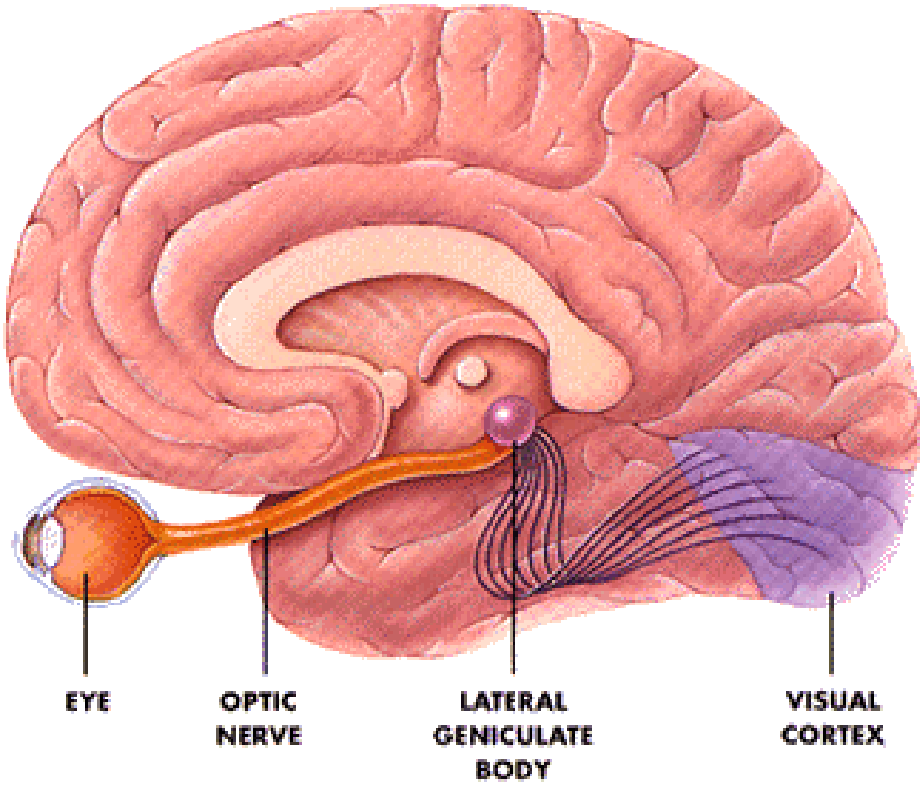
Selective Pruning of More Active Afferents When Cat Visual Cortex is Pharmacologically Inhibited

Yoshio Hata, Tadaharu Tsumoto, and Michael P. Stryker: 1999

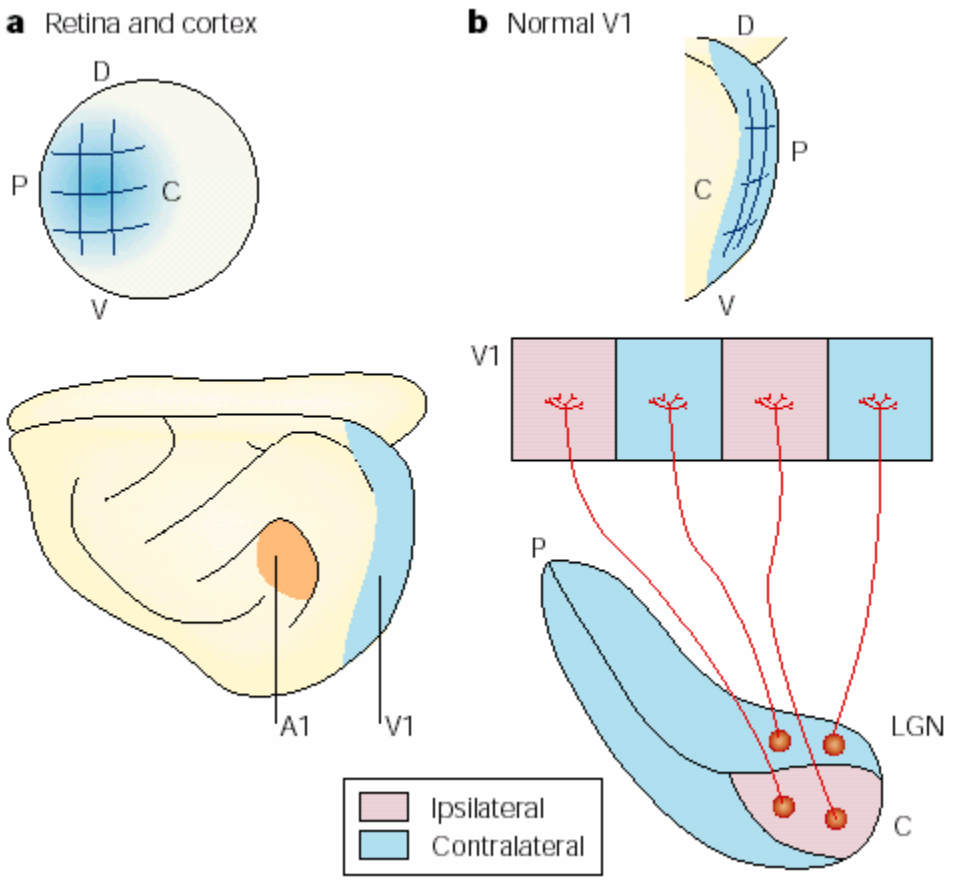
9.013 Presentation

4/26/04

Visual System Overview



Ocular Dominance Columns

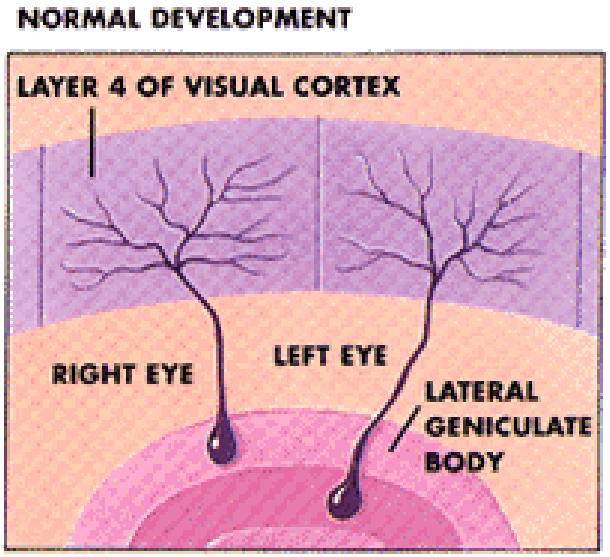


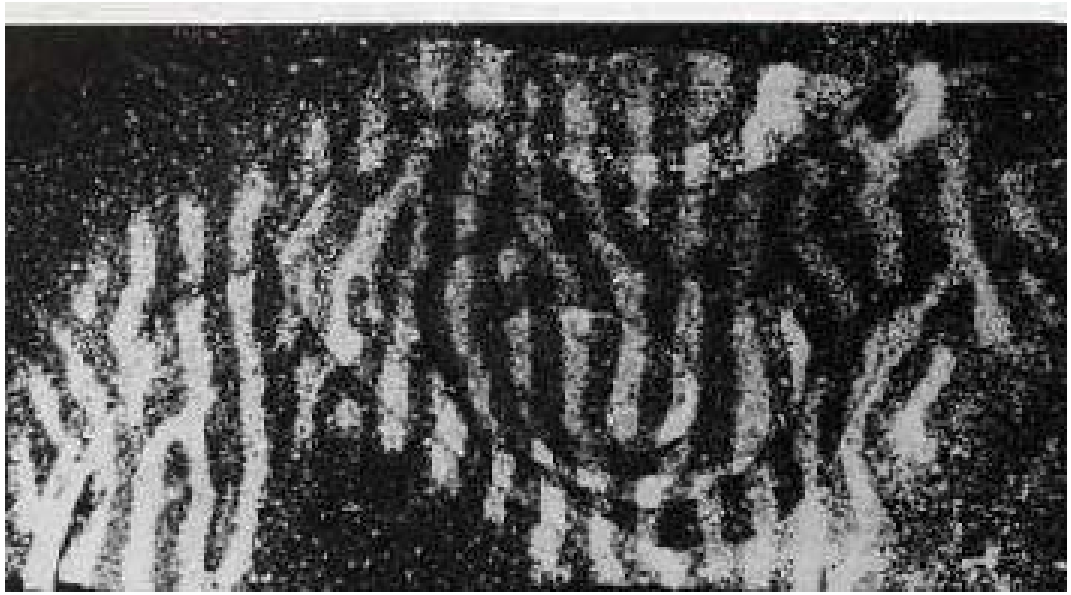
- Neurons in the LGN project to eye-specific regions of the cortex
- These regions alternate in V1 (area 17) to form ocular dominance columns

Sur and Leamey (2001)

Ocular Dominance Columns

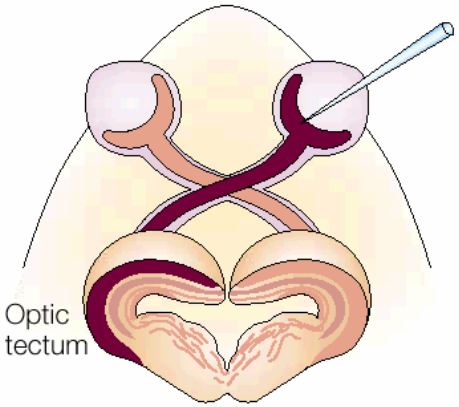
• Ocular dominance columns can be visualized by injecting one eye with [^{3}H]proline (light stripes in picture)

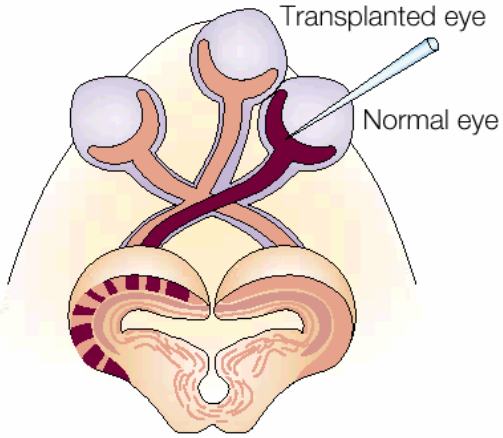


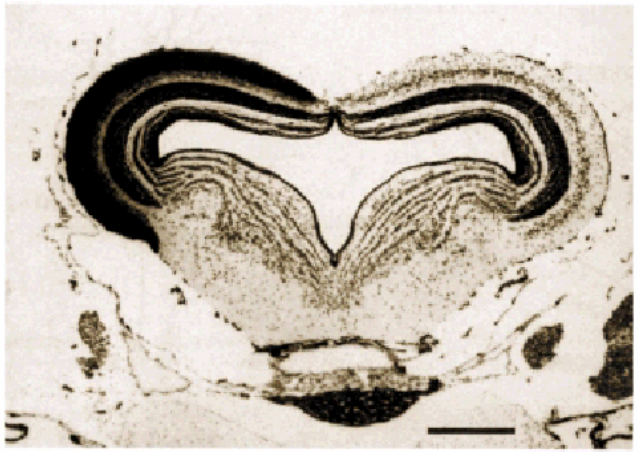


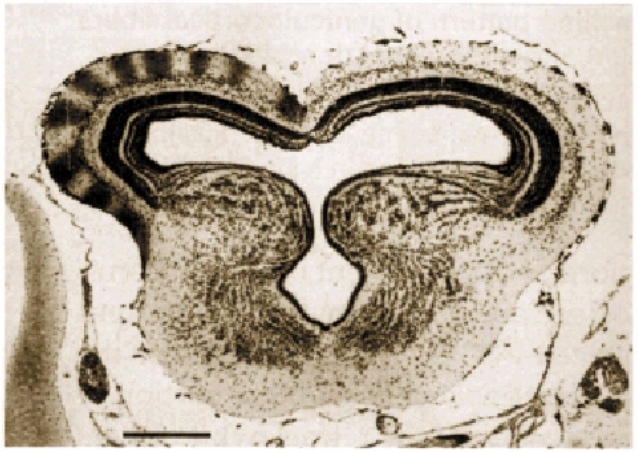
Hubel et al. 1977

Activity Based Segregation









- Normally ganglion cells from each eye in the frog only project contralaterally
- When a third eye is transplanted, there is competition between the two eyes projecting to the tectum and "columns" are formed

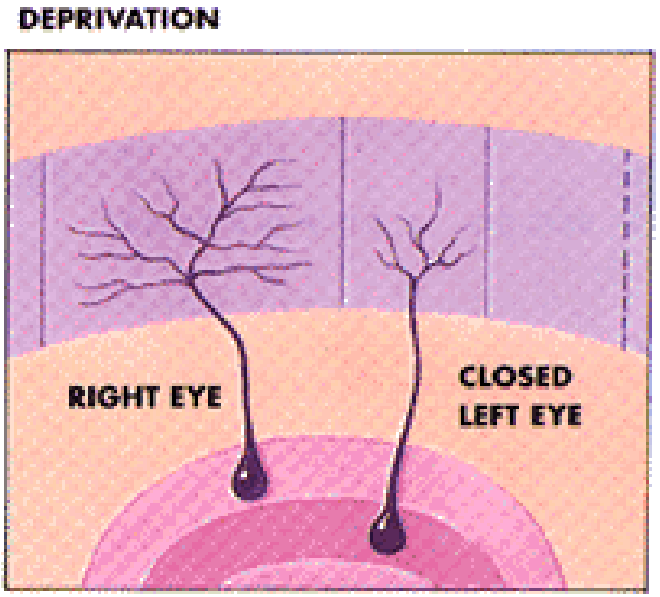
(Constantine-Paton and Law, 1978)

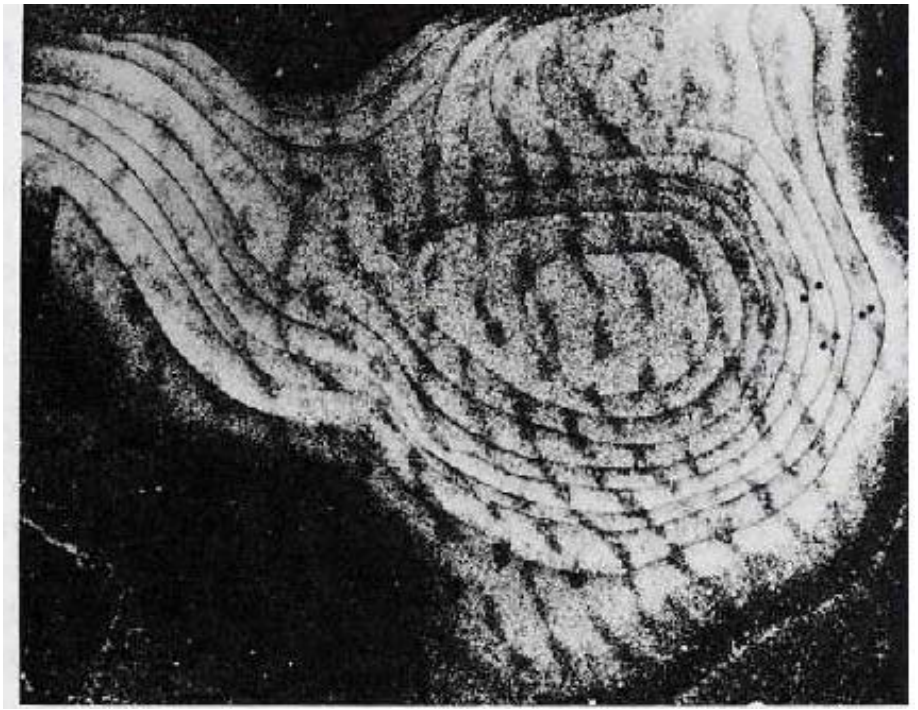
Activity Dependent Competition

- More active inputs become larger and stronger while less active inputs become smaller and weaker
- This theory was tested by monocularly depriving animals during the critical period of development
  - Occlude vision in one eye early in life: neurons in V1 lose electrophysiological responses to the deprived eye (Hubel and Wiesel 1963)

Ocular Dominance Plasticity

- Injection of [^{3}H]proline into the open eye
- Cortical territory for non-deprived eye expands and territory for deprived eye shrinks





LeVay, Wiesel, and Hubel 1980

Normal Axonal Arbors

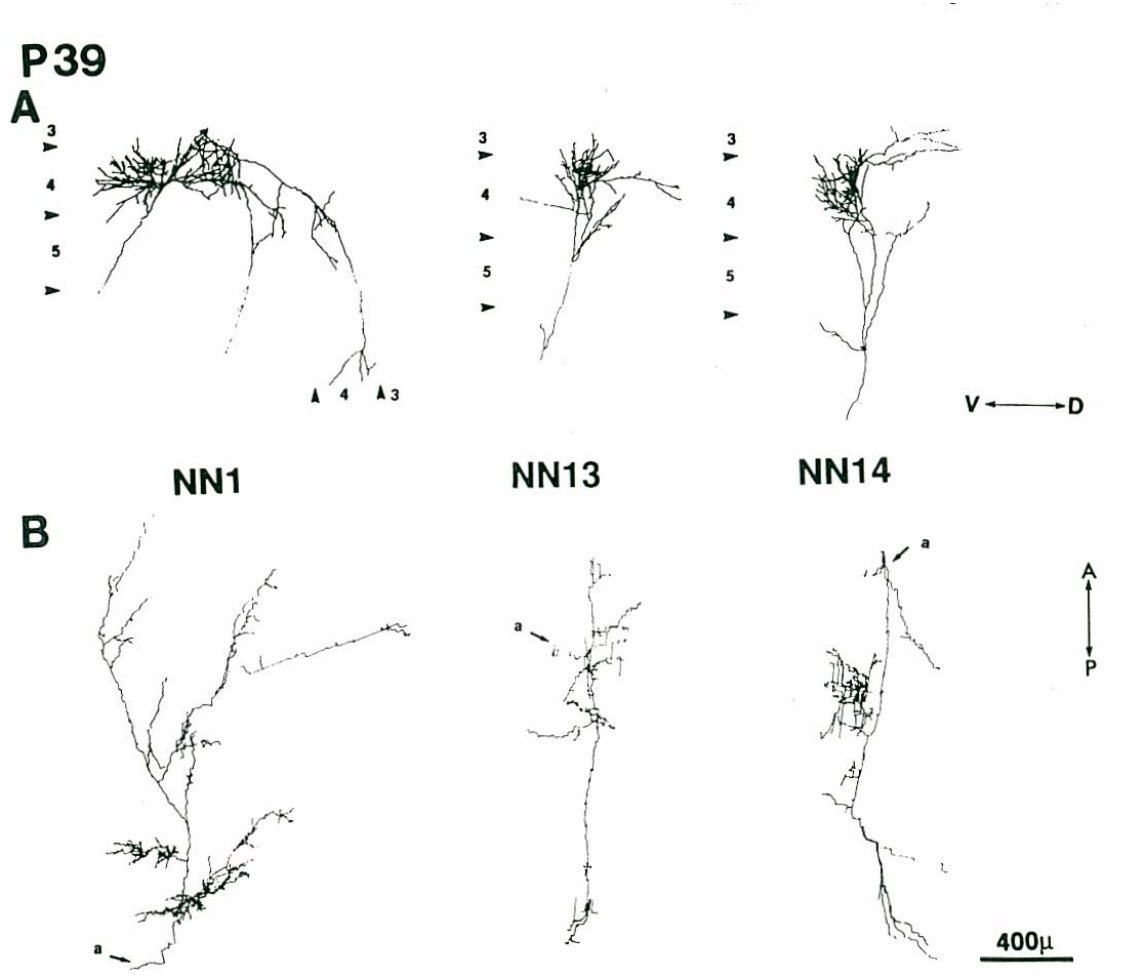


Figure 10. Axonal arbors (*NN1*, *NN13*, and *NN14*) reconstructed from kittens at P39. Axons are shown in coronal view (*A*) and in surface view (*B*). It is from this latter perspective that the terminal arborization in all three axons appears clearly segregated into one or two patches. In *B*, *a* indicates the main axonal trunk. The scale bar applies to both *A* and *B*.

- PHA-L injected into laminae A and A1 of kittens
- Kittens were raised in a normal environment with no visual deprivation

(Antonini and Stryker 1993)

MD Axonal Arbors

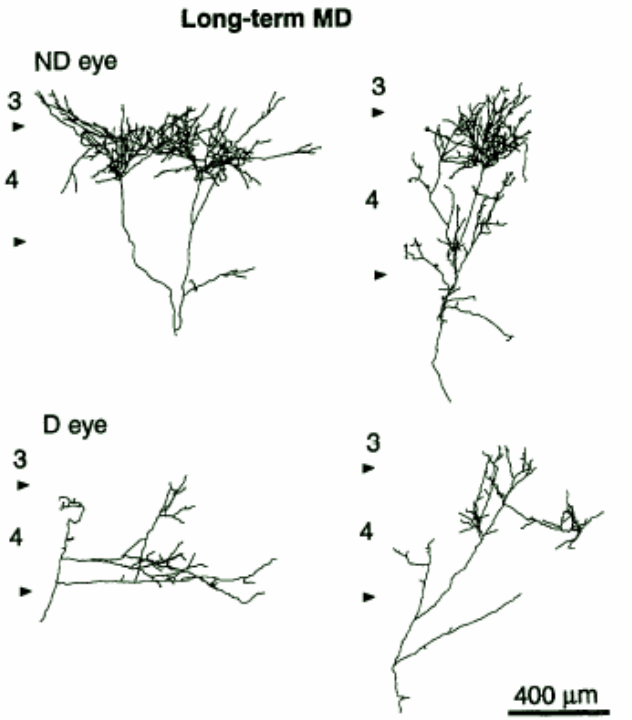


Fig. 1. Coronal view of geniculocortical arbors reconstructed in kittens in which one eye had been occluded for 33 days. The terminal arborization of the deprived (D) eye shows a dramatic reduction in complexity as compared to that of the nondeprived (ND) eye. Cortical layers 3 and 4 are indicated by arrowheads.

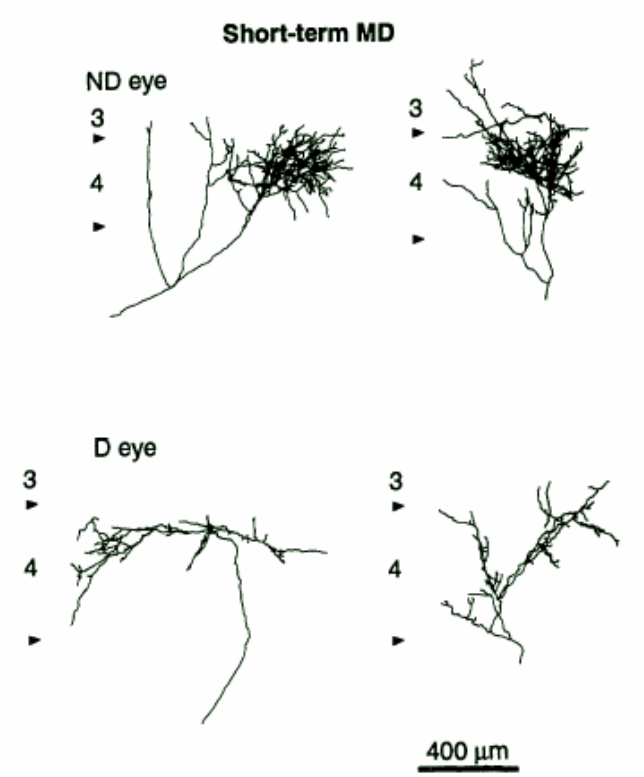
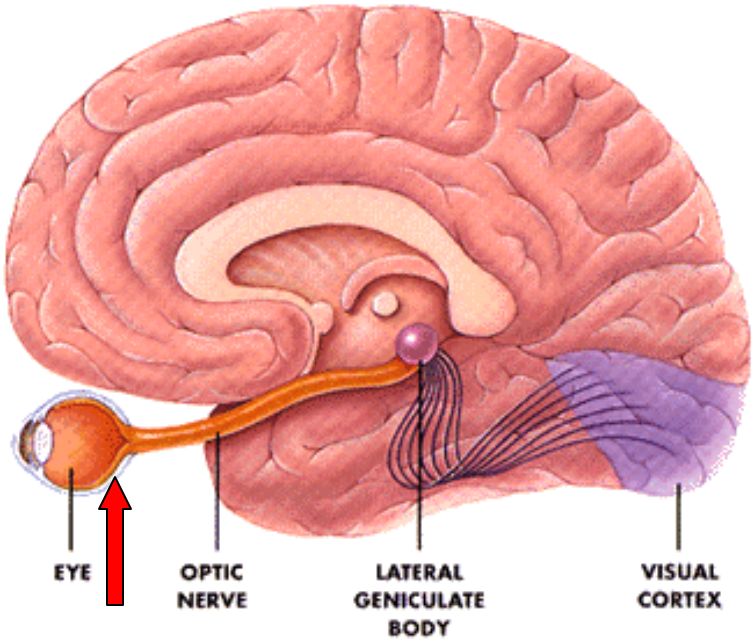


Fig. 2. Coronal view of geniculocortical arbors reconstructed in kittens in which one eye had been occluded for 6 to 7 days. The borders of cortical layers 3 and 4 are indicated by arrowheads.

- Short and long term monocular deprivation in kittens
- Afferents from the deprived eye lose half of their arbors in less than a week

Antonini and Stryker 1993

Pharmacological Experiments

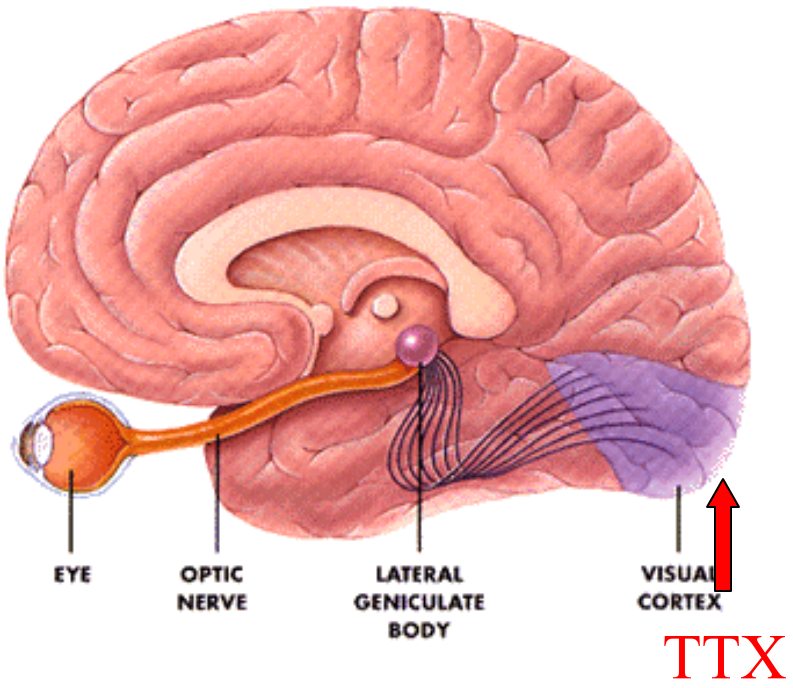


TTX

- Binocular blockade of retinal activity by TTX
- No formation of ocular dominance columns

(Stryker and Harris 1986)

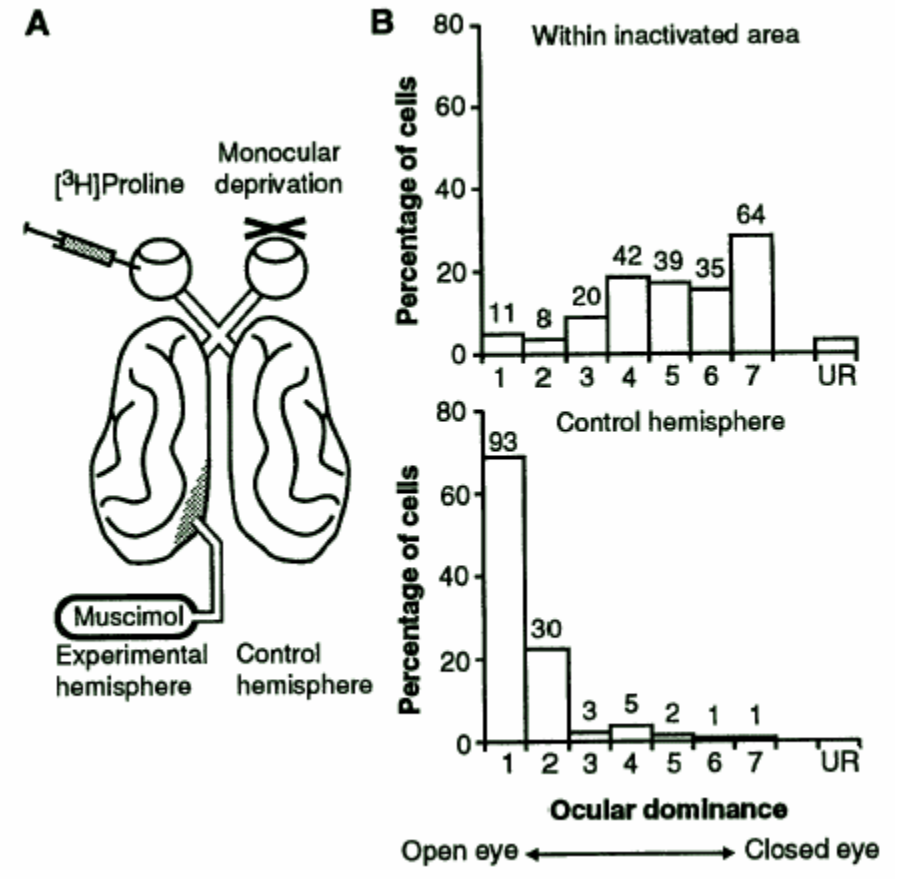
Pharmacological Experiments



- TTX infused into cortex during monocular deprivation
- TTX blocks pre-synaptic and post-synaptic activity in the cortex
- Normal formation of ocular dominance columns

(Reiter, Waitzman, and Stryker 1986)

Pharmacological Experiments



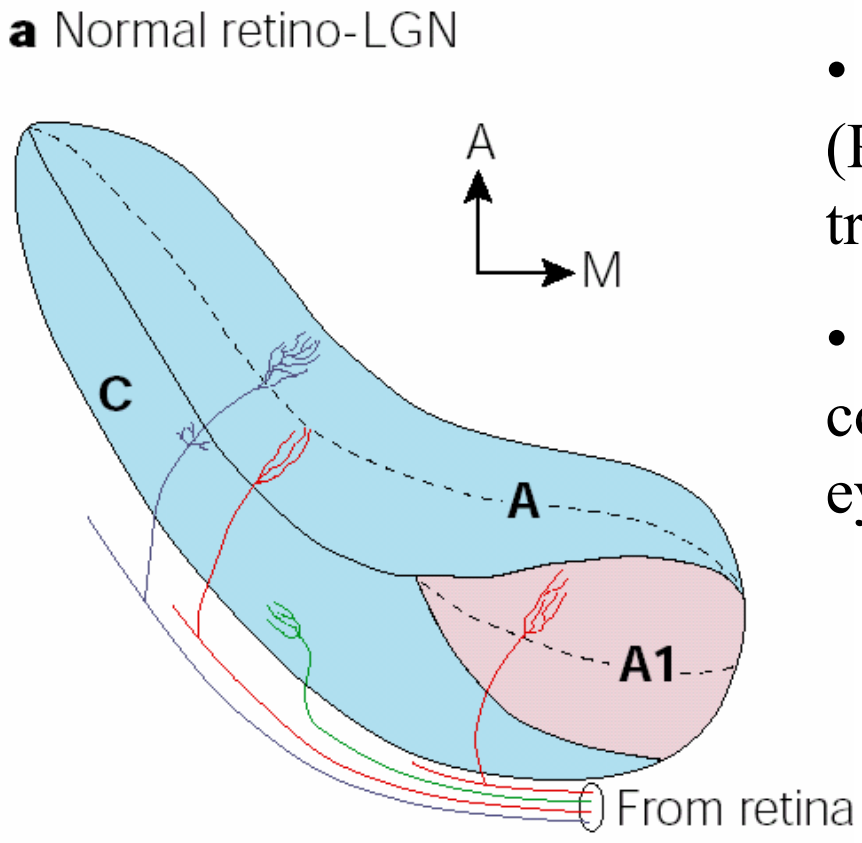
- Muscimol ($GABA_A$ agonist) infused into cortex during monocular deprivation
- Muscimol acts only post-synaptically
- Shift of e. phys. response to deprived eye and territory of non-deprived eye shrank

(Reiter and Stryker 1988)

Previous Conclusions

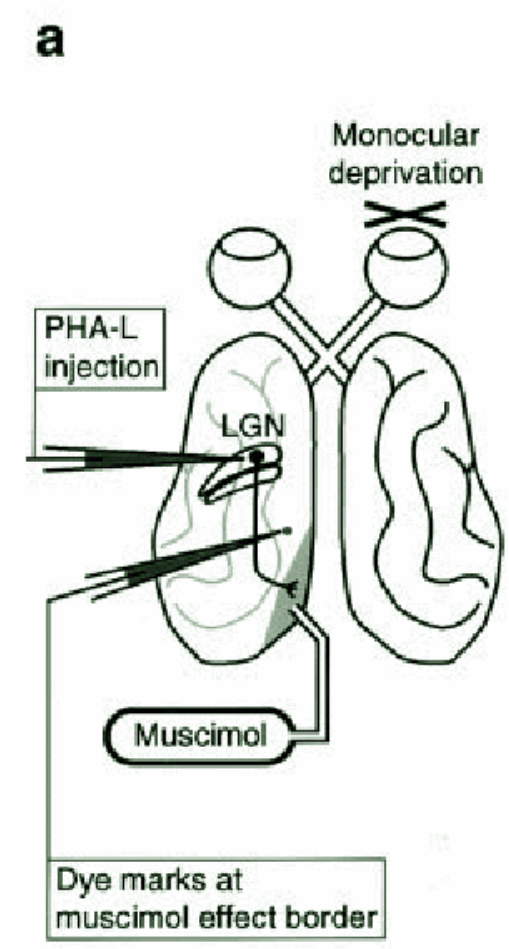
- Correlation between pre- and post-synaptic activity, not level of afferent activity, has a role in ocular dominance plasticity
- Problem: Previous study only measured relative changes
  - Want to measure by an absolute standard: Reconstruction of afferent arbors

Methods



- Microinjection of PHA-L (Phaseolus lectin, anterograde tracer) into lamina A of the LGN
- This labels afferents corresponding to the contralateral eye

Methods

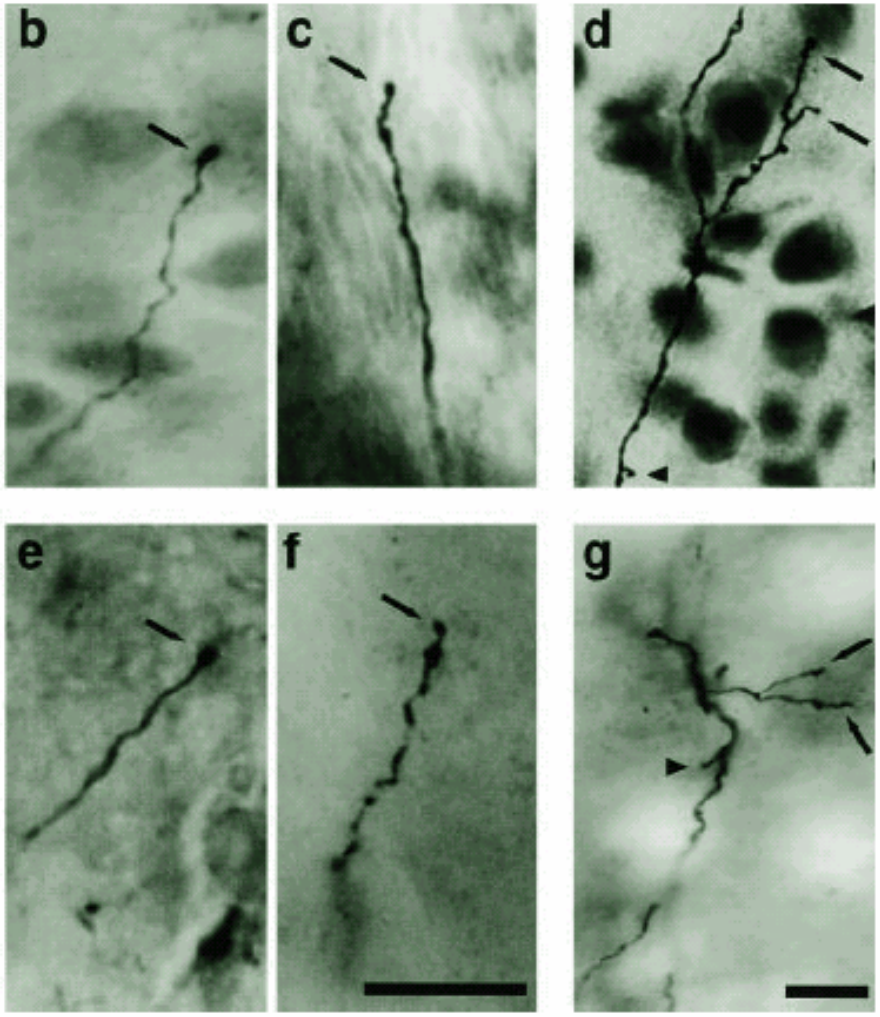


- 4 week old kittens had one eyelid sutured
- Muscimol was continuously infused into the primary visual cortex
- After 2 weeks, the inactivated region was mapped electrophysiologically and the boundaries were marked with dye
- Animals were perfused and the brain was sliced in the frontal plane and immunohistochemistry was performed to visualize the arbors

Methods

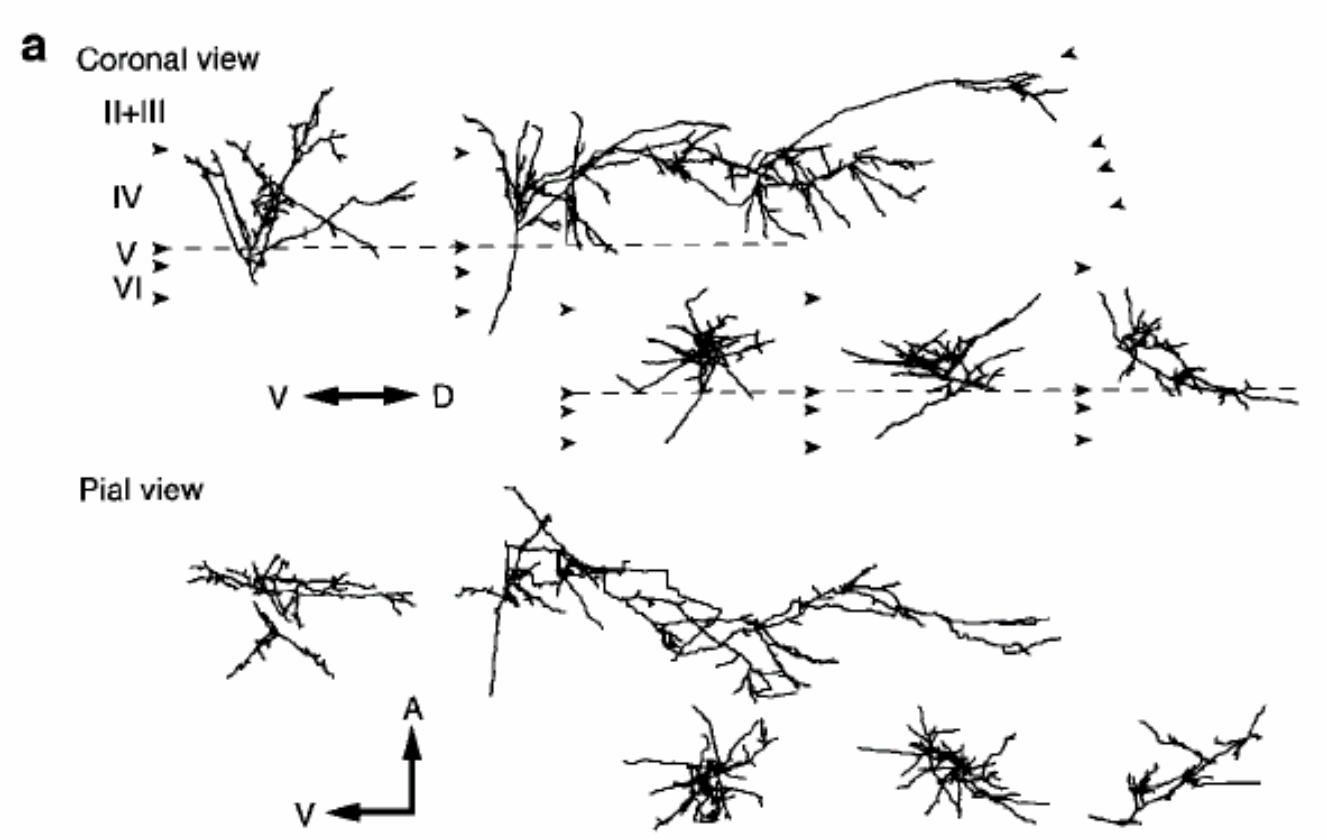
- The arbors were reconstructed from serial sections in 3-D
  - Pial view is the coronal view rotated 90°
- Three measurements for each arbor
  - Total length: Addition of the lengths of all the branches in the terminal field of the arbor (layers III and IV)
  - Number of branch points in layer IV
  - Density of terminal arborization: Determined from pial view, sum of total length of the portions of all branches that lay within the area enclosed by a 100 μm diameter. Done for each 5 x 5 μm square in the arbor territory

Figure 1

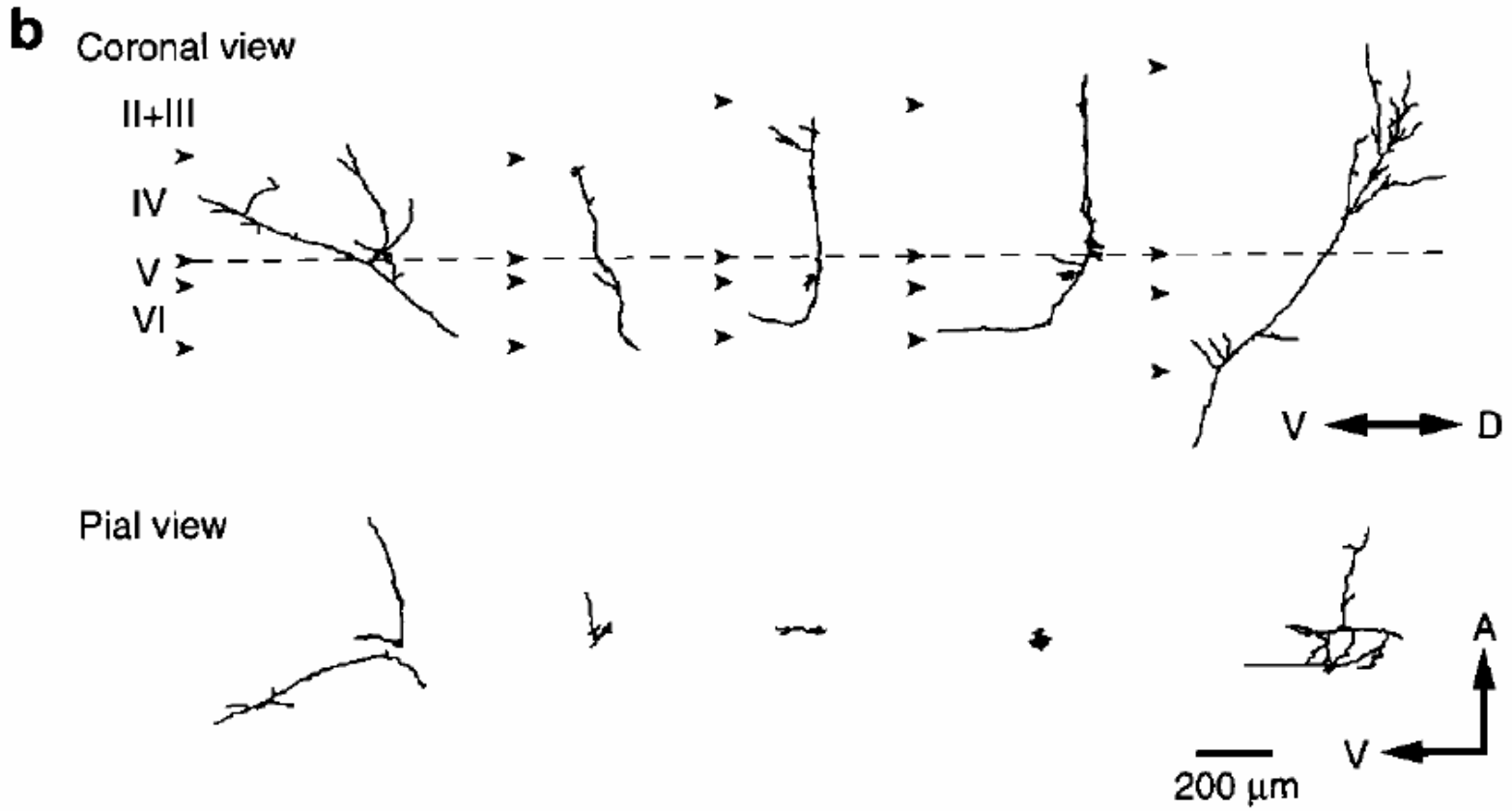


- Terminal swellings (arrows) could be observed
- Small varicosities (arrowheads) could be observed
- The terminal structures were seen equally well in deprived (b-d) and non-deprived (e-g) arbors
- Labeling worked

Deprived Axonal Arbors



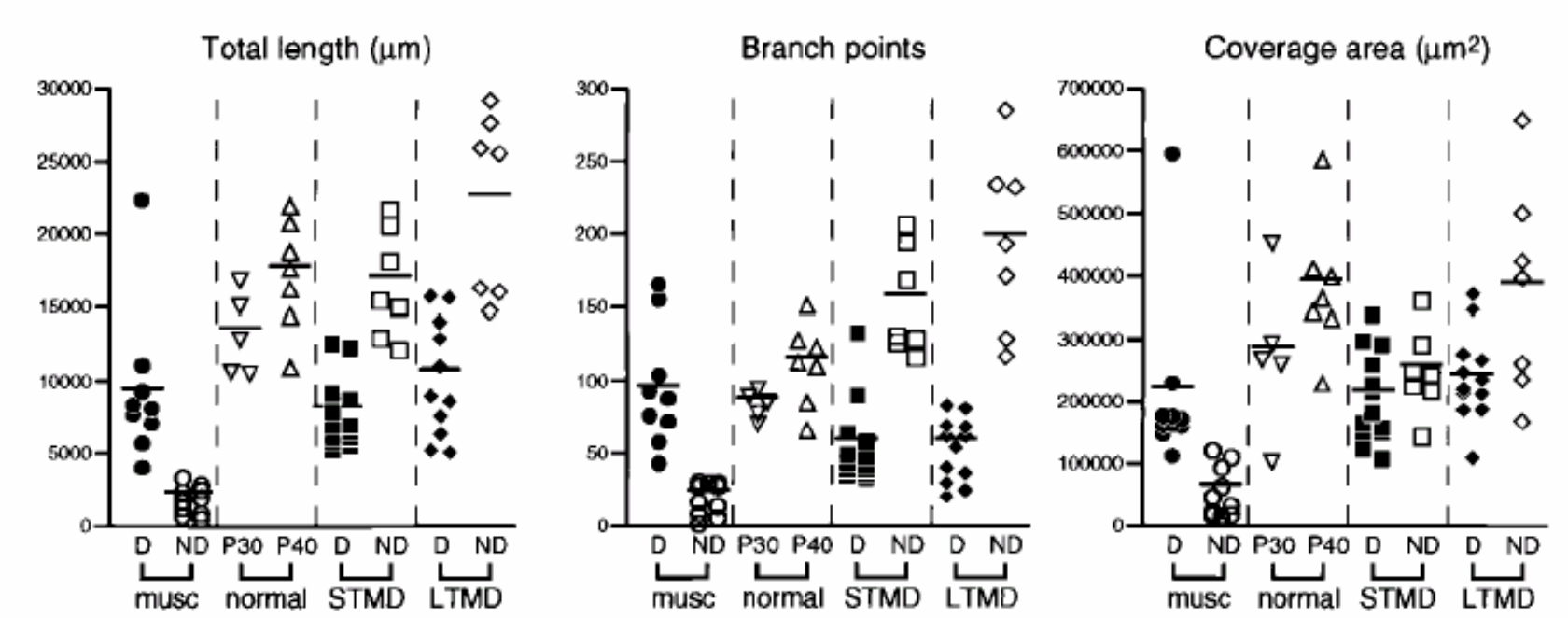
Non-deprived Axonal Arbors



“Reverse” Plasticity

- Less complex terminal arbors in the non-deprived eye
- The average cortical area of each non-deprived axon is much less than for the deprived eye
- The reconstruction allows for comparison with previous experiments without pharmacological intervention

Figure 3



- musc – current experiment
- D – deprived, ND – non-deprived
- normal – normal kittens (Antonini and Stryker 1993)
- STMD – Short term monocular deprivation (6-7 days, Antonini and Stryker 1996)
- LTMD – Long term monocular deprivation (from eye opening, Antonini and Stryker 1996)

Quantitative Comparison

Table 1. Quantitative Analysis of Geniculocortical Arbors

	Arbor Groups						
	musc-ND	P30	P40	STMD-D	STMD-ND	LTMD-D	LTMD-ND
Total length							
musc-D	0.0002 ↑	0.0275 ↓	0.0084 ↓	ns	0.0063 ↓	ns	0.0018 ↓
musc-ND	—	0.0022 ↓	0.0006 ↓	<0.0001 ↓	0.0006 ↓	<0.0001 ↓	0.0006 ↓
Major branch points							
musc-D	0.0002 ↑	ns	ns	0.007 ↑	0.0084 ↓	0.0147 ↑	0.0025 ↓
musc-ND	—	0.0022 ↓	0.0006 ↓	<0.0001 ↓	0.0006 ↓	0.0016 ↓	0.0006 ↓
Coverage area							
musc-D	0.0002 ↑	ns	0.0084 ↓	ns	ns	ns	0.0147 ↓
musc-ND	—	0.0048 ↓	0.0006 ↓	<0.0001 ↓	0.0006 ↓	0.0001 ↓	0.0006 ↓

Statistical comparisons among arbor groups are provided as *p* values (Mann-Whitney U test) (ns, not significant).
Arrows by the p values indicate whether each of the three measures of musc-D and musc-ND groups shown at left were larger (↑) or smaller (↓) than those of the arbor groups shown at the top.

- Arbors for the non-deprived eye were significantly shorter, with fewer branch points, and less coverage area than the deprived eye

Quantitative Comparison

Table 1. Quantitative Analysis of Geniculocortical Arbors

	Arbor Groups						
	musc-ND	P30	P40	STMD-D	STMD-ND	LTMD-D	LTMD-ND
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- Arbors for the non-deprived eye were statistically smaller in all three variables than any other group

Quantitative Comparison

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Arrows by the p values indicate whether each of the three measures of musc-D and musc-ND groups shown at left were larger (↑) or smaller (↓) than those of the arbor groups shown at the top.

- The authors claim that this difference in length is not really statistically different
- WHY?

Quantitative Comparison

Table 1. Quantitative Analysis of Geniculocortical Arbors

	Arbor Groups						
	musc-ND	P30	P40	STMD-D	STMD-ND	LTMD-D	LTMD-ND
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- Infusion of muscimol causes an overall shrinkage of the cortex, so when the values are adjusted for the size of the cortex they are no longer significant

Conclusions

- Muscimol is believed to only act on post-synaptic cells
  - Only afferents from one eye were affected
  - If it acted pre-synaptically, the cortex should have appeared as when treated with TTX

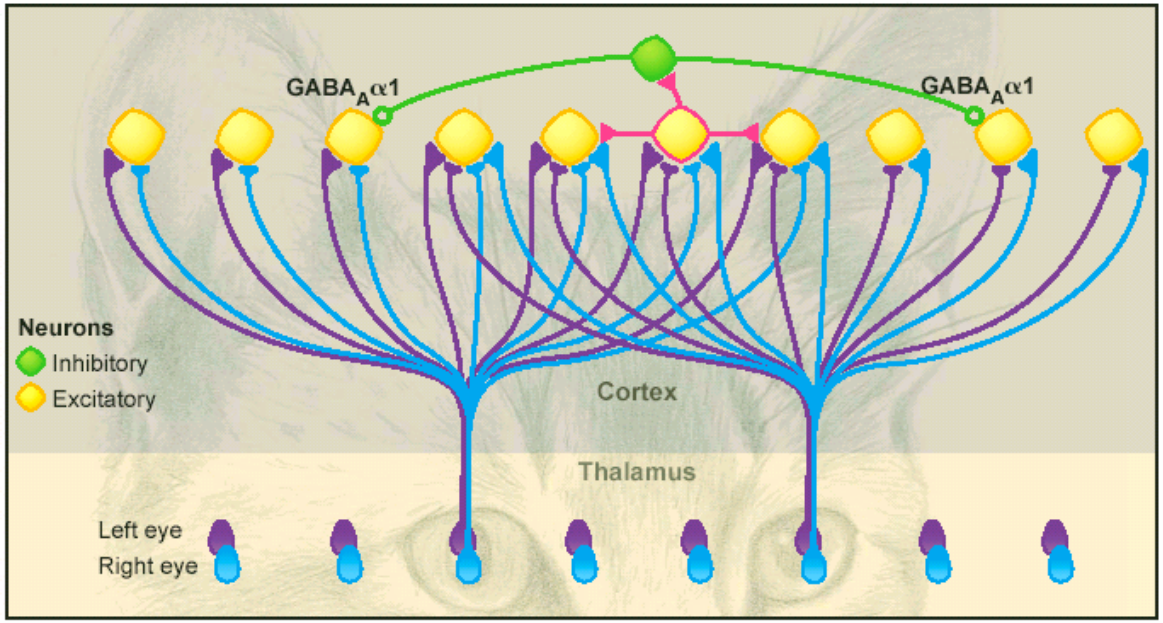
Conclusions

- These findings suggest that suppression of cortical activity causes a retraction of geniculocortical afferents, depending on their activity
- Signaling for activity-dependent plasticity can be bi-directional

Conclusions

- Neurotrophic hypothesis
  - Afferents for closed eye have a lower requirement for trophic support than the open eye
- “Activity Threshold” hypothesis
  - Pre-synaptic afferents need to have a certain level of activity to respond to a signal for retraction
- Third hypothesis
  - The signal for retraction is only delivered to active afferents resulting from synaptic interaction with cortical target neurons

Lateral Inhibition Model for Column Formation and the Role of GABA



Hebb rules in the visual cortex. Model of neuronal connections in the developing kitten visual cortex (*9*). At birth, thalamic neurons from the two eyes project their afferent axons (blue, purple) to completely overlapping regions of the visual cortex. Activity in thalamic neurons driven by the same eye is correlated; activity in neurons driven by opposite eyes is not correlated. Short-range excitatory connections within the visual cortex (pink triangular synapses) increase correlation in activity among neighboring cortical neurons (yellow). Long-range inhibitory connections (small green circular synapses) with GABAergic interneurons (green) decrease correlations among cortical neurons that are farther apart from one another. The scale of these inhibitory connections is critical for determining the width of fully developed ocular dominance columns.

Miller, Keller, and Stryker 1989

- Model for column formation
- Cells near each other have correlated activity through excitatory connections (pink)
- Cells far away from each other are less correlated due to long range inhibitory connections (green)

Recent GABA Studies

- Infusion of diazepam (GABA agonist) broadened the width of cortical columns
- Infusion of DMCM (diazepine inverse agonist) narrowed the width of cortical columns (Hensch and Stryker 2004)
- Mouse knock-in models demonstrated that the α1 subunit of the GABA receptor drives cortical plasticity (Fagiolini et al. 2004)