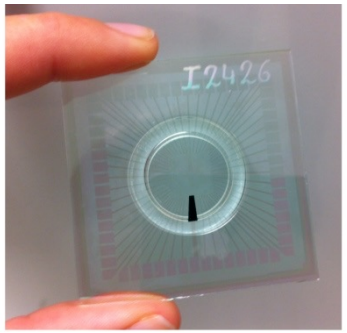


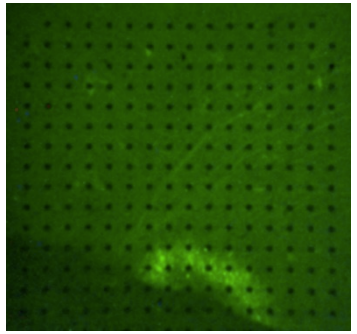
Activation par CatCh dans les cellules ganglionnaires

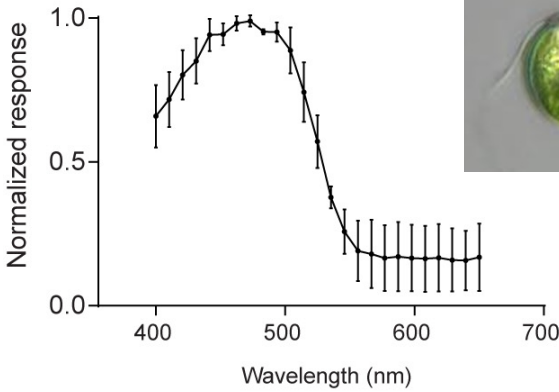




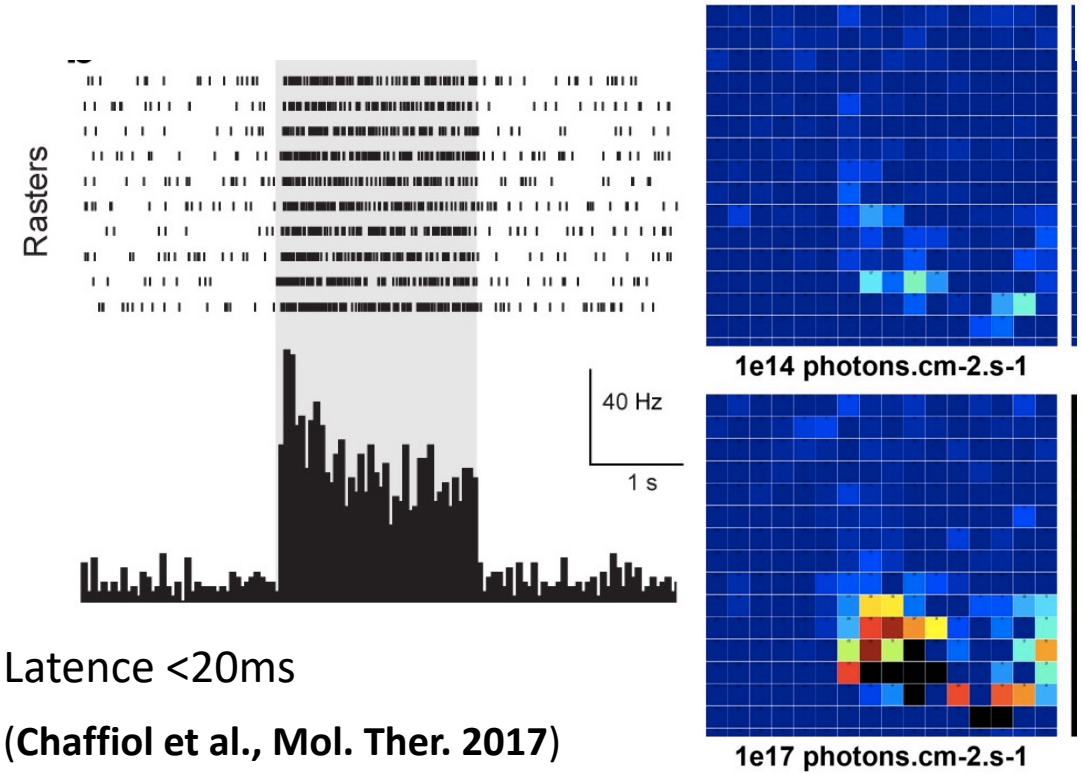


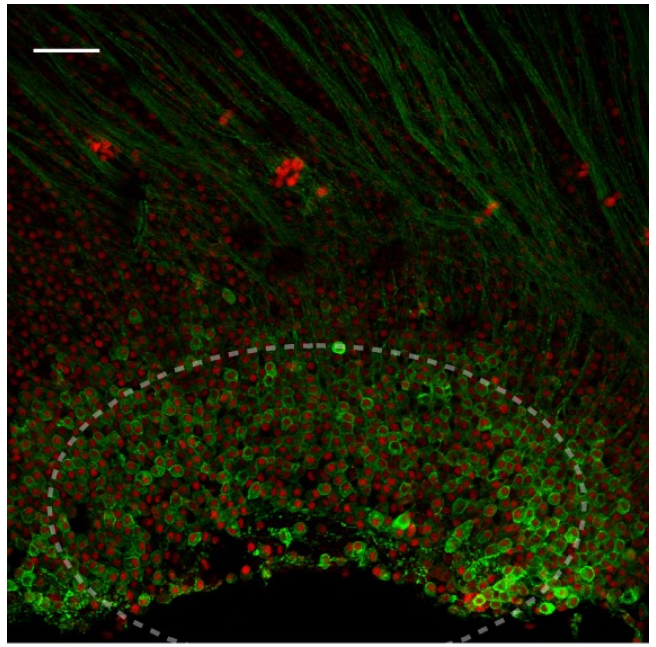












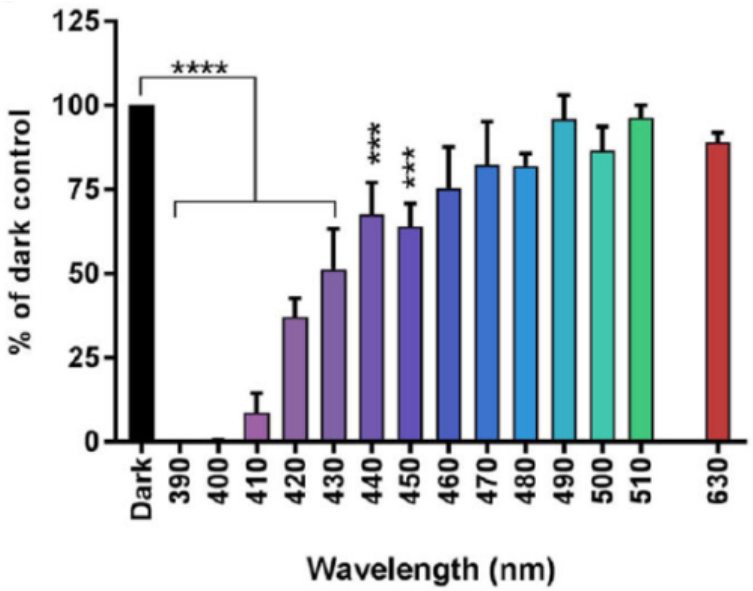
Latence <20ms

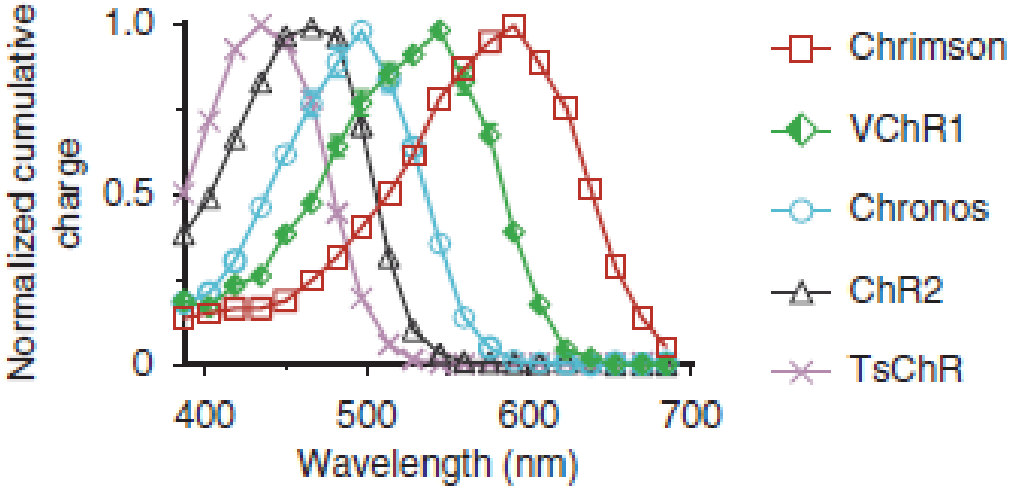
(**Chaffiol et al., Mol. Ther. 2017**)

Visual acuity: 20/72, **Ferrari et al., Plos Comp. Biol.. 2020)**

Selection of the red-shifted opsin, ChrimsonR

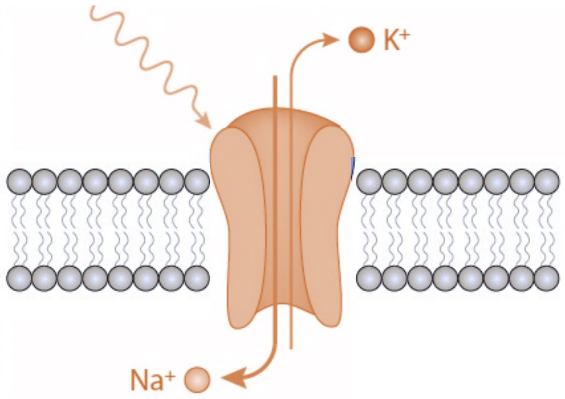
GS030





Engineered AAV variant

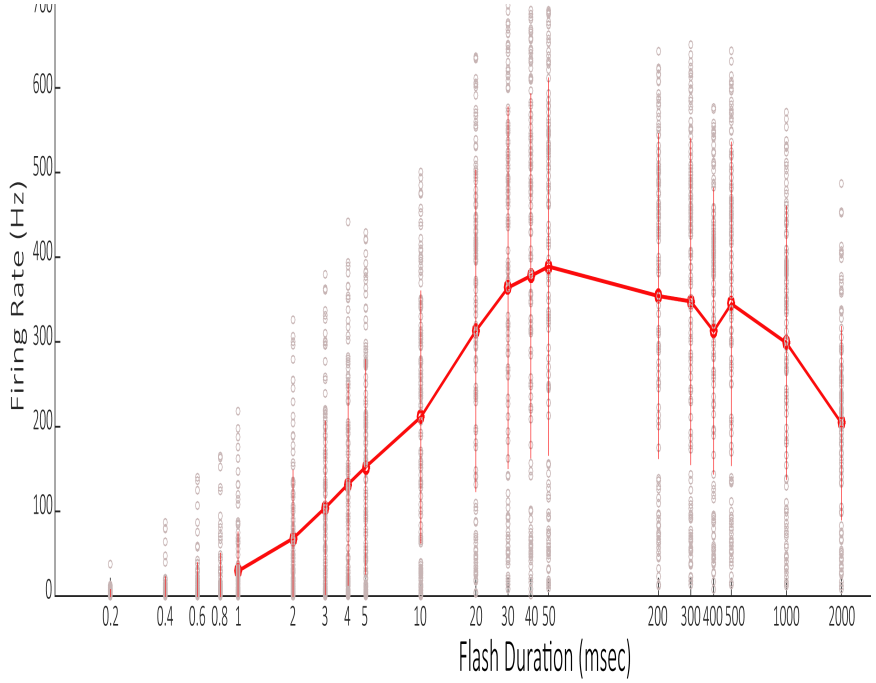
AAV2.7m8

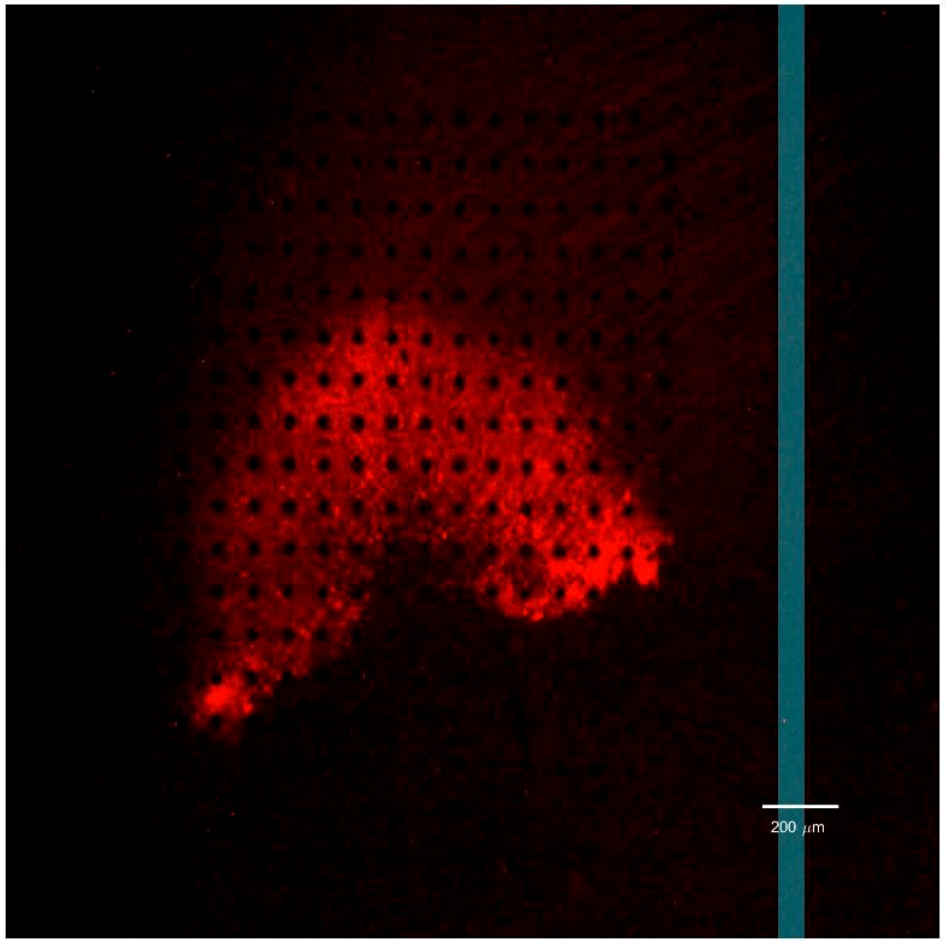


ChrimsonR-tdTomato

Temporal and spatial resolution of the responses







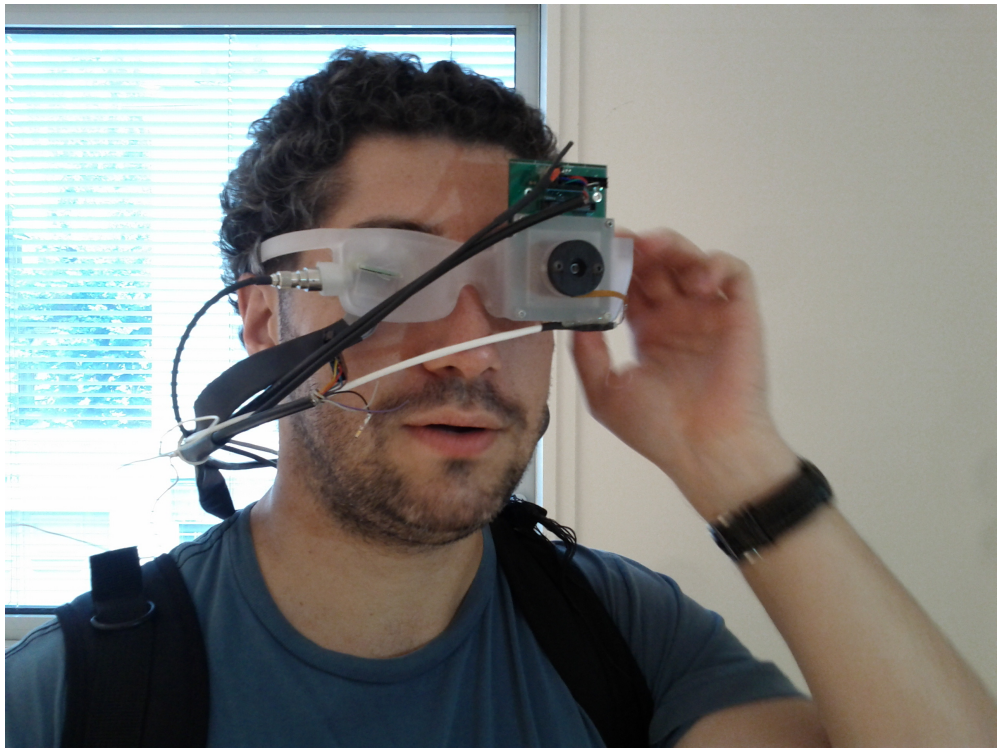
(**Gauvain et al., Communication Biology 2021**)



R. BENOSMAN

Preparing the visual stimulators for the clinical trials

A first goggle prototype



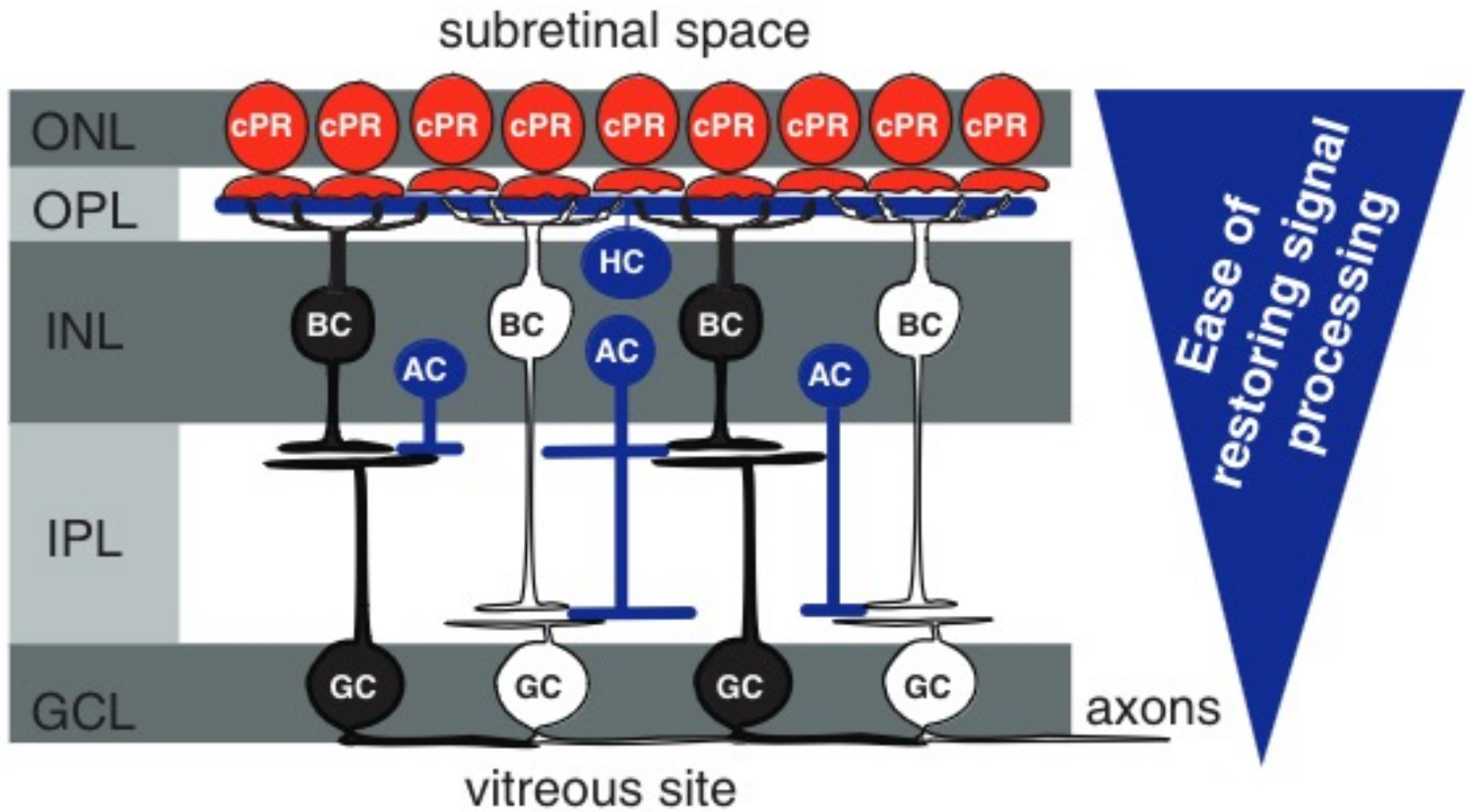


First report in a human patient

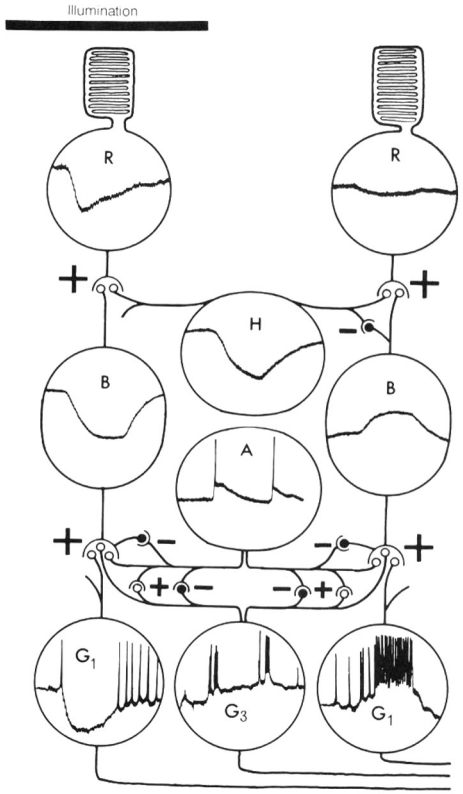


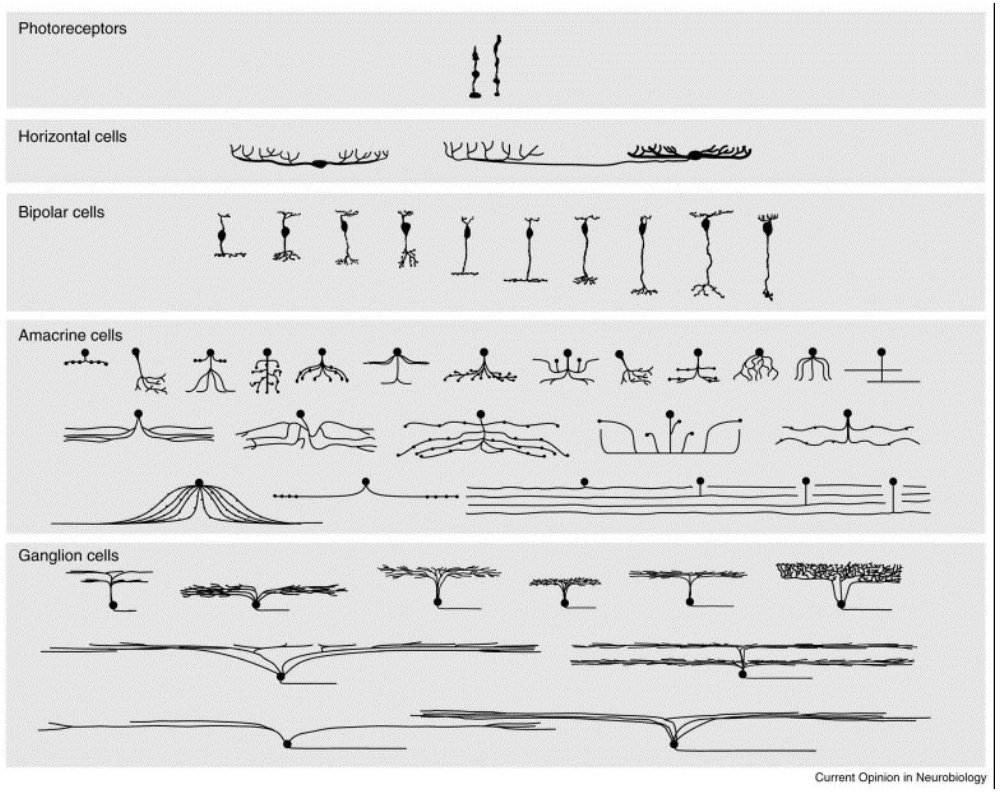
Sahel et al., 2021

GenSight BIOLOGICS

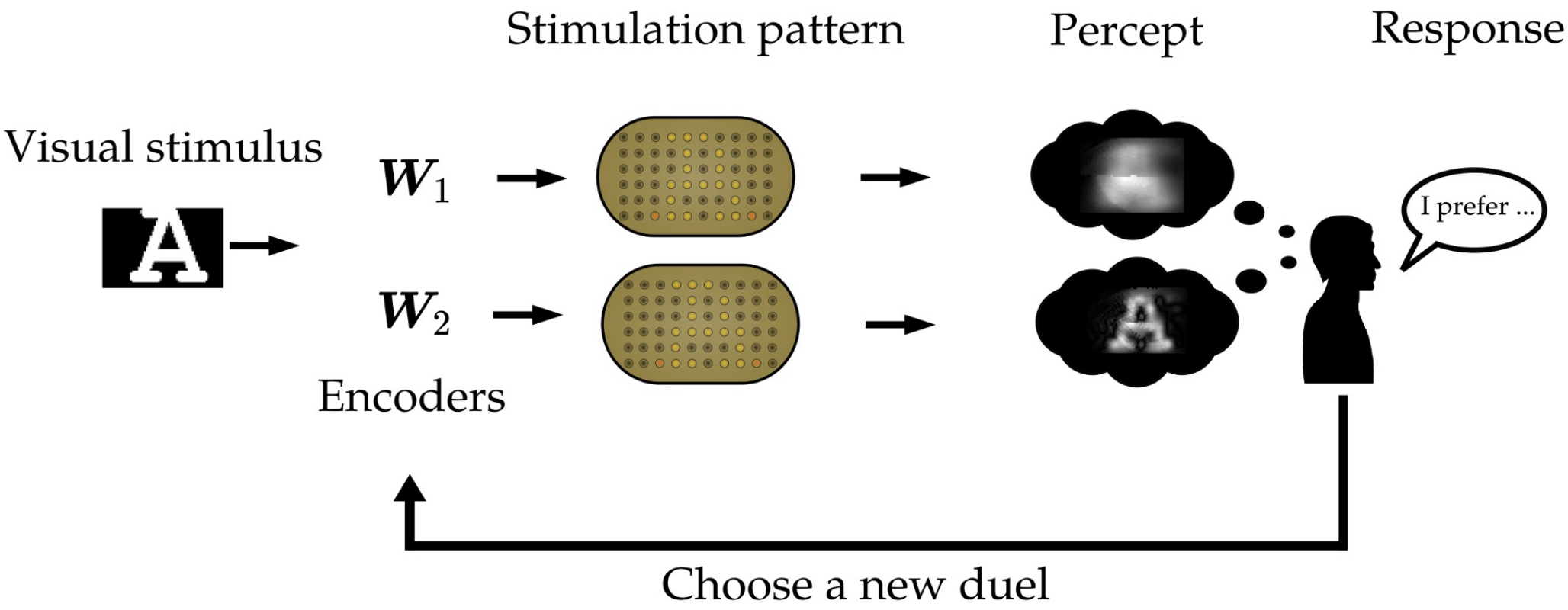

subretinal space
ONL
OPL
INL
IPL
GCL
cPR
HC
BC
AC
GC
axons
vitreous site
Ease of restoring signal processing

The different cell targets





Optimizing the stimulation



Fauvel & Chalk, 2022

Conclusions

- Visual restoration in blind patients with RP or ARMD
- **best visual acuity with PRIMA:** close to threshold of legal blindness (1/20)

- An alternative solution : **Optogenetic therapy** (Theory 20/249- 20/72)
- Ongoing clinical trials on RP patients

- **Future project**:

  Visual restoration at the cortical level by sonogenetic therapy.