

# Local GABA Circuit Control of Experience-Dependent Plasticity in Developing Visual Cortex

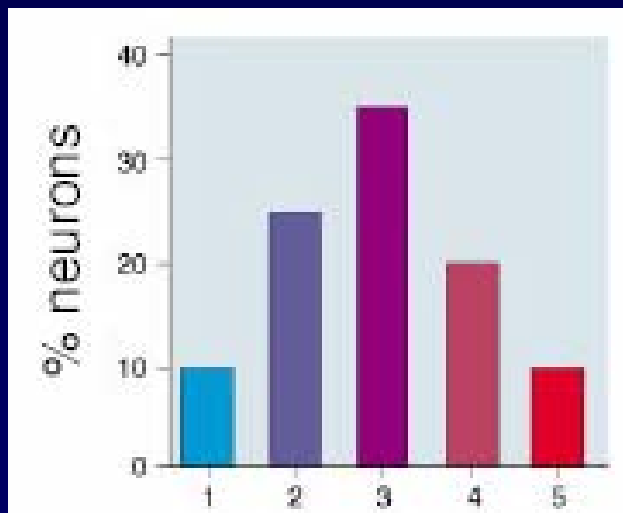
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Presented by Lena Khibnik

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# Hubel & Wiesel: Ocular Dominance Plasticity in Kittens

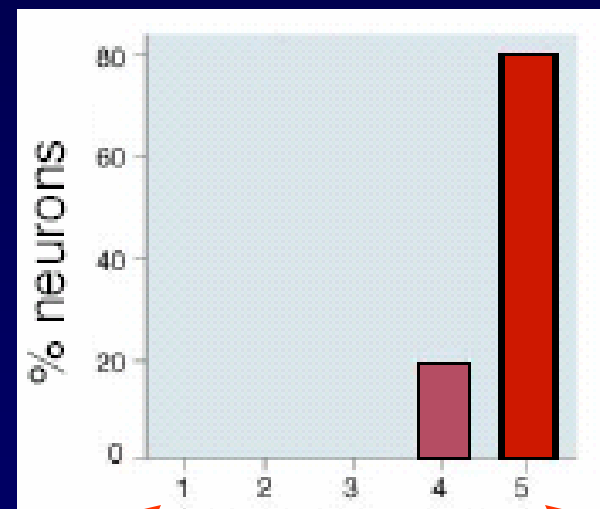
- Cells in V1 area of visual cortex respond to input from contralateral eye, ipsilateral eye or both
- Monocular deprivation (during critical period) shifts the response distribution towards the open eye



**Contra**

**Ipsi**

Monocular  
Deprivation



**Closed eye**

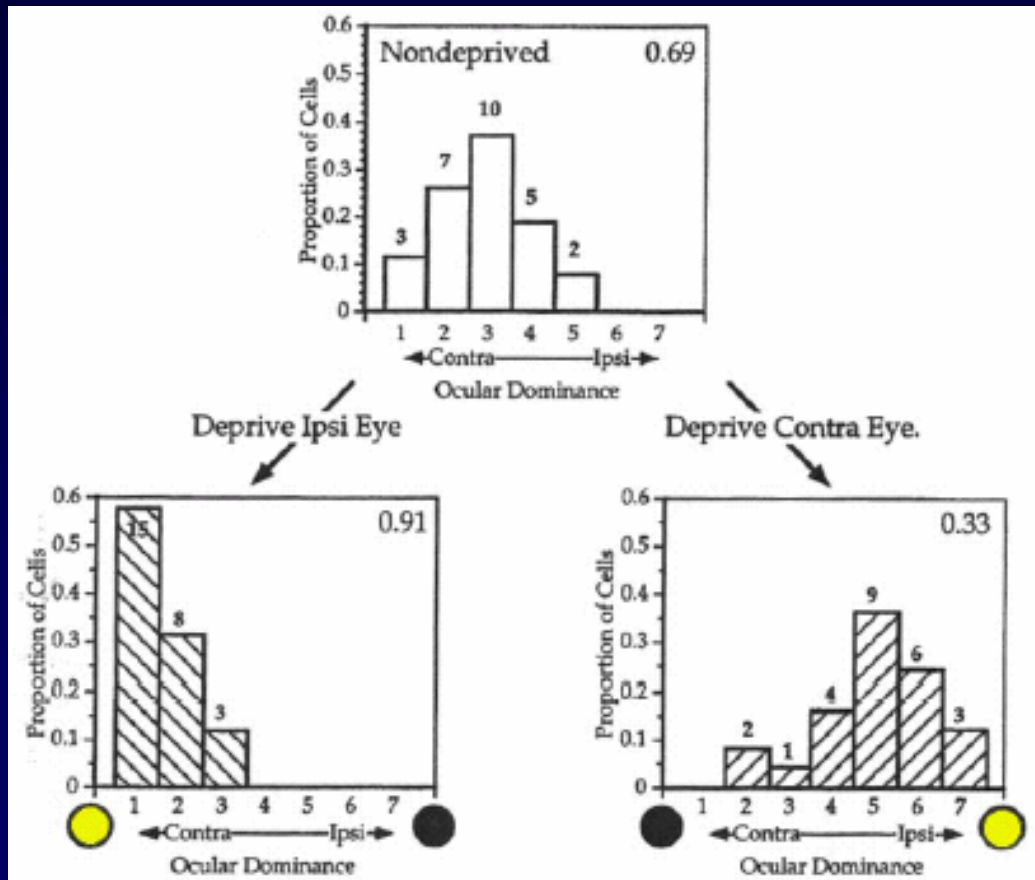
**Open eye**

# OD Plasticity Revealed in Mice

There's intrinsic contralateral bias due to a greater number of projections from contra eye

Quantification is Contralateral Bias Index (CBI):

$$\frac{\text{Contra Response}}{\text{Ipsi Response}}$$



## Why study OD plasticity?

- Provides a model system for studying how sensory experience shapes the brain

## Why is mouse a great model to study OD plasticity?

- Can perform a variety of manipulations in the same animal (in vivo measurements, slice recordings, biochemistry, etc.)
- Can perform genetic manipulations
- Mouse has a relatively undifferentiated visual system, which is an advantage in studying general principles of organization/plasticity

# What are the mechanisms governing OD plasticity?

Several mechanisms have been proposed to account for the ocular dominance shift...

- Long-term depression (LTD)/Long-term potentiation (LTP)
- Intracortical inhibition

## Strategy of paper:


Genetically alter inhibition to manipulate ocular dominance plasticity in vivo and then check for LTD/LTP inducing mechanisms in vitro

# Genetic Manipulations

Two isoforms of GABA-synthesizing enzyme, GAD, exist:

1. GAD67 - soma and dendrites

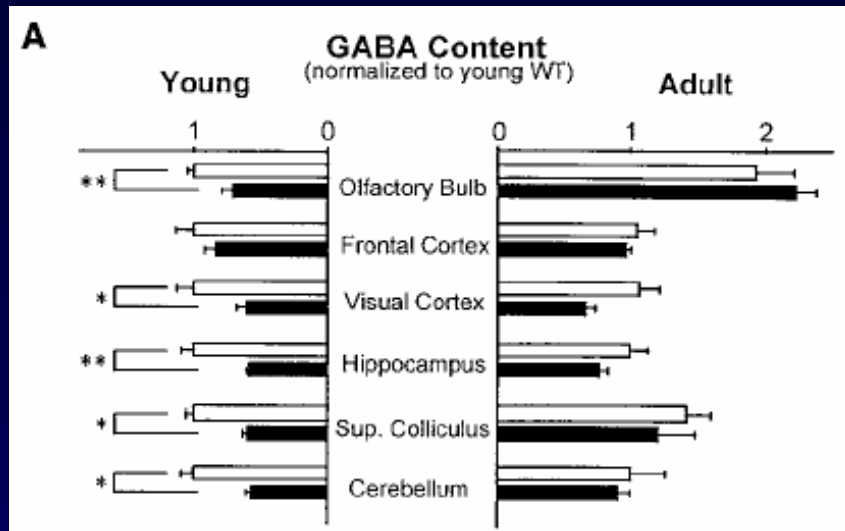
- constitutive synthesis of GABA
- essential for survival

2.  GAD65 - synaptic terminal

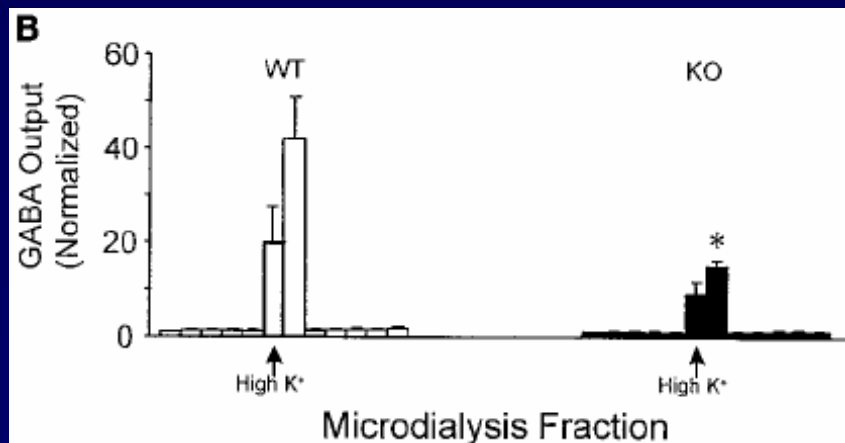
- readily recruitable inactive reservoir
- not essential for survival (probably responsible for fast inhibition)

# Fig. 1 GAD65 KO: Consequences

## Functional Consequences:



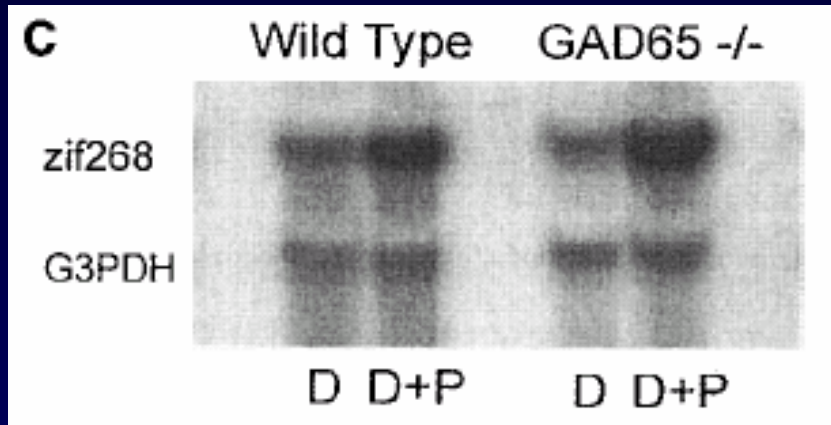
GAD65 contributes significantly to GABA conc. during early postnatal development



Stimulated GABA release is compromised by loss of GAD65

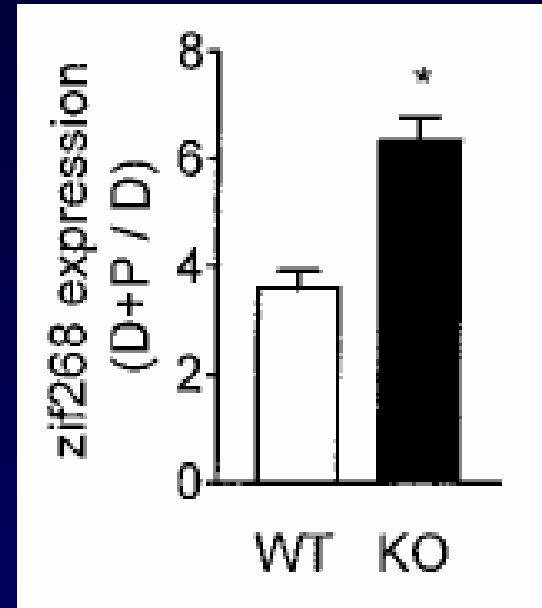
# Fig. 1 GAD65 KO: Consequences (cont.)

## Physiological Consequences:



D = dark rearing; D+P = dark rearing+photostimulation

GAD65 KO exhibits heightened sensitivity to visual stimulation after dark rearing

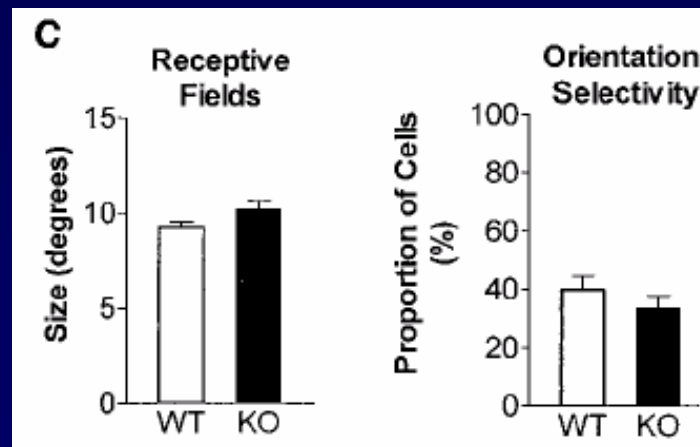
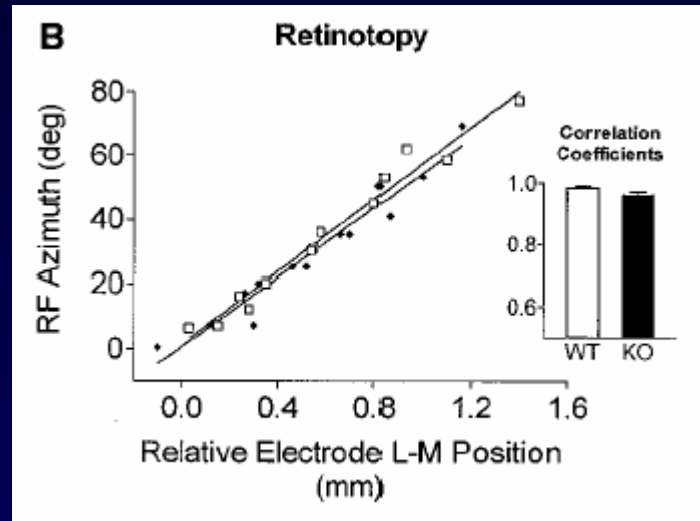
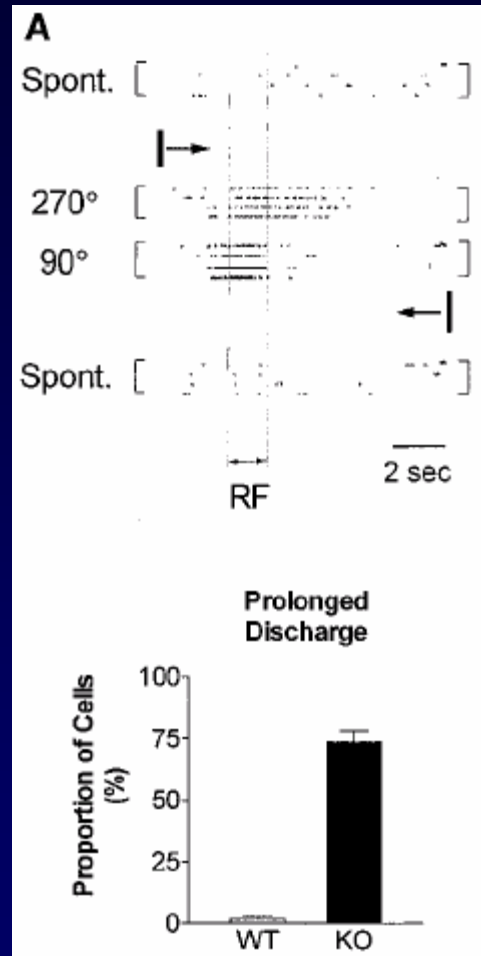


zif268 = endogenous marker of neuronal activity

G3PDH = housekeeping gene

# Are Receptive Field Properties Normal in GAD65 KO?

Fig. 2



Retinotopy is normal

RF size is normal

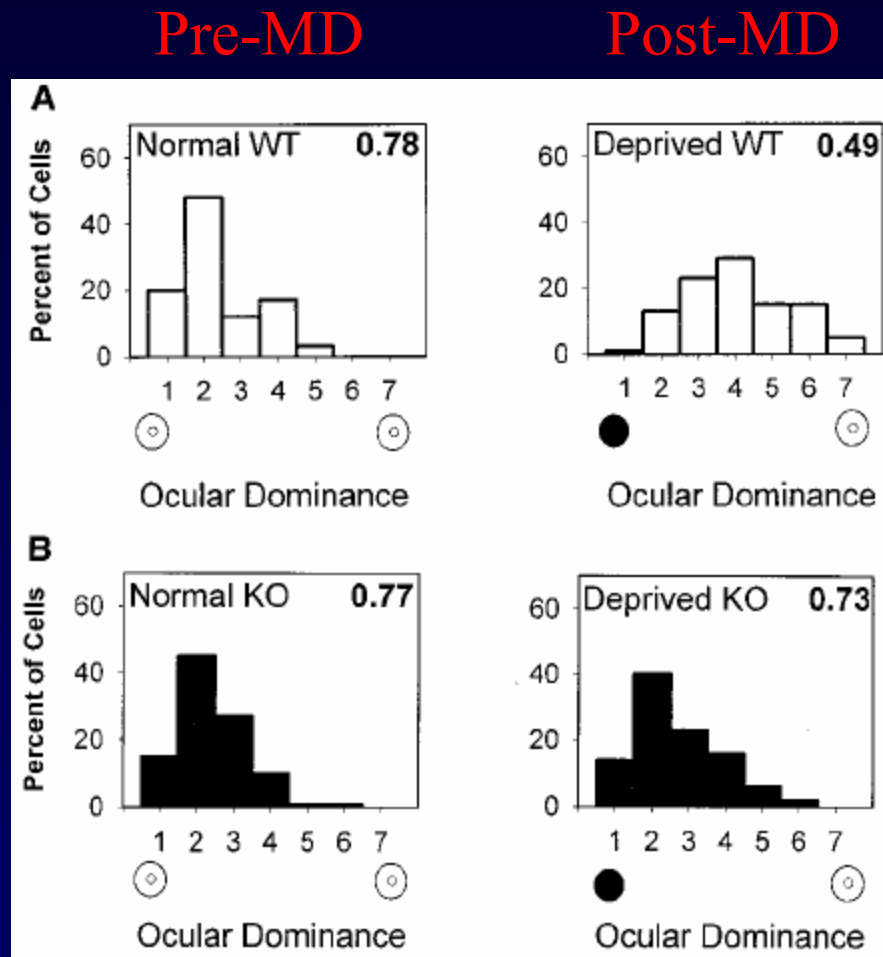
RF orientation selectivity is normal

Single-unit recordings exhibit prolonged response as stimulus exits RF

????

# OD Shift is Blocked in GAD65 KO

Fig. 3



WT cells shift responsiveness in favor of open eye

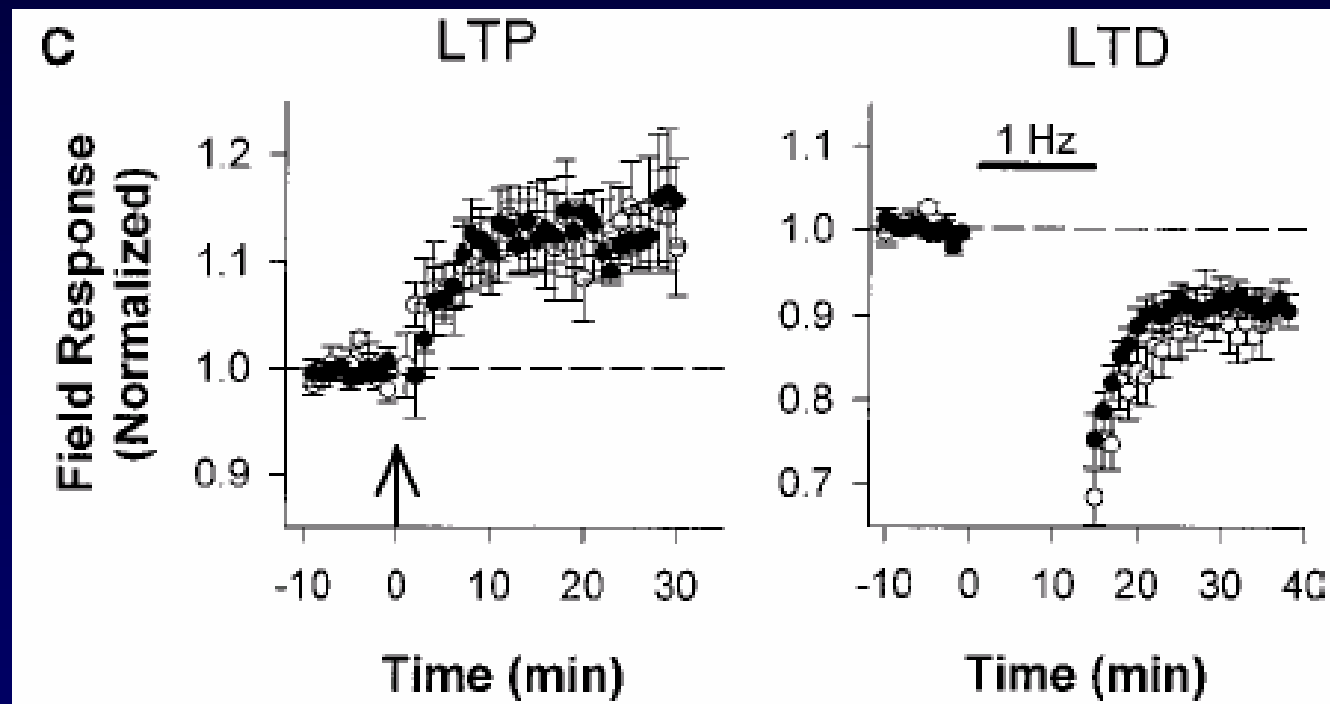
GAD65 KO mice showed no change in eye preference

Distribution of ocular dominance in binocular zone of KO is unaltered

# Is Activity-Dependent Plasticity Normal?

Assayed LTD and LTP in layer 2/3 in coronal slices of visual cortex using theta-burst and low-frequency stimulation respectively

Fig. 3

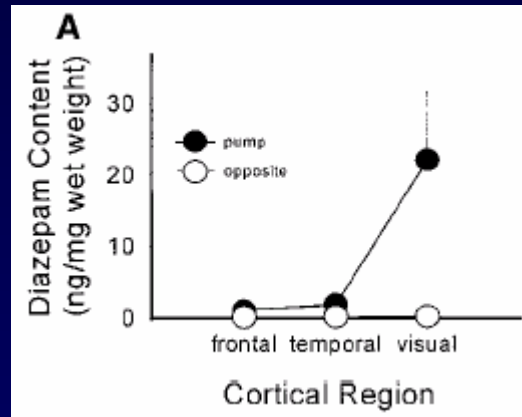


Both WT and KO exhibited **normal potentiation and depression** (therefore, LTP/LTD *might not* be mechanisms that explain sensory disruption in intact GAD65 KO mice)

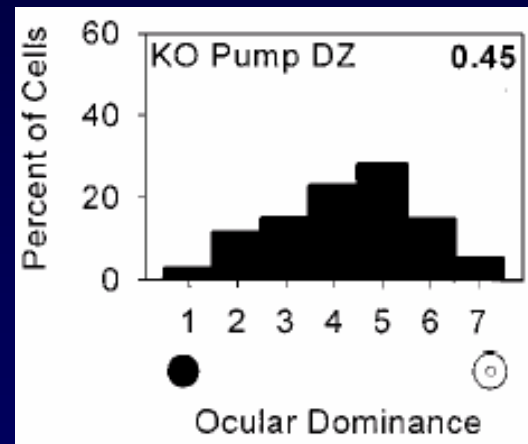
# Fig. 4 Can OD Plasticity Defect Be Rescued?

Postsynaptic impact of reduced GABA release can be compensated with benzodiazepine agonists

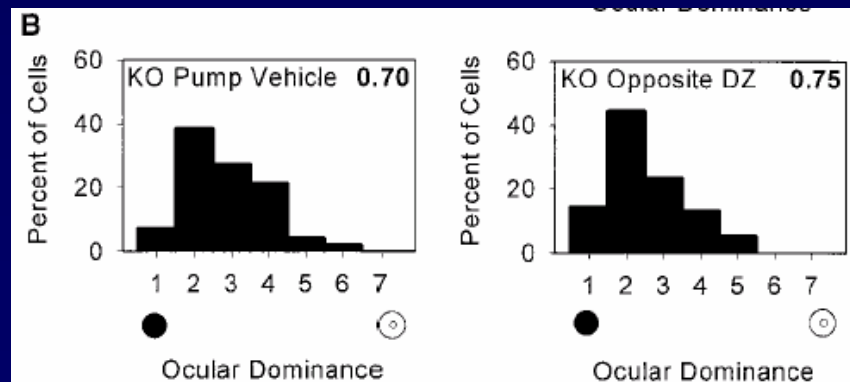
Infuse diazepam locally into one hemisphere of mutant mice during MD



Diazepam is localized specifically to visual cortex



Complete OD shift in infused mutant visual cortex



No rescue of plasticity with vehicle into same hemisphere or diazepam into opposite hemisphere

\*\* Global diazepam treatment (intraventricular injection) also restores plasticity

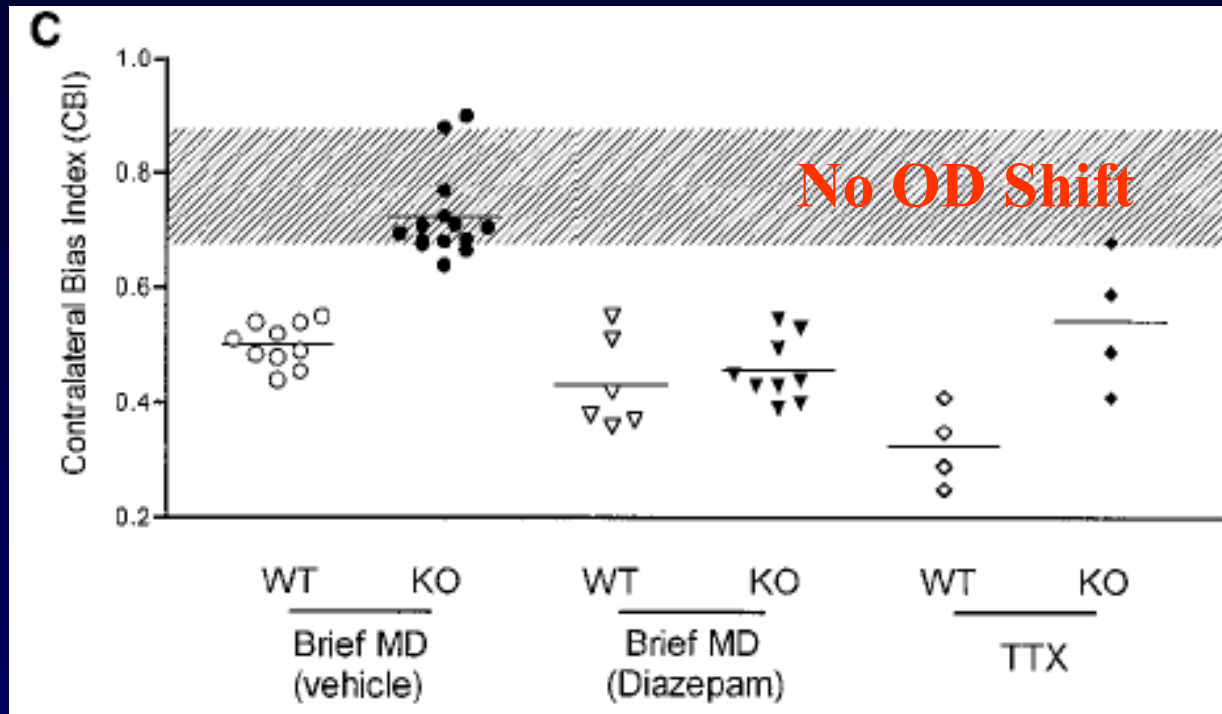
# Their model so far...

- There are competing inputs between two eyes
- This competition is mediated by GABA<sub>A</sub> circuitry which is both necessary and sufficient to detect imbalance of activity between the two competing eyes

➡ Intracortical inhibition determines the threshold for detecting competition

- If so, maximizing the contrast between excitatory activity of two eyes in GAD65 KO should reveal limited plasticity
- Maximization of contrast in activity can be achieved by completely silencing retinal activity of one eye with TTX

## Fig. 4 Maximized competition reveals...



Histogram?

Control for  
TTX group?

Is retina  
intact?

TTX produces a  
significantly  
stronger OD shift  
in WT mice

Only some GAD65 KO mice  
show detectable changes, weaker  
than WT shift and more variable  
than diazepam group

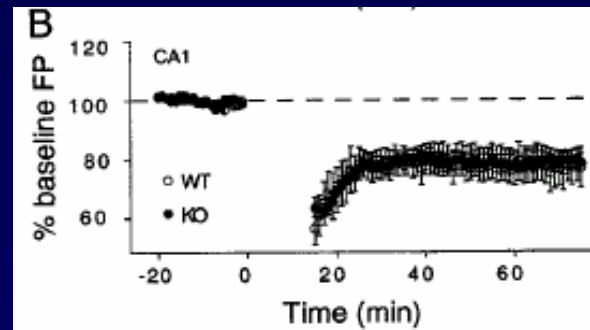
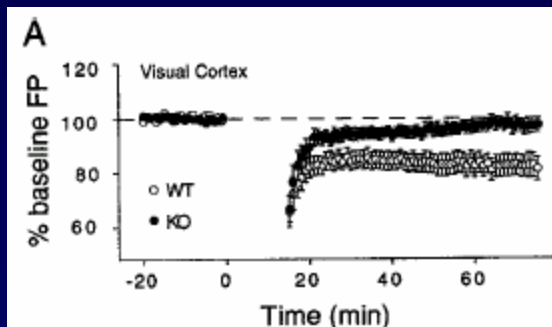
# Conclusions

- OD plasticity occurs as a result of competition between inputs from two eyes
- This competition is mediated by fast inhibitory transmission, which is both necessary and sufficient to detect imbalance between the two competing inputs
- GAD65 KO mice lack *in vivo* plasticity, while still maintaining *in vitro* plasticity, as shown by normal induction of LTP/LTD, suggesting that LTP/LTD are not the mechanisms that account for *in vivo* plasticity
- *In vivo* plasticity can be restored by use-dependent potentiation of GABA<sub>A</sub> responses via treatment with diazepam, a GABA<sub>A</sub> receptor agonist
- Maximizing the disparity between two inputs through retinal silencing with TTX reveals limited plasticity in GAD65 KO mice

# Some counterarguments...

Other theories exist about mechanisms governing OD plasticity...

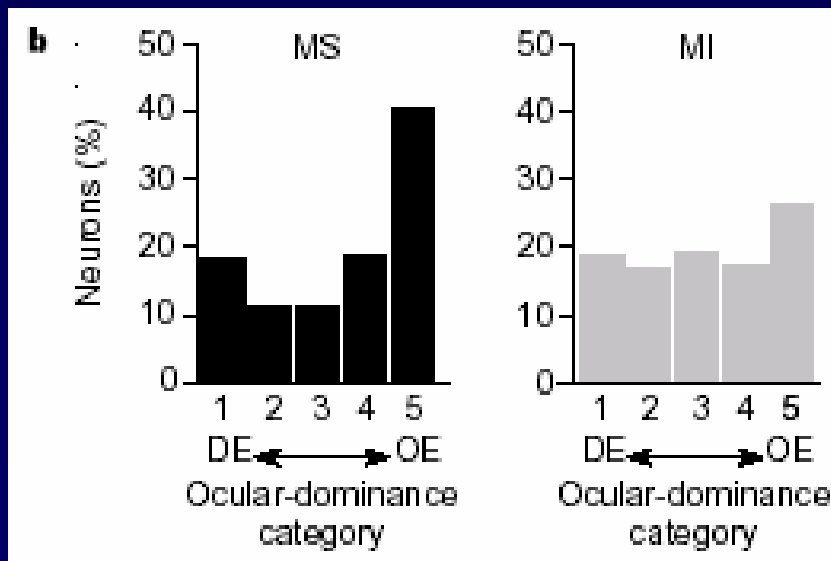
- One of the assumptions is that LTD is the underlying basis for depression of the contralateral response manifested in OD shift
- Choi et al, 2002: LTD is impaired in visual cortex of GAD65 KO mice (\*in mice after P30, 1Hz LFS no longer induces much LTD, so the smaller magnitude of LTD in WT would not reveal deficit in LTD)



- Also found that efficacy of GABAergic synapses during repetitive activation is reduced in KO and chronic but not acute treatment with diazepam restores LTD, suggesting that the inhibitory tone plays an important role in the regulation of synaptic plasticity in visual cortex

# Some counterarguments... (cont.)

- Another prediction of the counter-theories is that uncorrelated firing and not complete lack of firing of the deprived input causes its depression during MD
- According to this prediction, residual activity in the visually deprived retina should yield greater synaptic depression than complete elimination of activity during TTX treatment
- Rittenhouse et al, 1999: confirmed this in kitten visual cortex



MS = monocular suture

MI = monocular inactivation by TTX

DE = deprived eye

OE = open eye

# Implications and Future Directions

- Hensch et al., 1999 revealed an important role of inhibitory transmission in regulating experience-dependent plasticity
- Whether LTD induction mechanism is fundamentally altered in GAD65 KO or LTD is really not the basis for *in vivo* plasticity remains to be investigated
- Drastic disparity in TTX data from various investigators remains a mystery... Any suggestions???
- How is spatiotemporal organization of the inhibitory circuit influences the balance between excitation and inhibition?
- Are specific types of interneurons involved? What are they?
- How does maturation of this circuit take place?

