Restoration of vision by retinal sheet transplants in rats with retinal degeneration

Leo Scholl
Department of Cognitive Science
UC Irvine

November 2, 2016

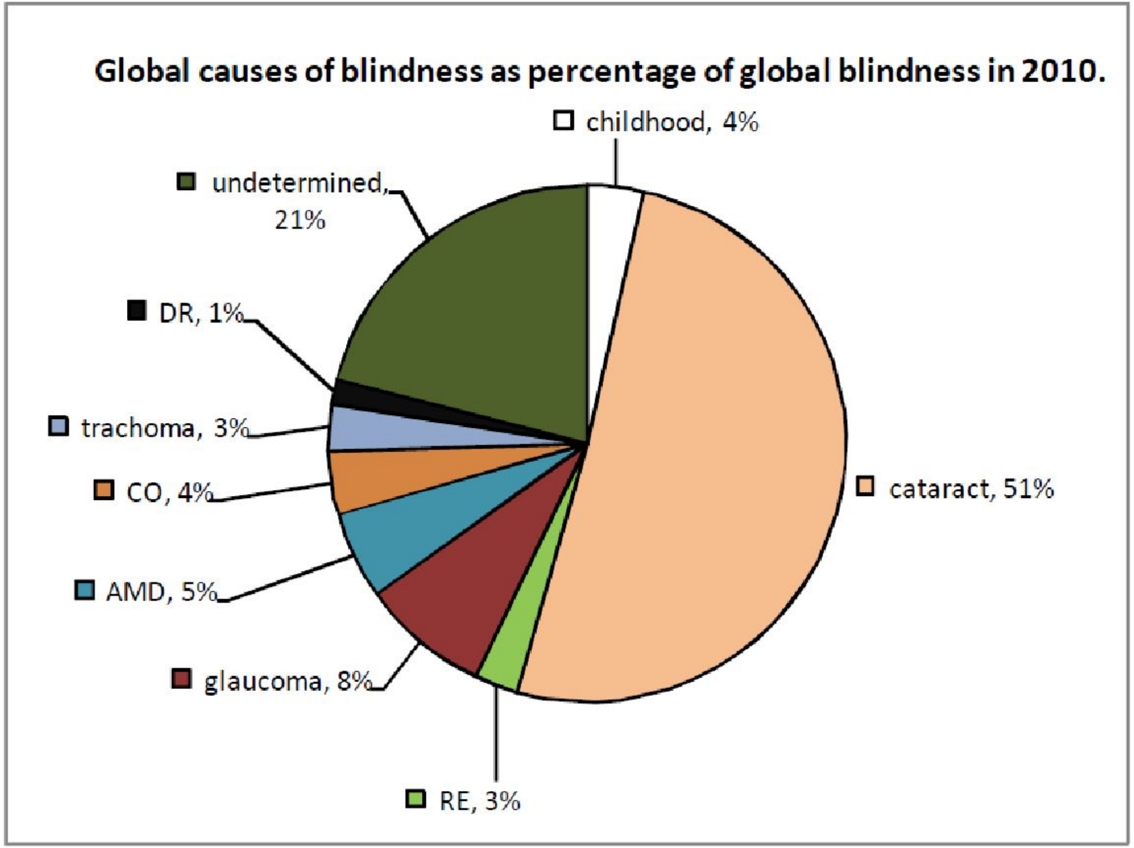
Global causes of blindness in 2010

285 million people visually impaired

39 million are blind

80% of all visual impairment can be prevented or cured

All listed causes of blindness except AMD are avoidable

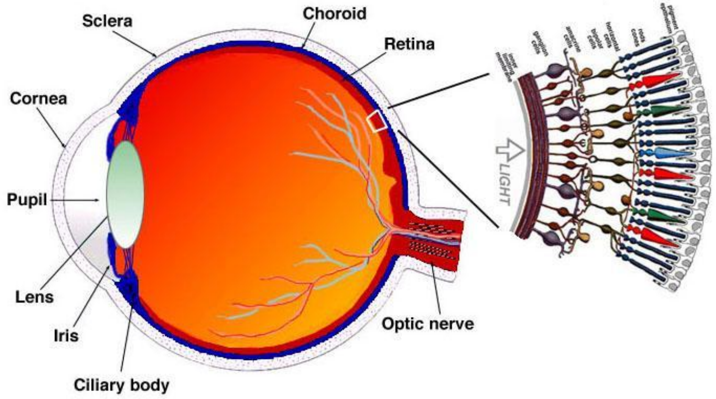


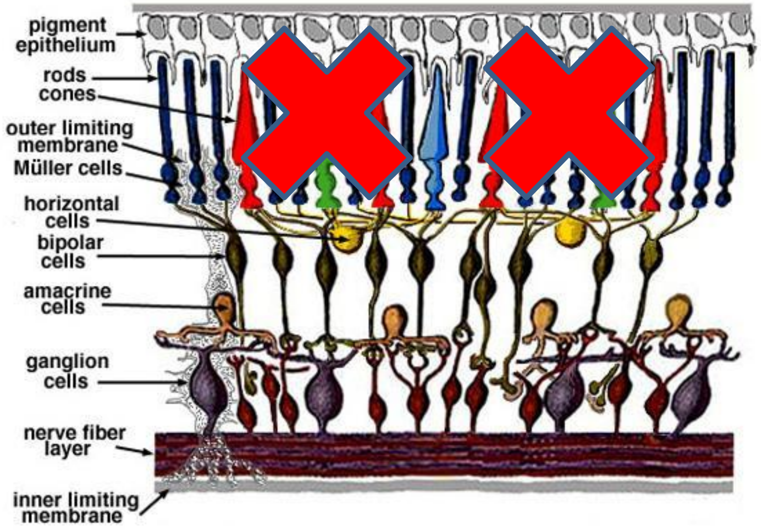
Retinal degeneration

Destruction of photoreceptors or retinal pigment epithelium (RPE)

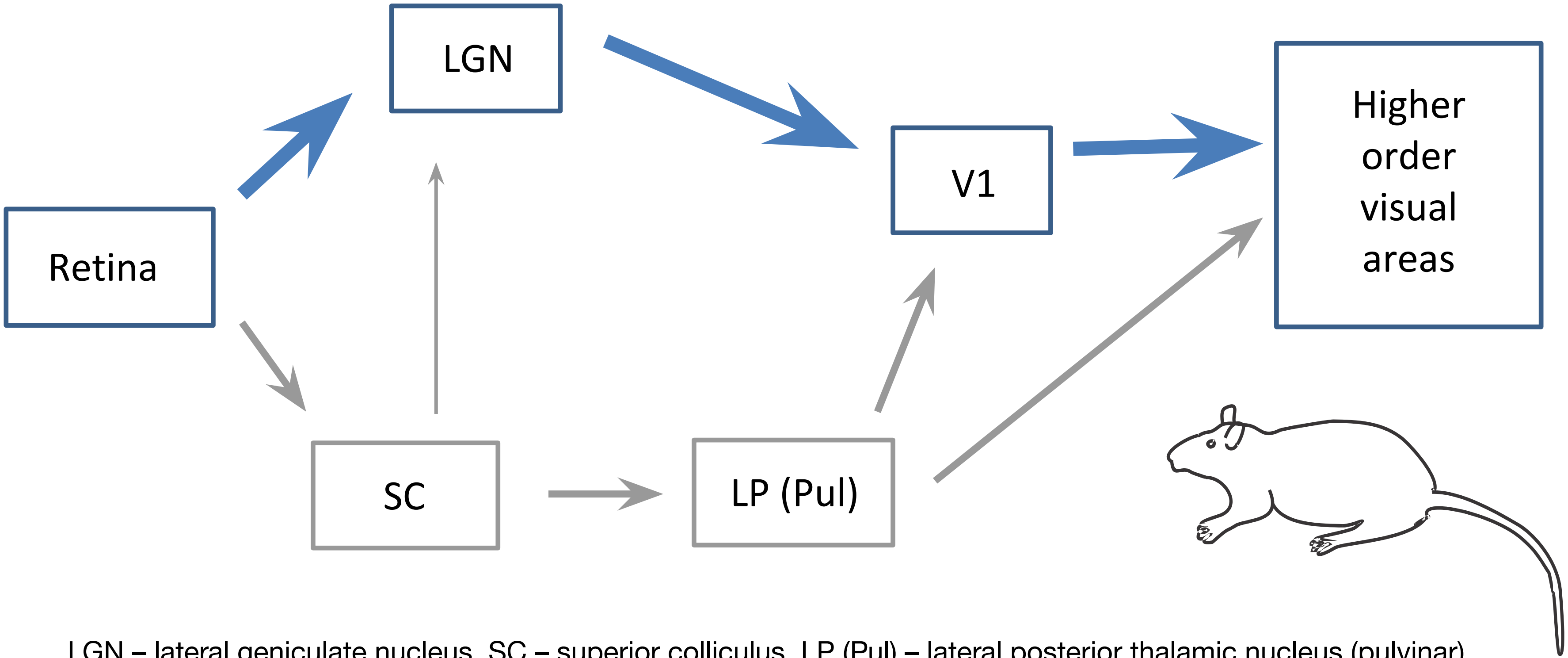
Examples include:

- Age-related macular degeneration
- Retinitis pigmentosa



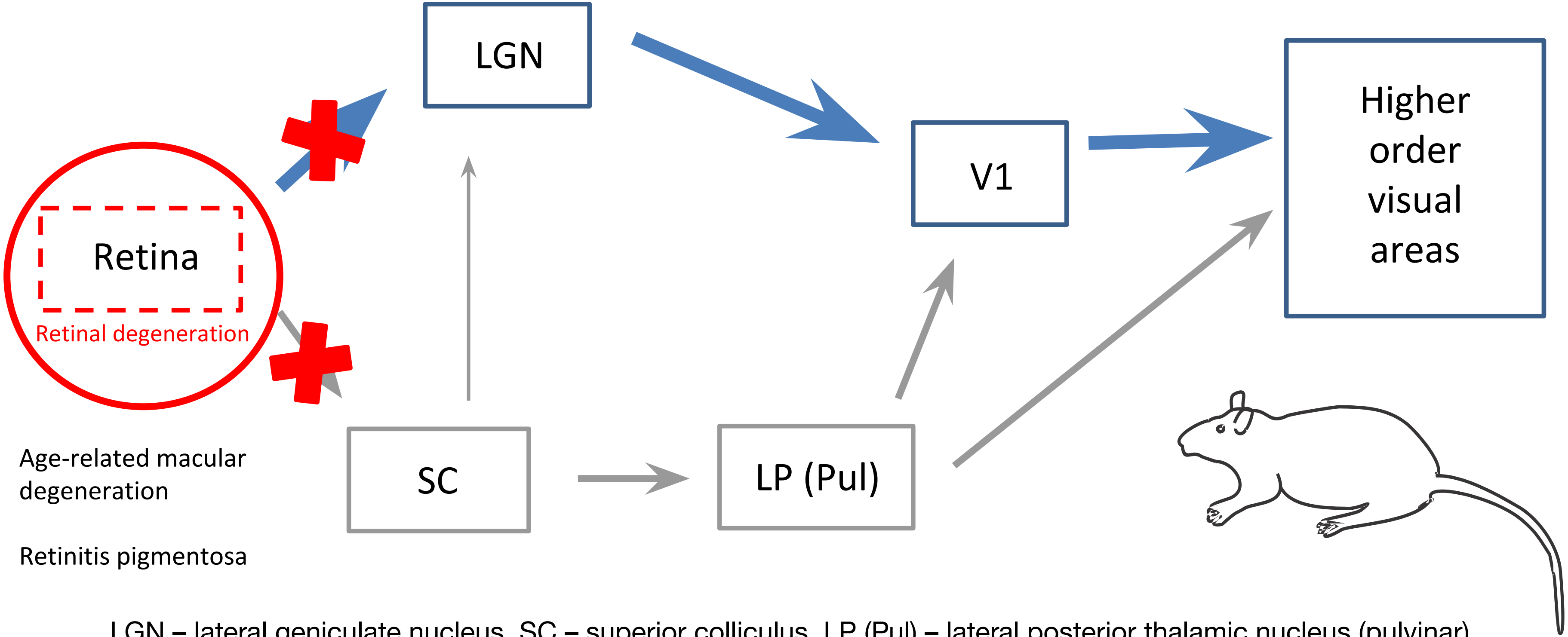


Visual system



LGN – lateral geniculate nucleus, SC – superior colliculus, LP (Pul) – lateral posterior thalamic nucleus (pulvinar)

Visual system

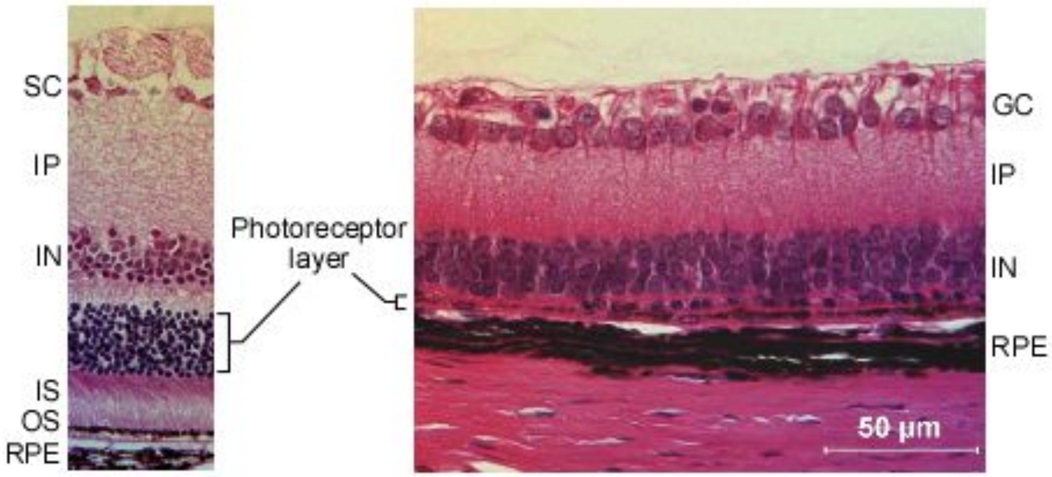


Age-related macular degeneration

Retinitis pigmentosa

LGN – lateral geniculate nucleus, SC – superior colliculus, LP (Pul) – lateral posterior thalamic nucleus (pulvinar)

Retinal degeneration models



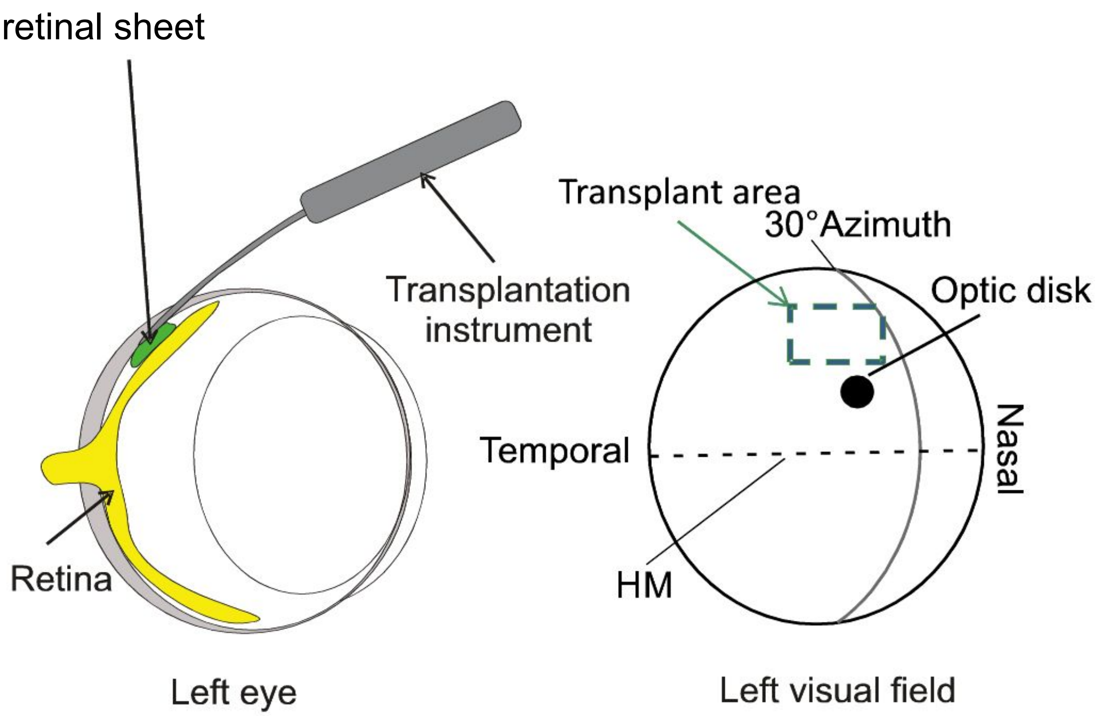
Normal rat retina

Degenerated retina in 4 weeks old transgenic Rho S334-ter line 3 rat

GC, ganglion cell layer; IP, inner plexiform layer; IN, inner nuclear layer; RPE, retinal pigment epithelium; OS, outer segment layer; IS, inner segment layer

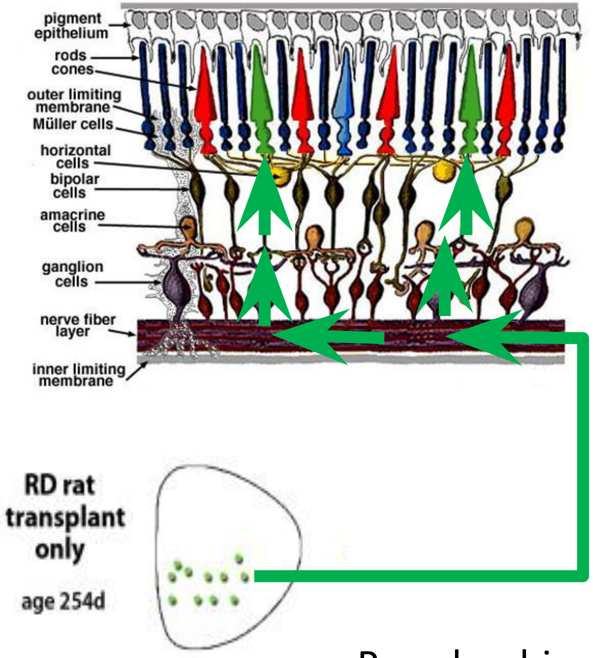
Seiler et al.
2008

Transplantation method



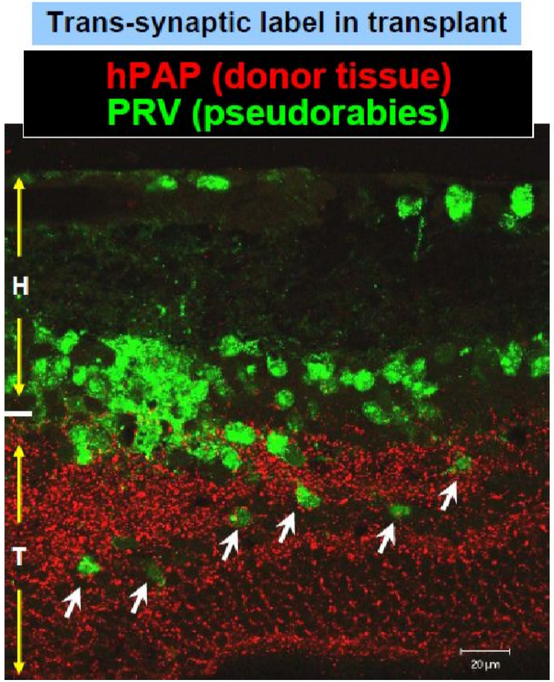
Seiler lab

Transplant makes connections with host



Pseudorabies injection

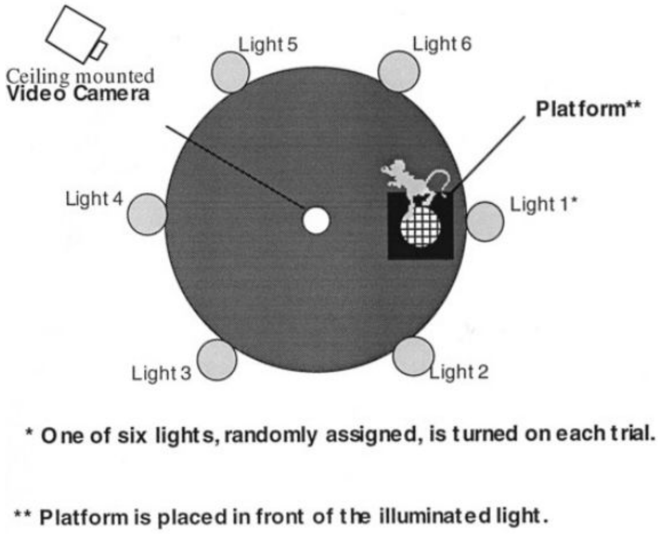
Seiler et al. 2008



PRV (green) - labeled cells in transplant (red), 52 hours after virus injection into the visually responsive site in SC.

Recovery of visual behavior

A



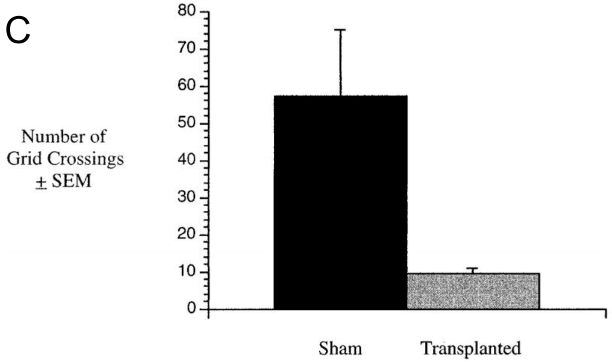
Water maze apparatus

B

GROUP	TRIAL									
	1	2	3	4	5	6	7	8	9	10
SHAM	58.4 ± 1.6	26.6 ± 11.4	32.8 ± 12.4	22.4 ± 10.0	19.8 ± 8.4	13.0 ± 4.8	38.8 ± 8.6	35.2 ± 10.0	22.2 ± 9.1	33.0 ± 10.4
HF RPE	39.2 ± 9.0	52.6 ± 7.4	38.8 ± 11.1	29.8 ± 10.6	38.2 ± 7.3	31.0 ± 7.9	15.0 ± 7.8	17.6 ± 6.1	6.4 ± 2.3	8.2 ± 1.7

Mean time to find platform for sham and transplanted RCS rats

C



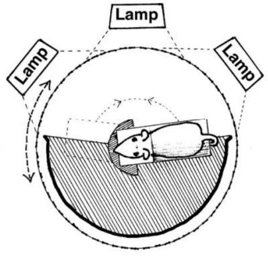
Estimated path length

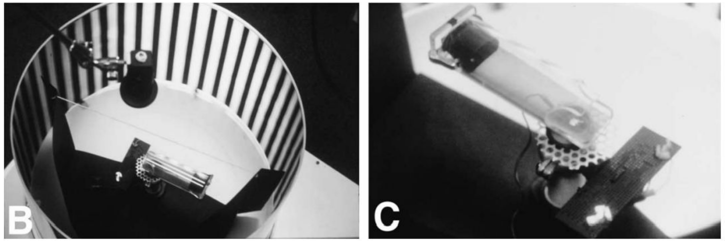
Cerro, 1998

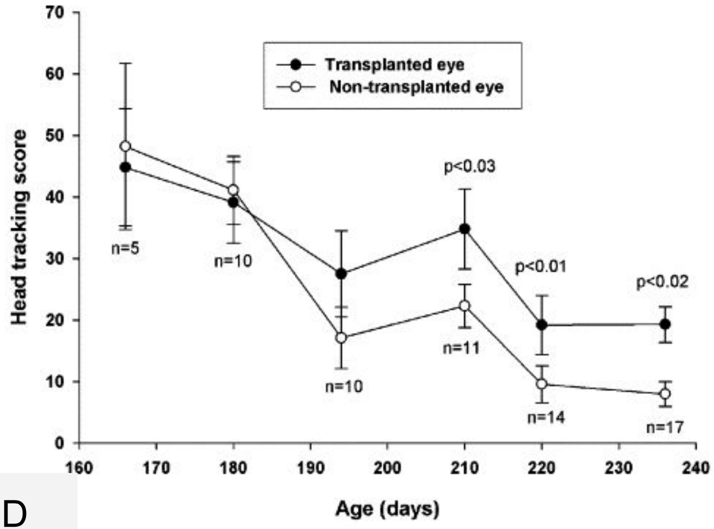
Recovery of visual behavior

Optokinetic Nystagmus

A

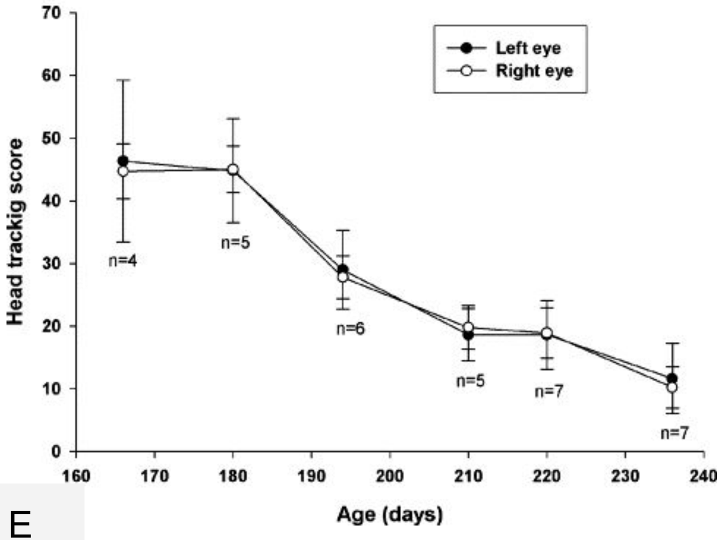






D

S334ter-3 rats with transplants

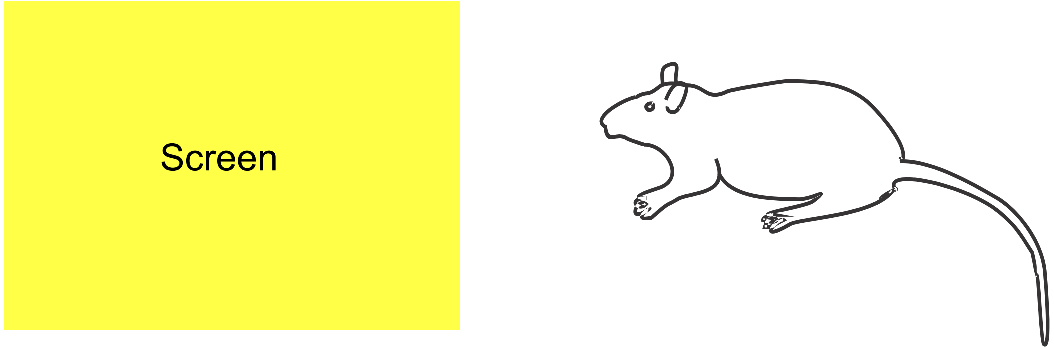


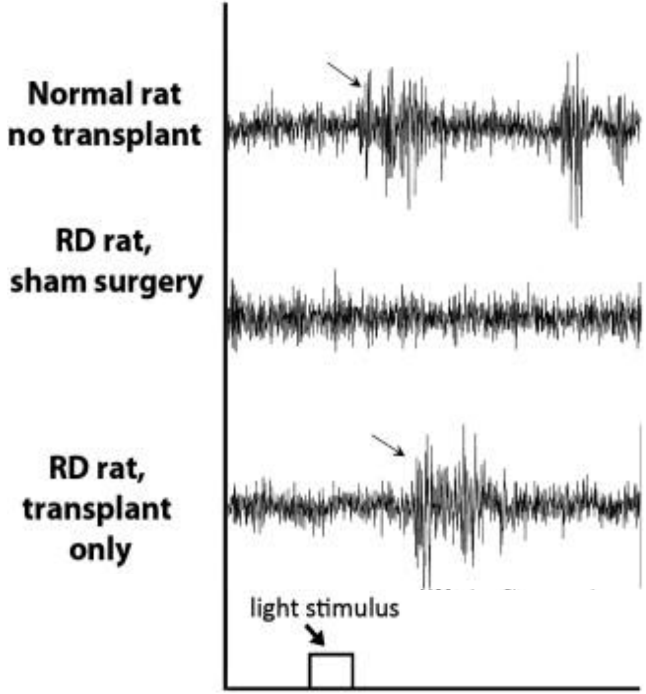
E

Age-matched controls

Thomas et al., 2004

Retinal transplant restores visual responses in SC

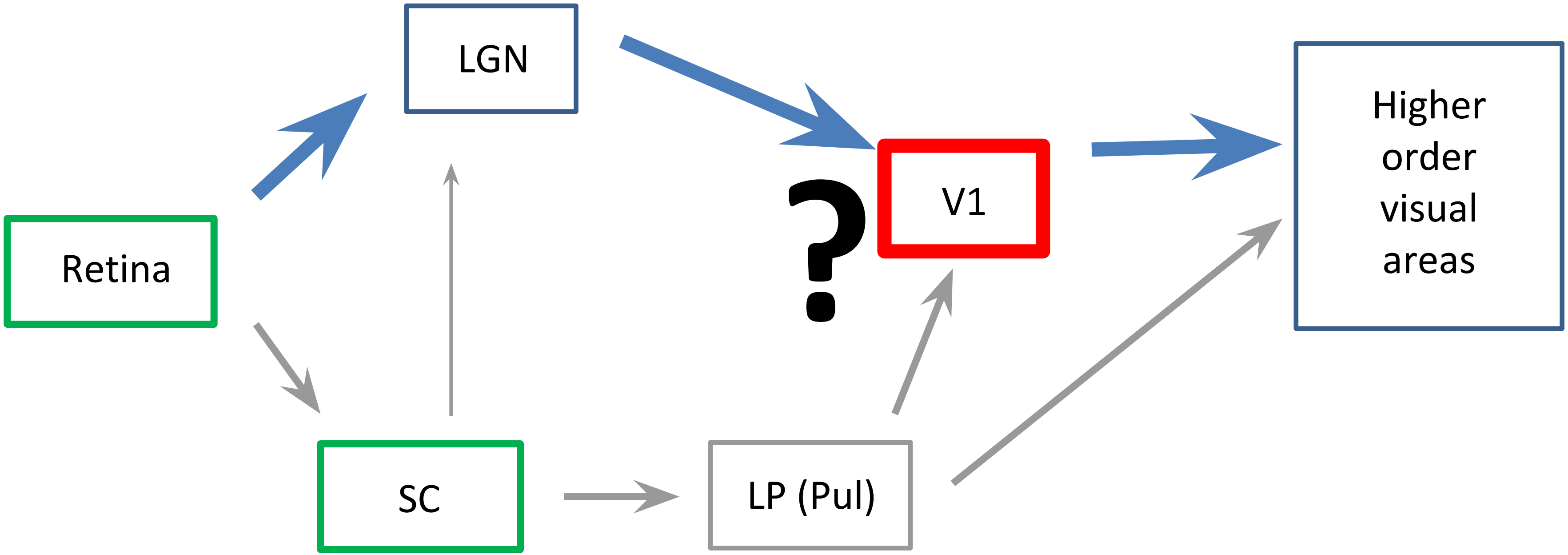




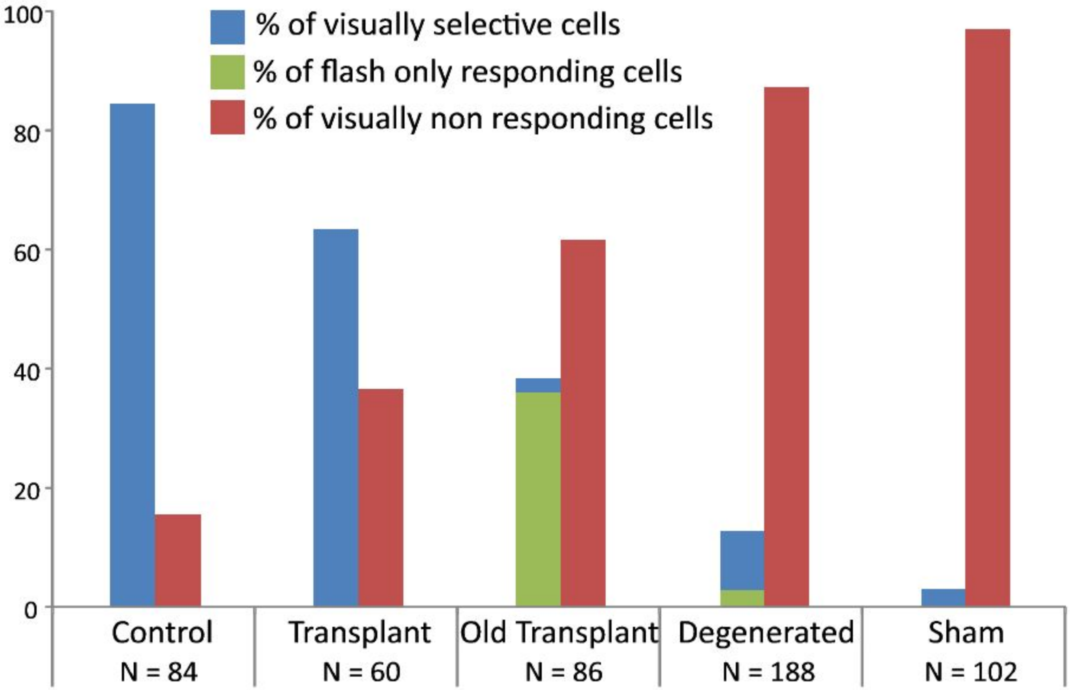
Multi-unit activity recorded in the SC in response to flash of light

Yang, Seiler et al. 2010

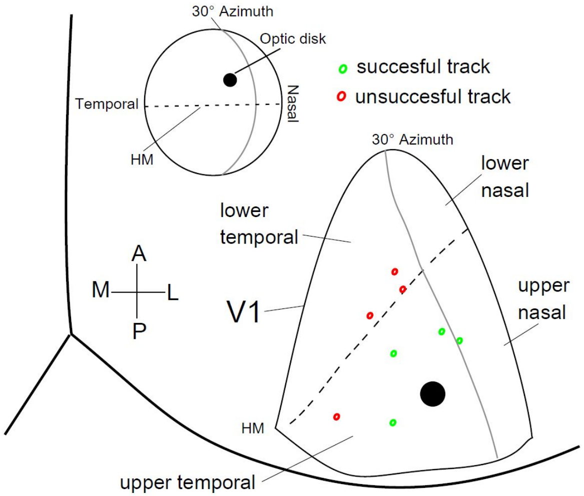
Retinal transplant restores visual responses



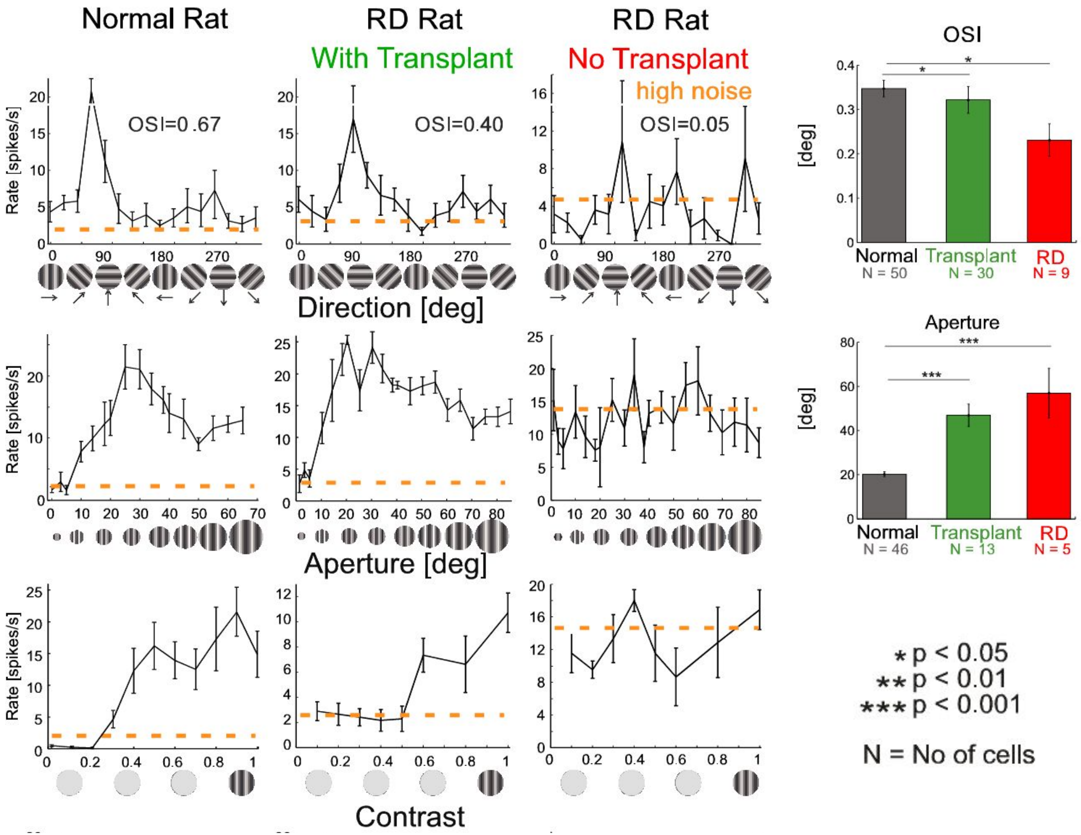
Retinal transplant restores visual responses



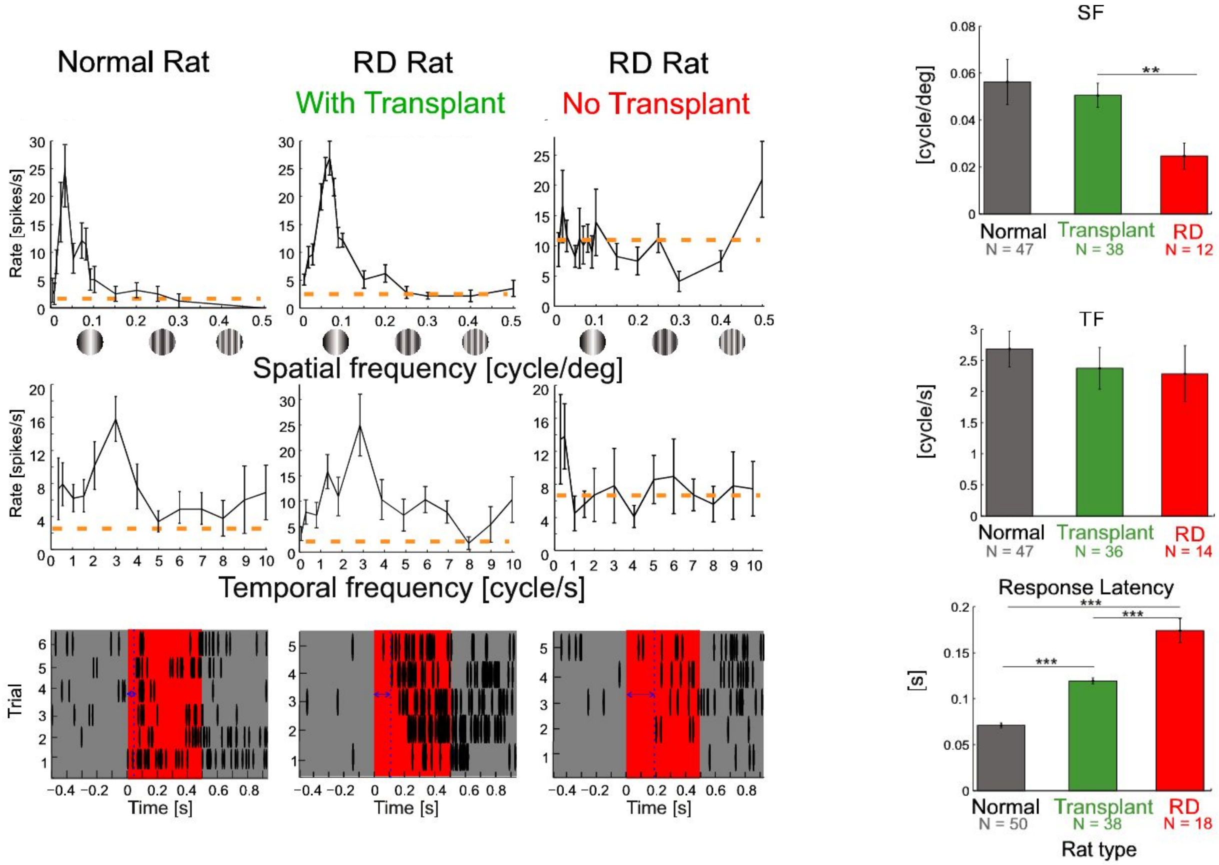
V1 recording sites



Retinal transplant restores visual responses



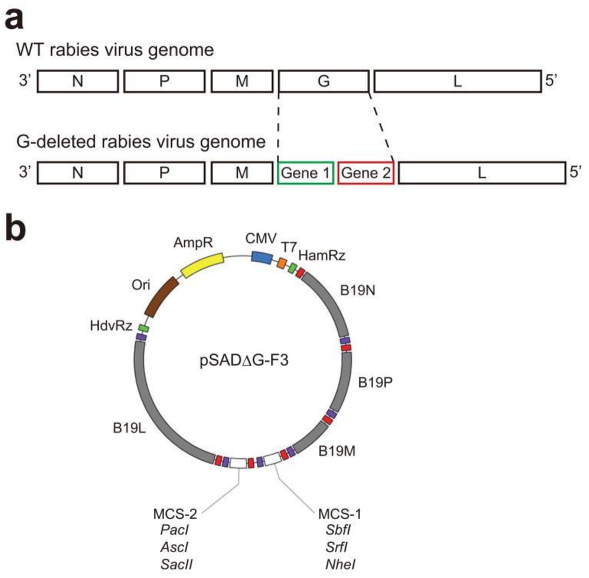
Retinal transplant restores visual responses



* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

N = No of cells

Using rabies virus to identify circuitry

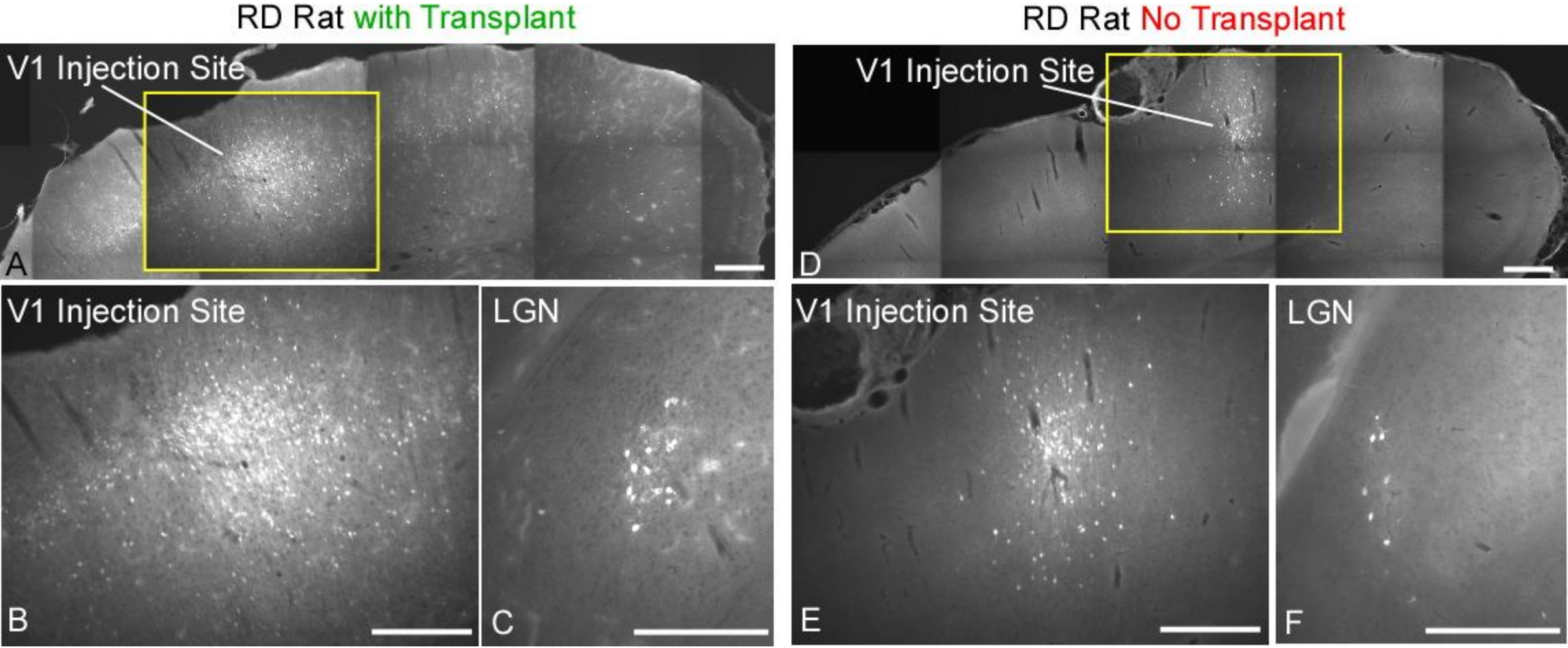


(a) Rabies WT and G-deleted genomes
(b) G-deleted rabies viral genomic vector

Okasada, 2011

Name	Envelopes	Expresses
G-Deleted Rabies-eGFP	Rabies B19G	Enhanced GFP
G-Deleted Rabies-mCherry	Rabies B19G	mCherry
G-Deleted Rabies BFP	Rabies B19G	Blue Fluorescent Protein
G-Deleted Rabies-ChR2-mCherry	Rabies B19G, EnvA	Channelrhodopsin 2-mCherry Fusion
G-Deleted Rabies eGFP-ArchT	Rabies B19G, EnvA	Enhanced GFP, Archaerhodopsin

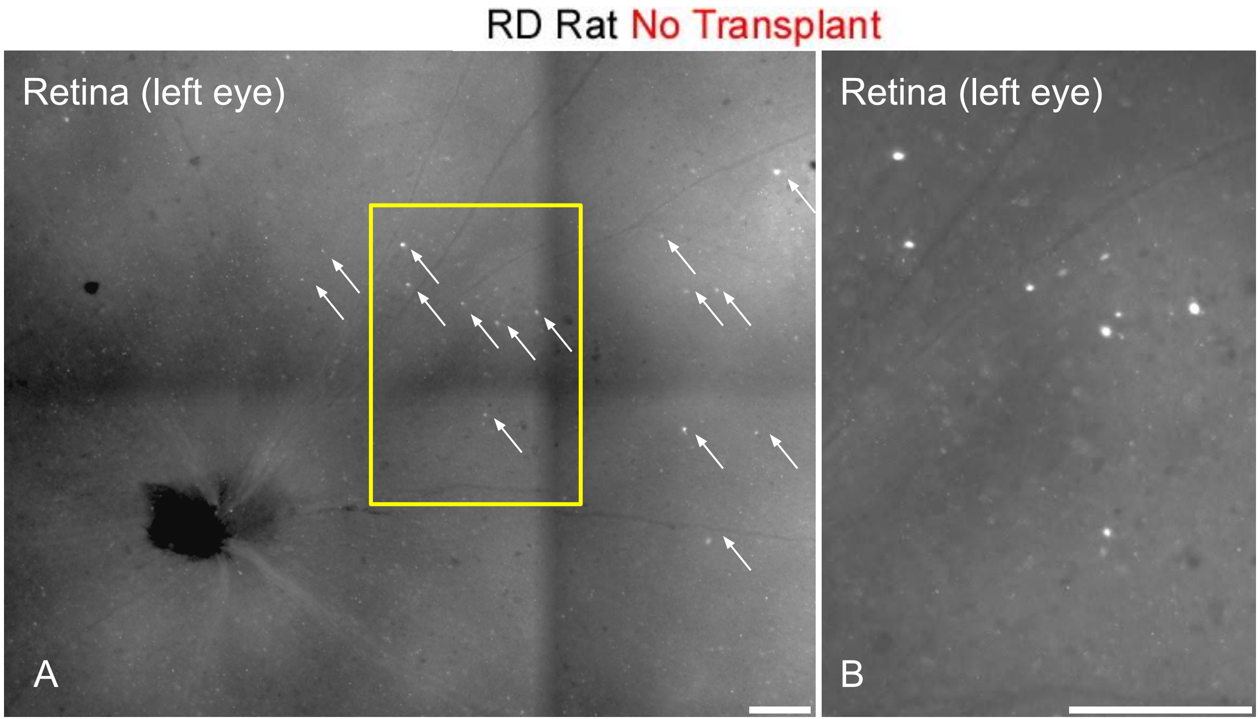
Retinal transplant restores projections to V1



RD-rats have projections to SC

Loss of photoreceptors happens early – no visual responses at ~30 days old

Do connections from retina develop properly?



Summary

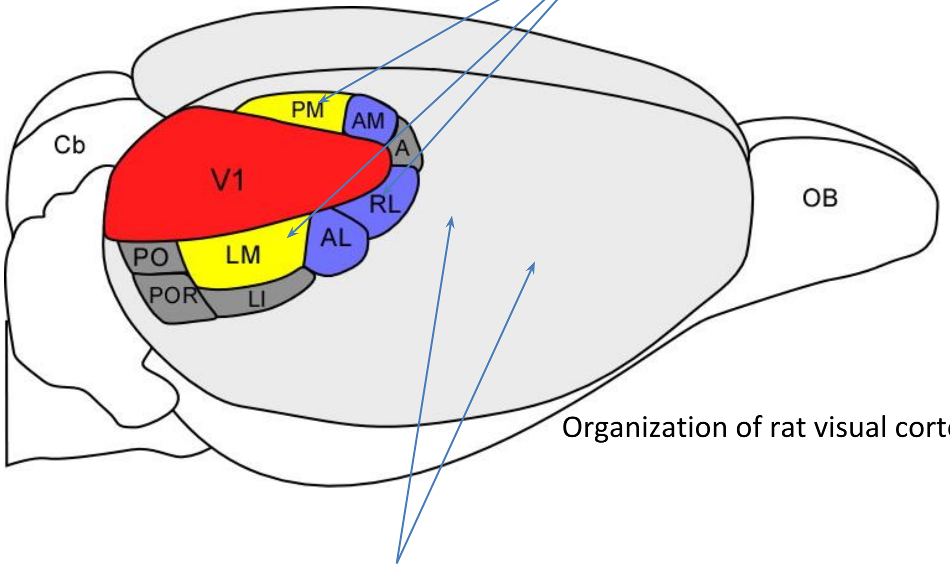
Transplants improve visual response in primary visual cortex:

- A majority of neurons were visually responsive and show selectivity on par with normal rats
- Receptive fields correspond to the transplant location in the retina.

Retrograde tracing shows that visual circuitry is in place even in RD rats without transplants. However, long range connections within V1 appear to be lost in non transplanted RD rats.

Future directions

Recovery of function in higher order visual cortex



Organization of rat visual cortex.

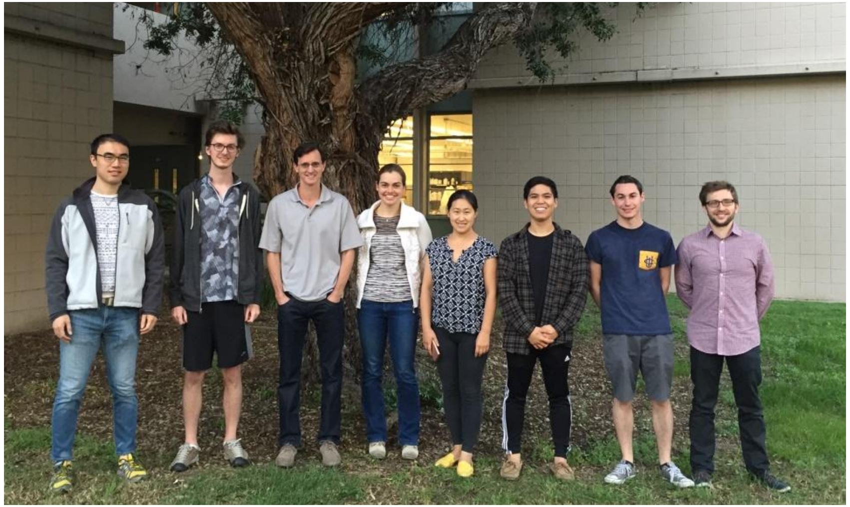
Changes in neuronal network organization/connectivity in visual cortex (preliminary data)

Differentiating human embryonic stem cells (hESCs) into sheets of retinal progenitor tissue

Transplants into nude (immunocompromised) rats

(Seiler lab, unpublished)

Acknowledgements



Lyon Lab

Seiler Lab

References

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Yang PB, Seiler MJ, Aramant RB, Yan F, Mahoney MJ, Kitzes LM, Keirstead HS. 2010. Trophic factors GDNF and BDNF improve function of retinal sheet transplants. Experimental Eye Research

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Cerro, M. del Cerro. 1998. Correlates of photoreceptor rescue by transplantation of human fetal RPE in the RCS rat. Exp. Neurol., 149 , pp. 151–160

Seiler MJ, Thomas BB, Chen Z, Wu R, Sadda SR, Aramant RB. 2008. Retinal transplants restore visual responses: trans-synaptic tracing from visually responsive sites labels transplant neurons. Eur J Neurosci.

Future directions

Nucleus of the pulvinar complex in the thalamus

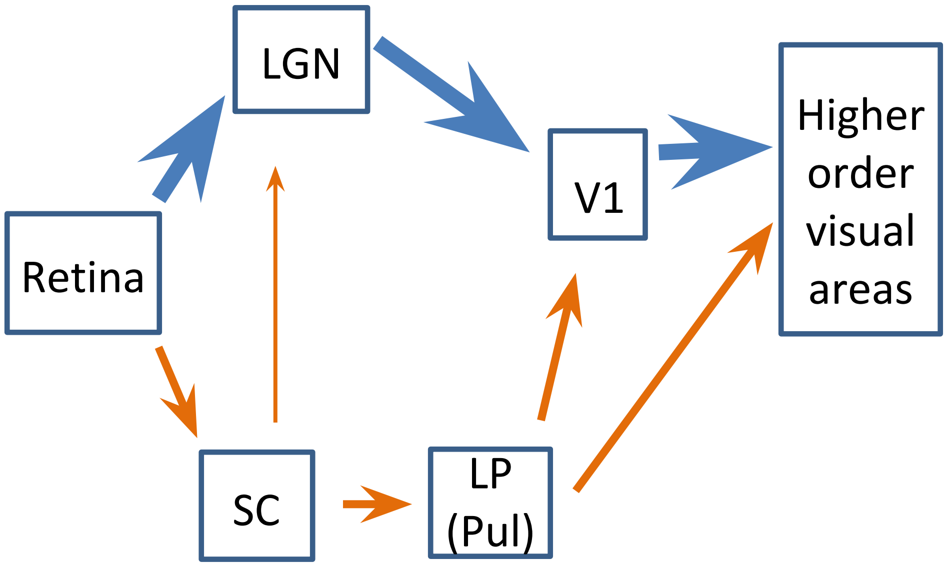
In rodents, there are 3 subdivisions

-Lateral (LPl)

-Rostromedial (LPrm)

-Caudomedial (LPcm)

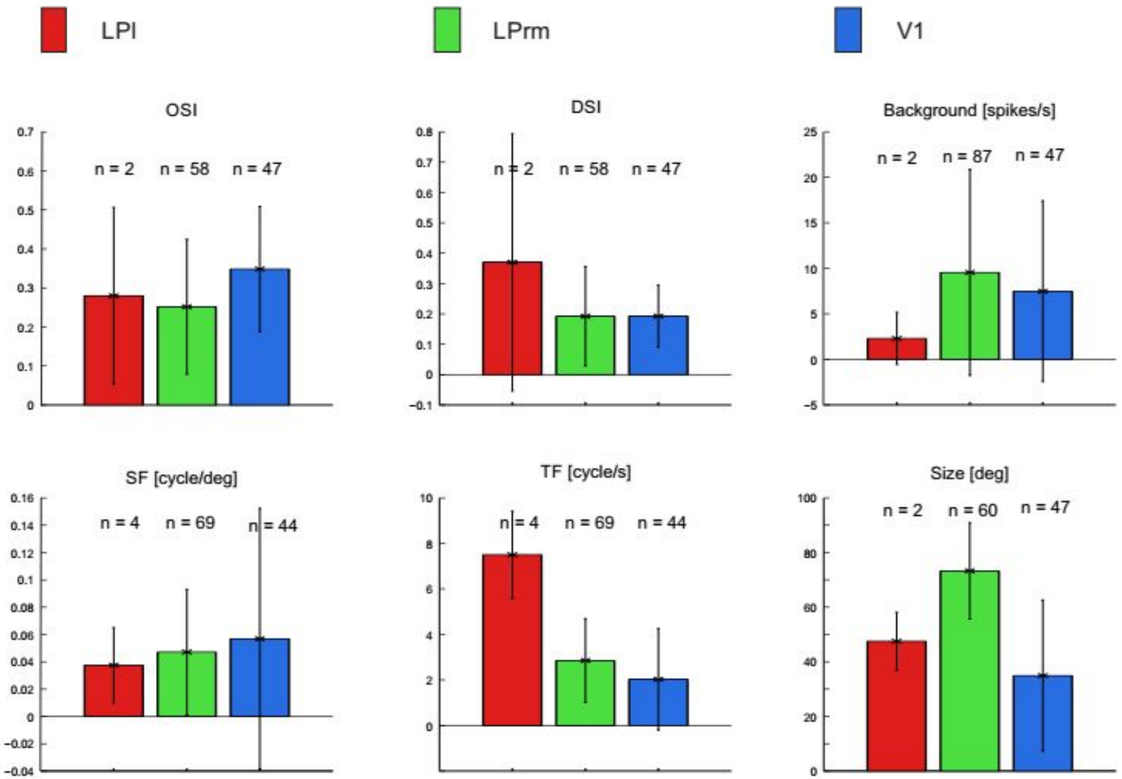
(Takahashi, 1985)



LGN – lateral geniculate nucleus, SC – superior colliculus, LP (Pul) – lateral posterior thalamic nucleus (pulvinar)

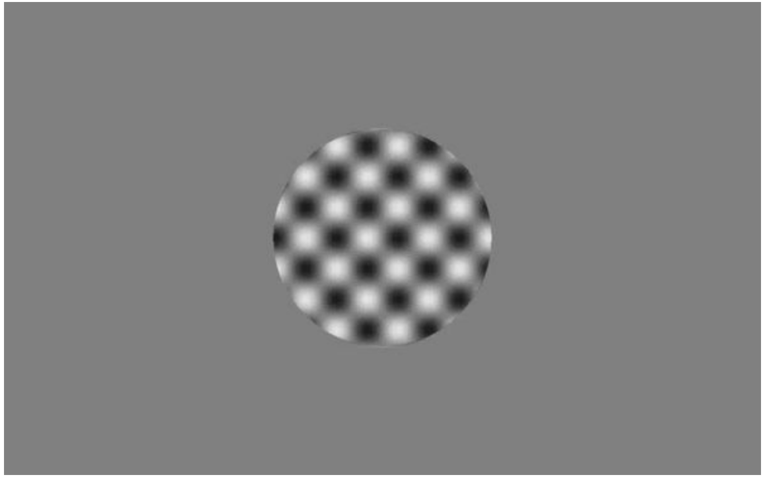
Lateral posterior nucleus

Subdivisions have distinct tuning properties

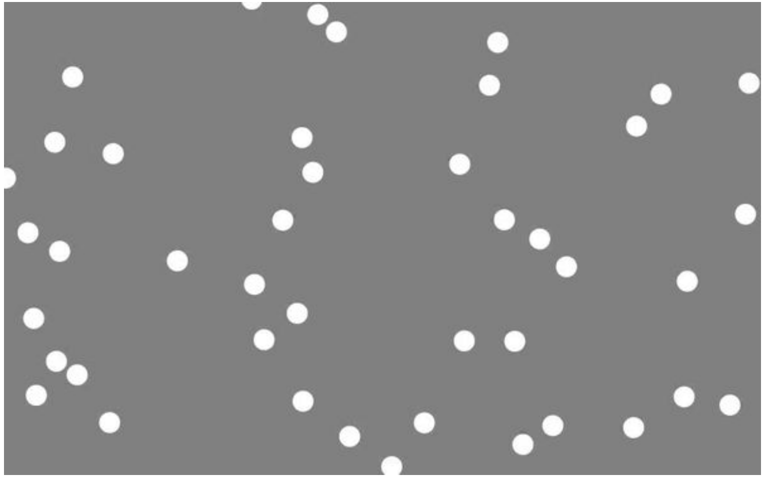


Lateral posterior nucleus

Higher order motion (preliminary data)

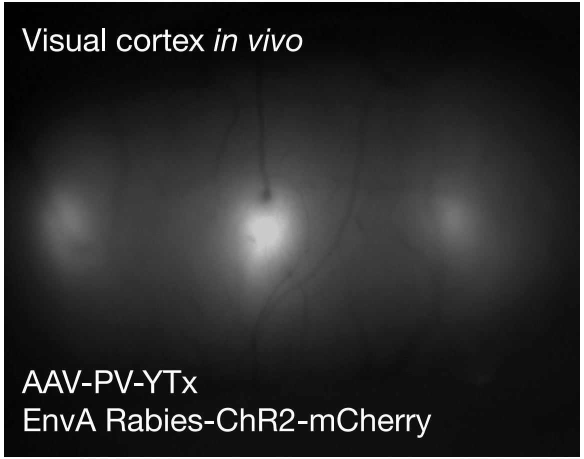


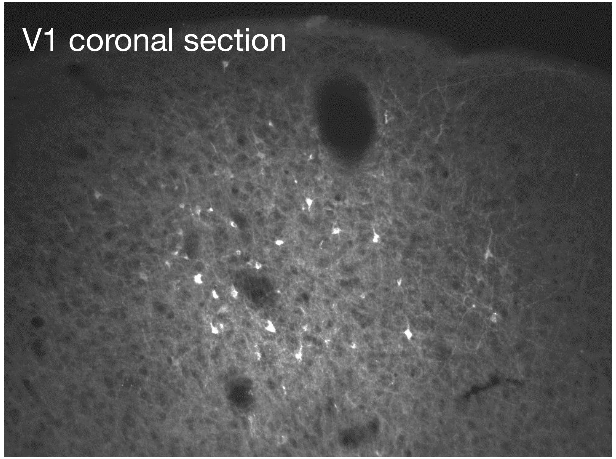
Velocity tuning (Tohmi et al., 2014)



Rabies virus

Optogenetics,
pseudotyping





G-Deleted Rabies-ChR2-mCherry

EnvA Rabies-ChR2-mCherry

EnvA Rabies eGFP-ArchT