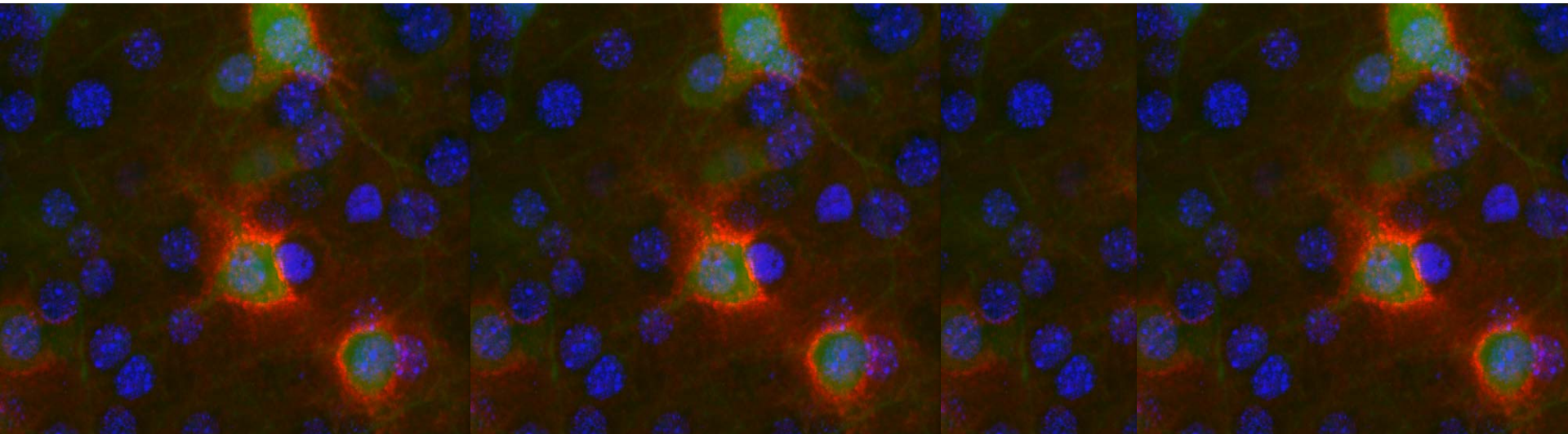


Shaping neural circuits by experience: Uncovering aberrant plasticity in mouse models of Rett Syndrome

Dr. Keerthi Krishnan
Cold Spring Harbor Laboratory



MeCP2 mutations cause Rett Syndrome

Methyl-CpG-binding

- Binds to DNA

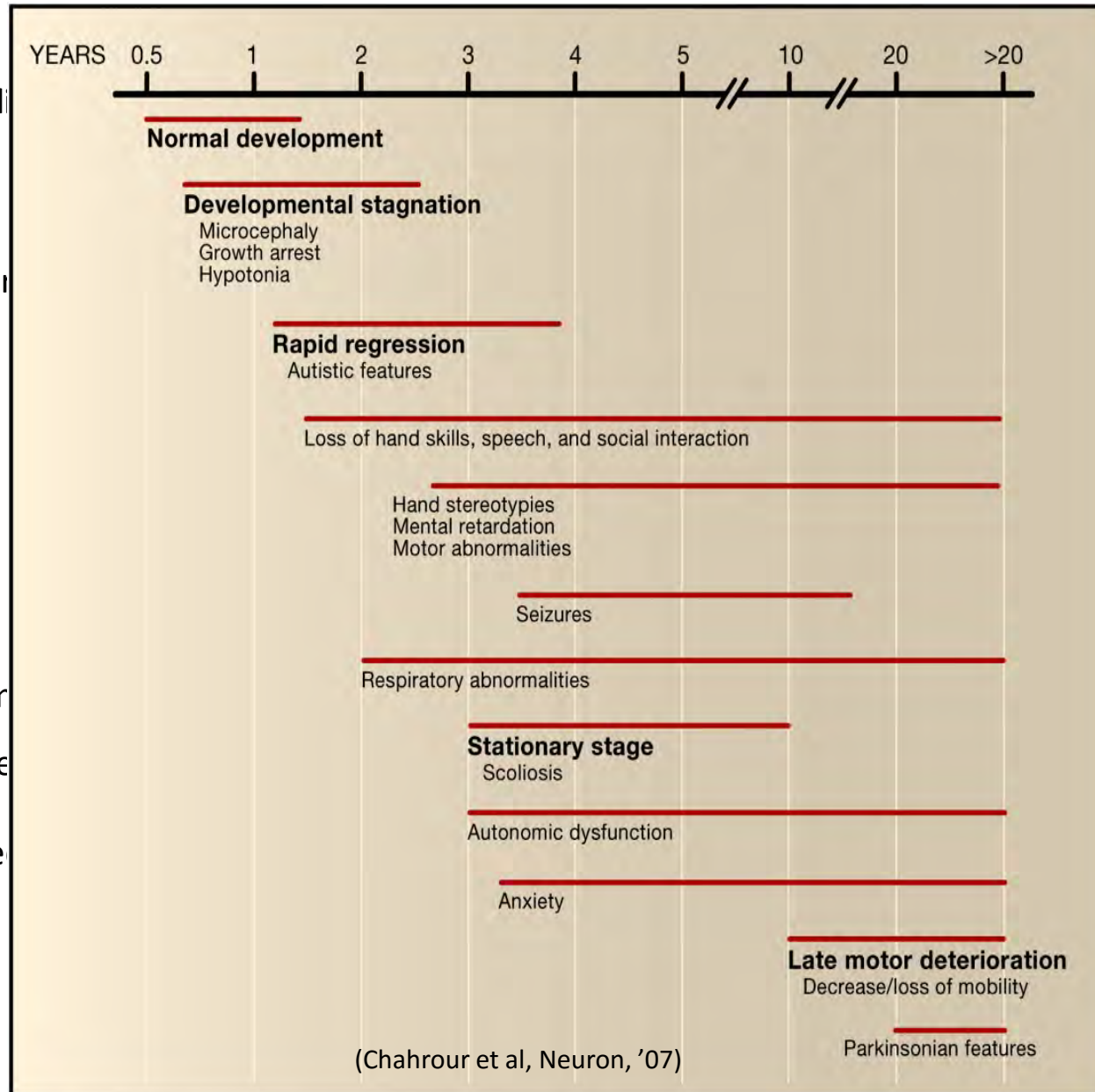
- chromatin and transcription

Rett Syndrome

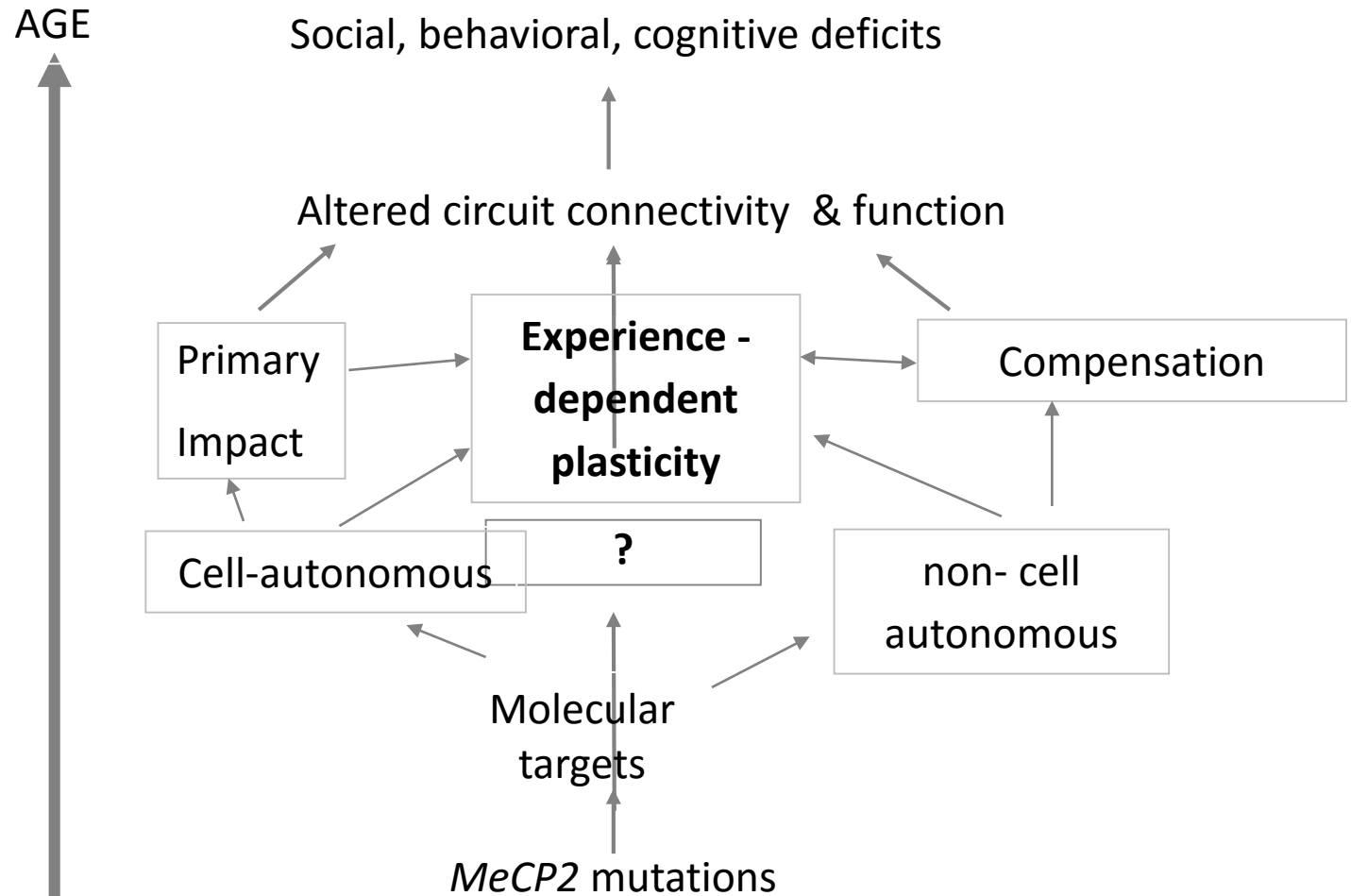
- May result from

experience-dependent

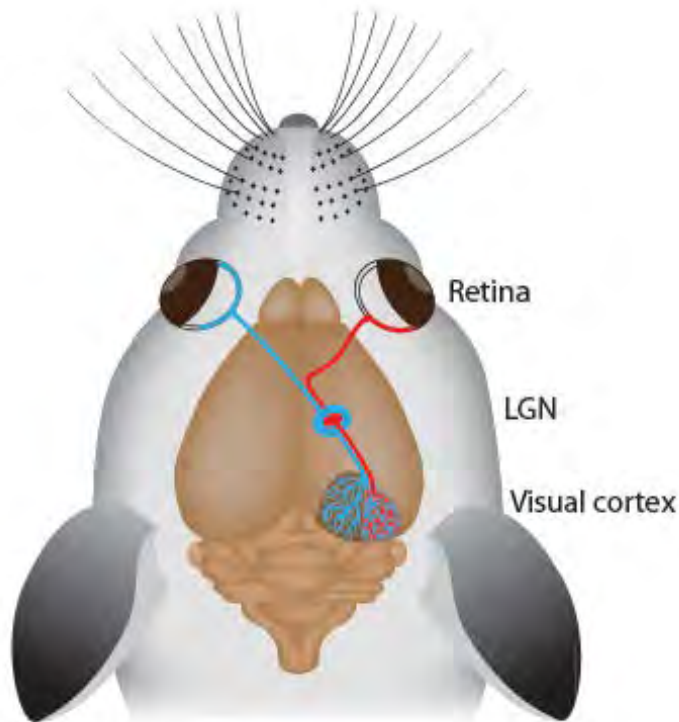
- pathogenic mechanism



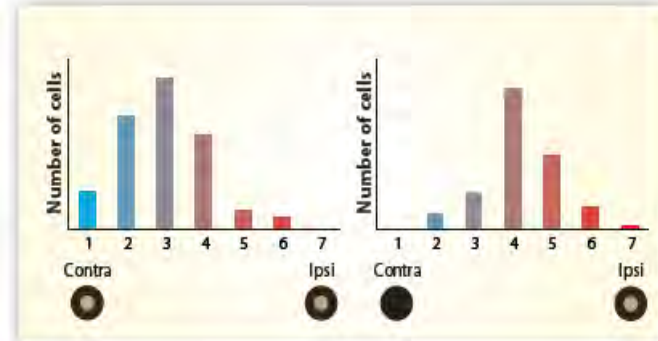
Challenges in determining the pathogenesis of Rett Syndrome (RTT)



Critical period of plasticity and experience-dependent wiring of neural circuits in primary visual cortex (V1)

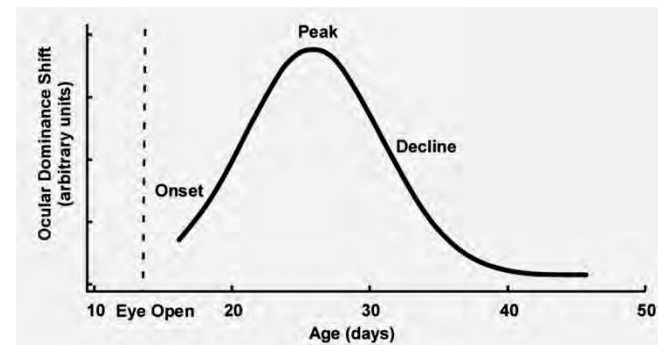


Ocular dominance shift



Hubener 2012

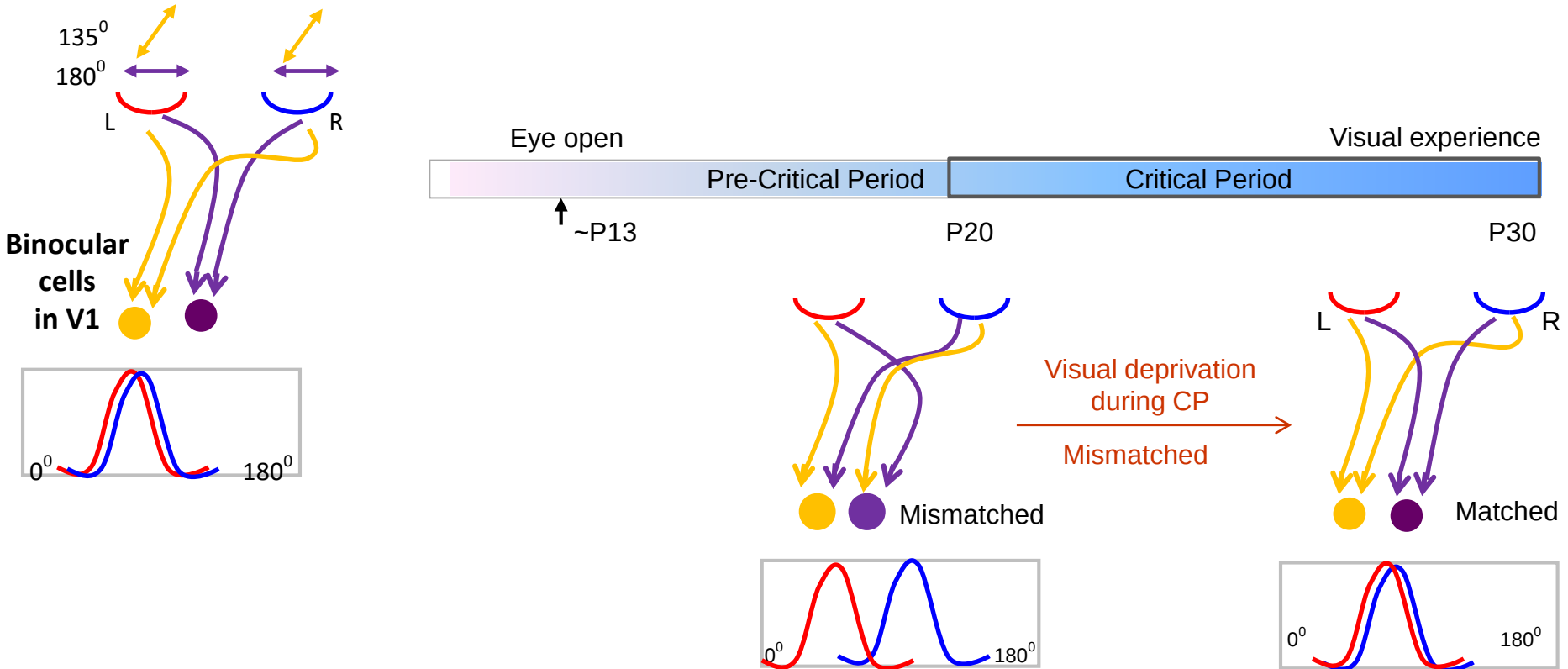
Critical period of plasticity



Gordon & Stryker 1996

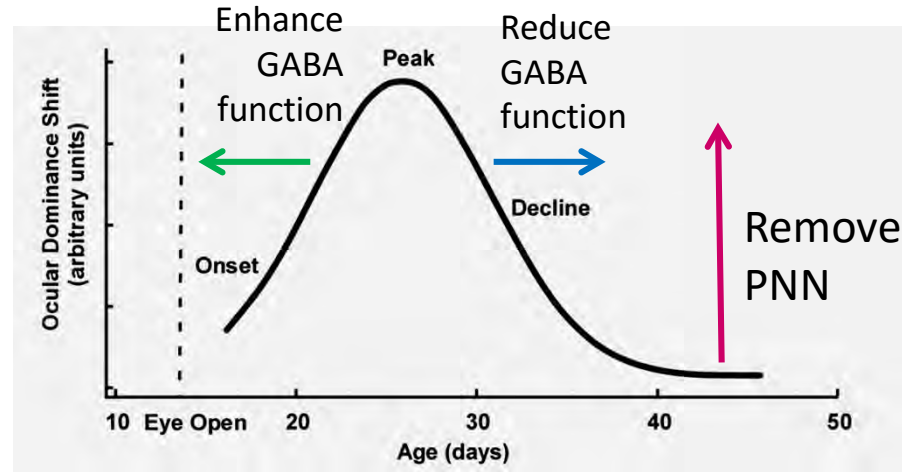
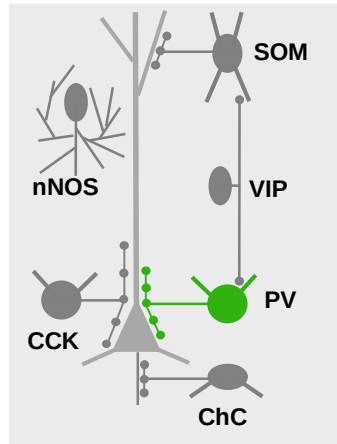
Critical period of plasticity and experience-dependent wiring of neural circuits in primary visual cortex (V1)

Orientation Selectivity

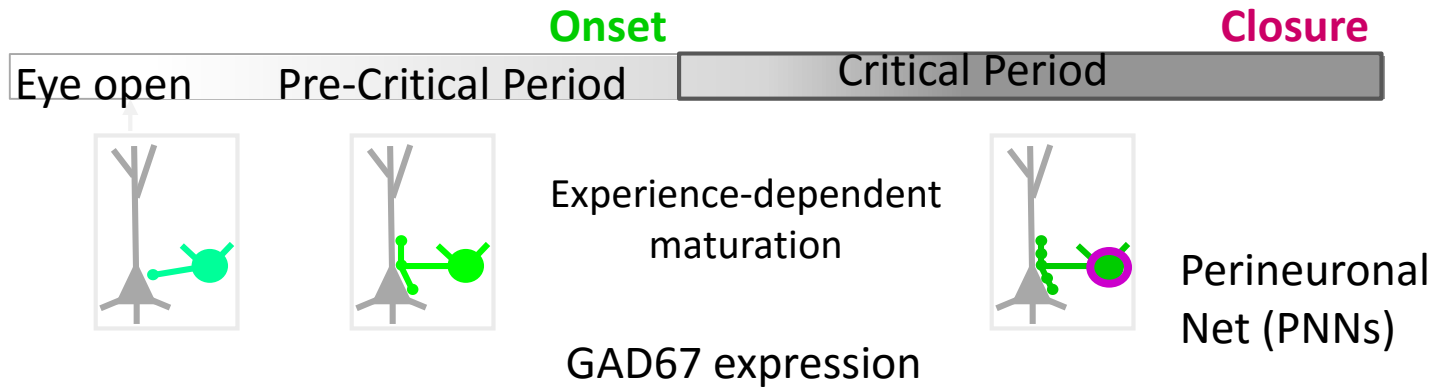


Critical period allows visual experience to drive the matching of orientation tuning onto binocular V1 cells

Maturation of GABA inhibition and Parvalbumin (PV) interneurons regulate the timing of critical period



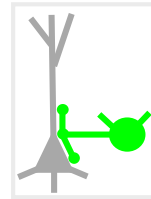
Hensch et al., 1998
Huang et al., 1999
Fagiolini et al., 2004
Pizzorusso et al., 2002



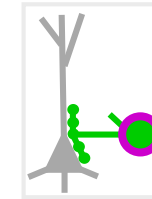
PNNs - Extracellular matrix proteins that inhibit axon growth and structural plasticity

Experience-dependent wiring of V1 circuits: knowledge of developmental trajectory allows better tracking of its alterations

- Maturation of GABA circuits

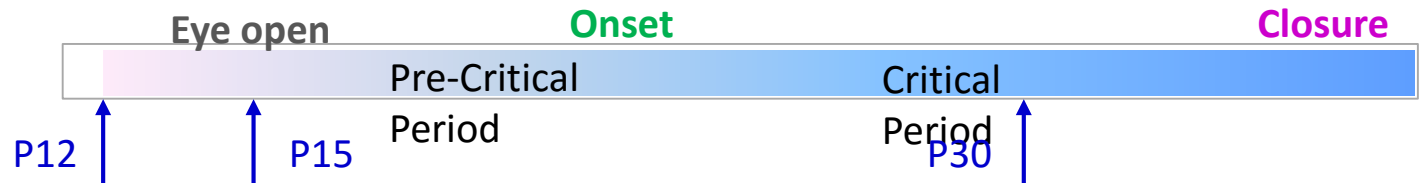


Exp.-dep. maturation →

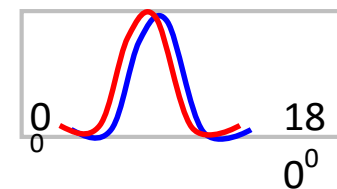
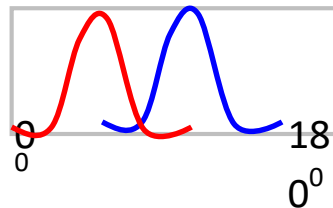


Perineural Net

- Timing of Critical period

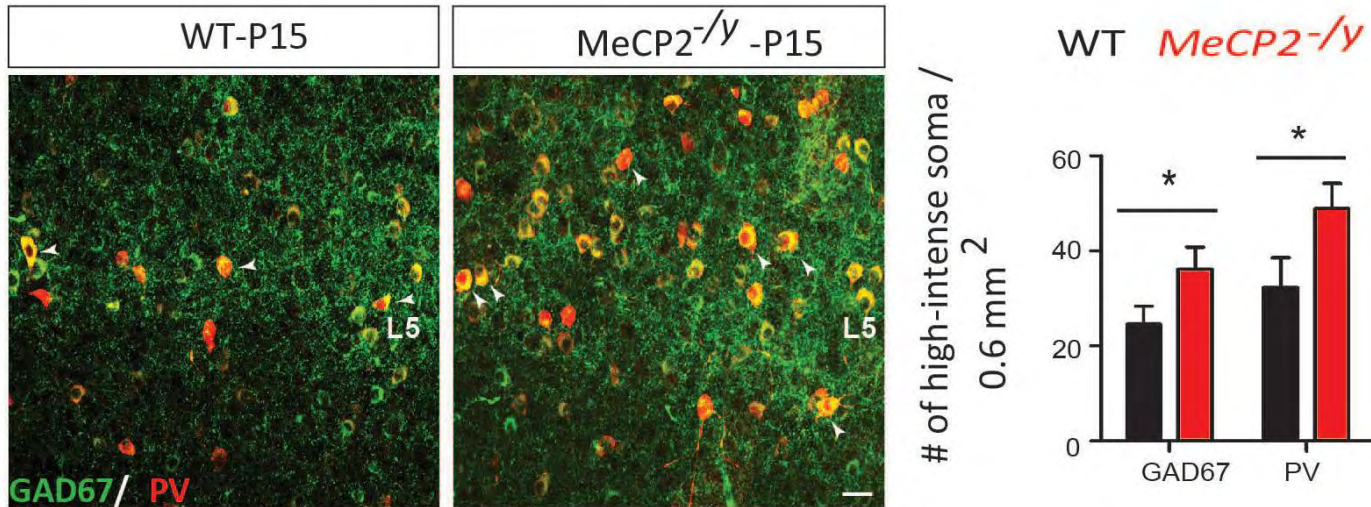


- Development of Visual function



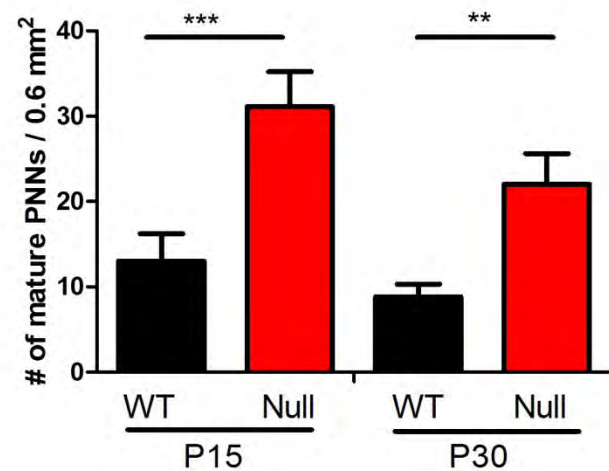
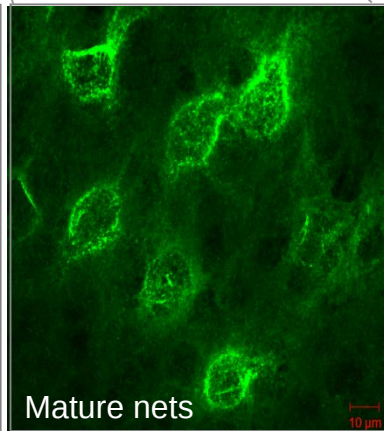
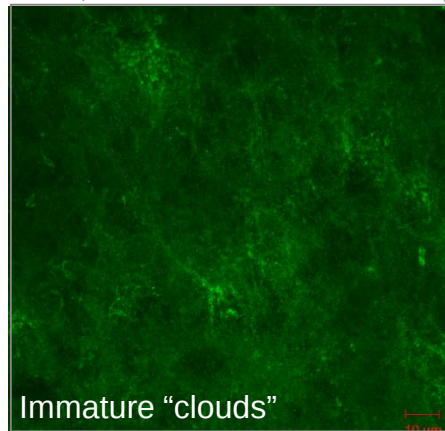
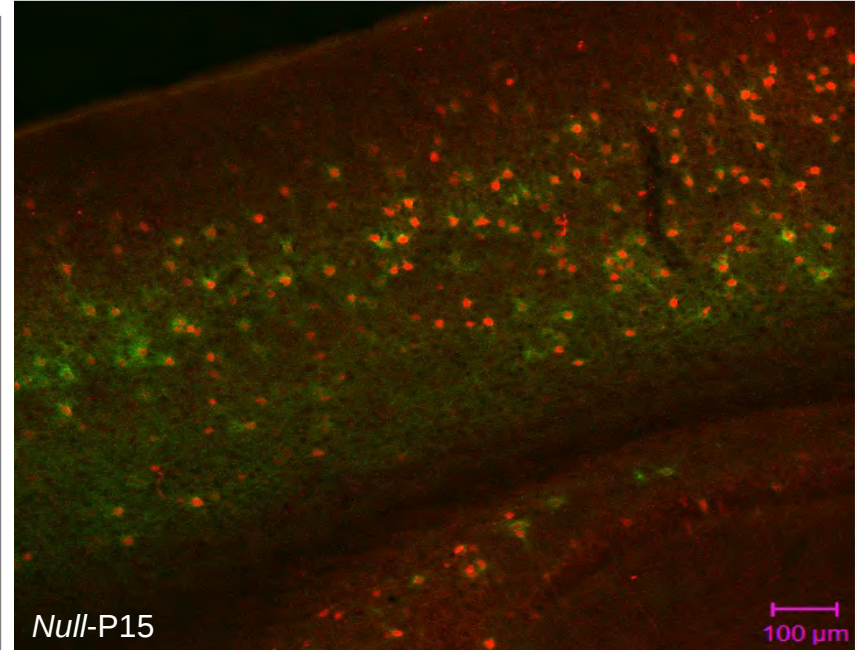
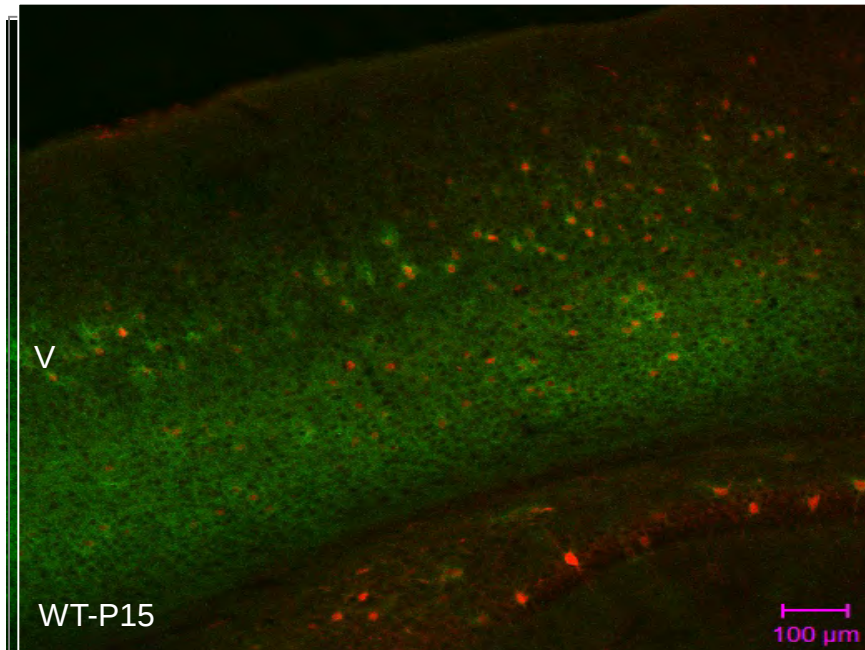
What is the impact of MeCP2 deletion in germ-line male mice (MeCP2^{-/y}) ?

Precocious increase in key components of GABA transmission in Null V1

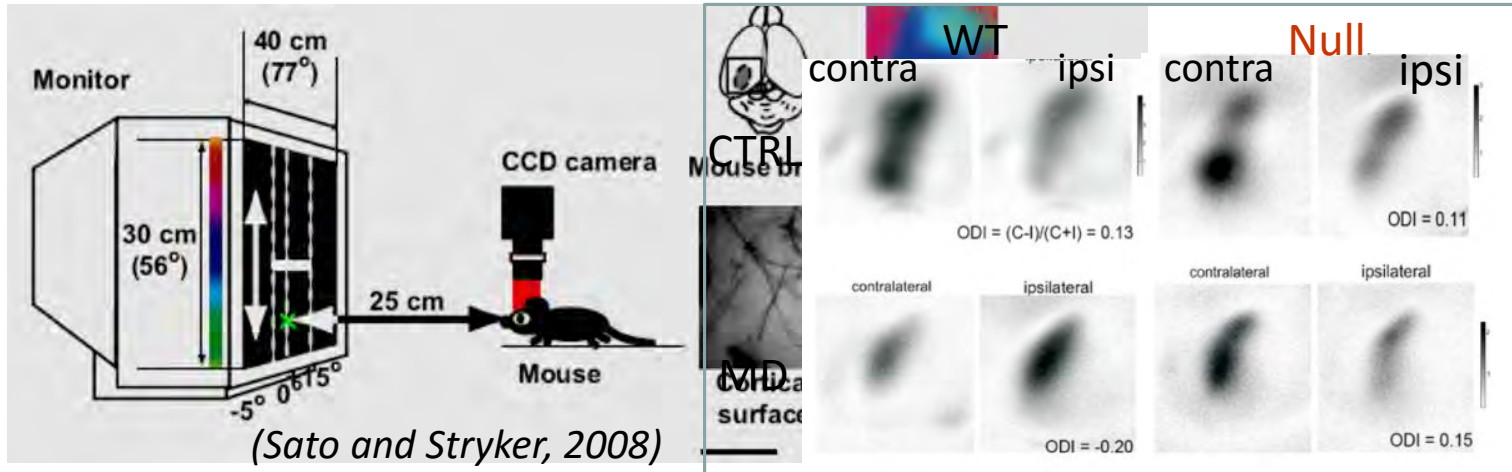


PNN formation on PV⁺ neurons is accelerated in Null cortex

WFA

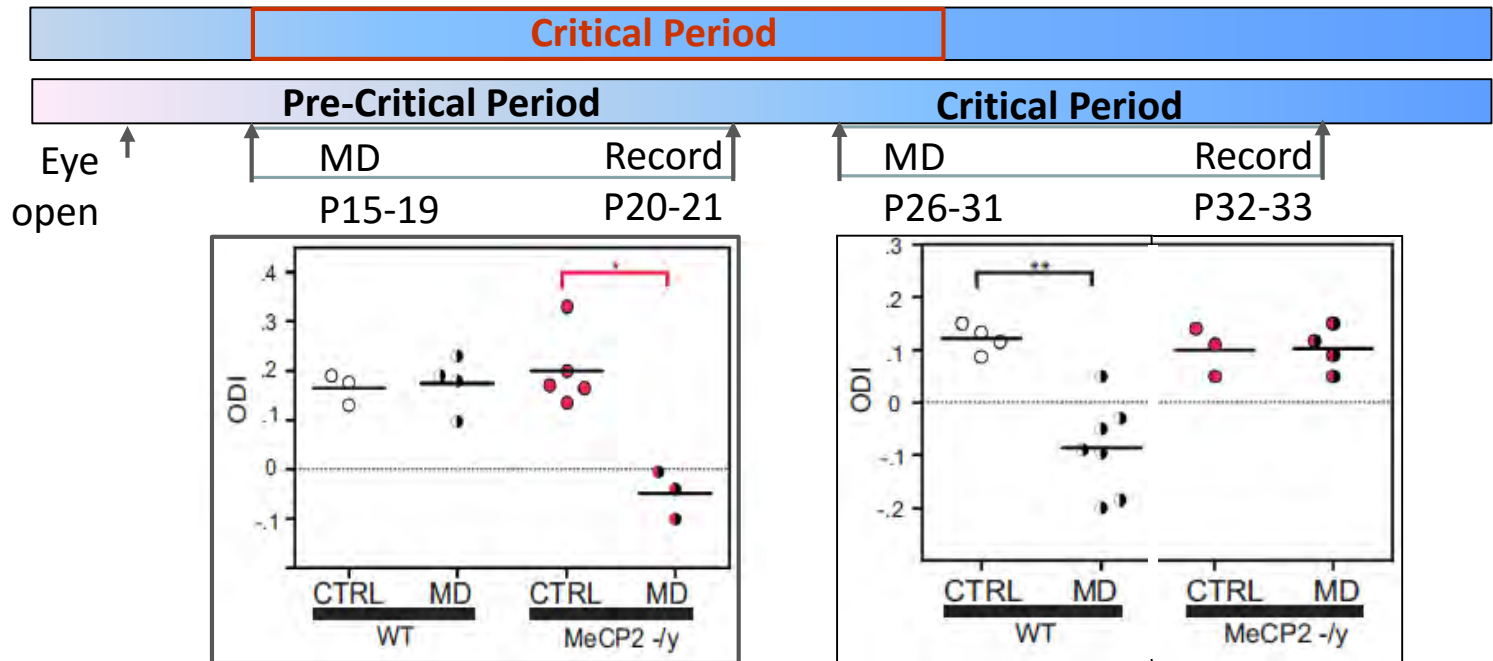


Precocious critical period of plasticity in Null V1

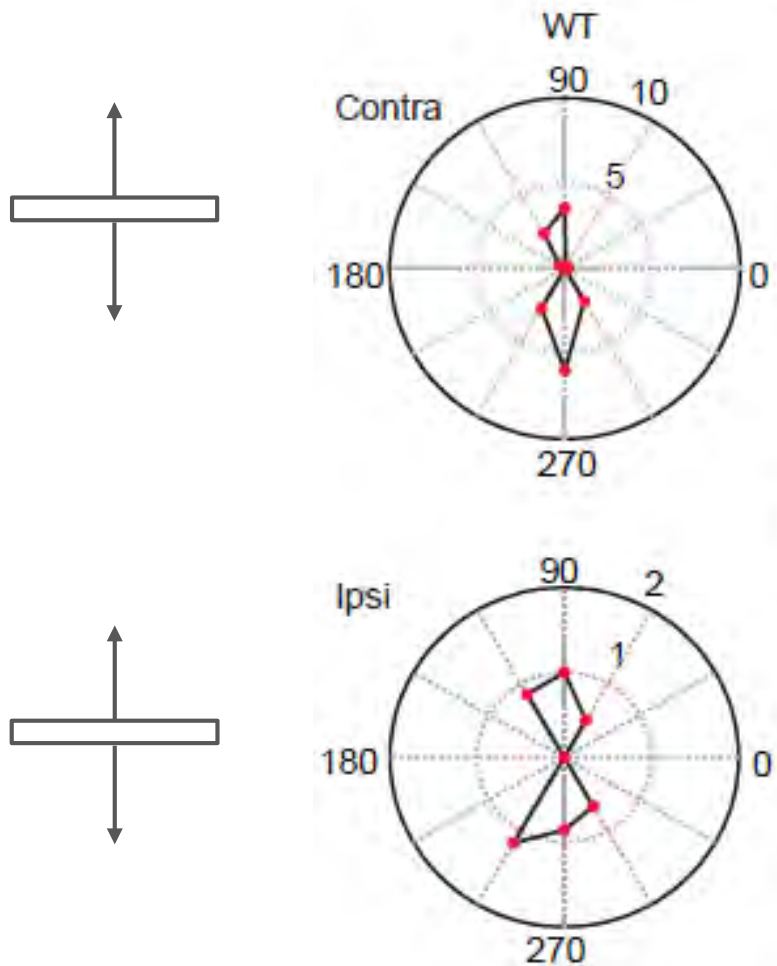


MeCP2-Null

WT



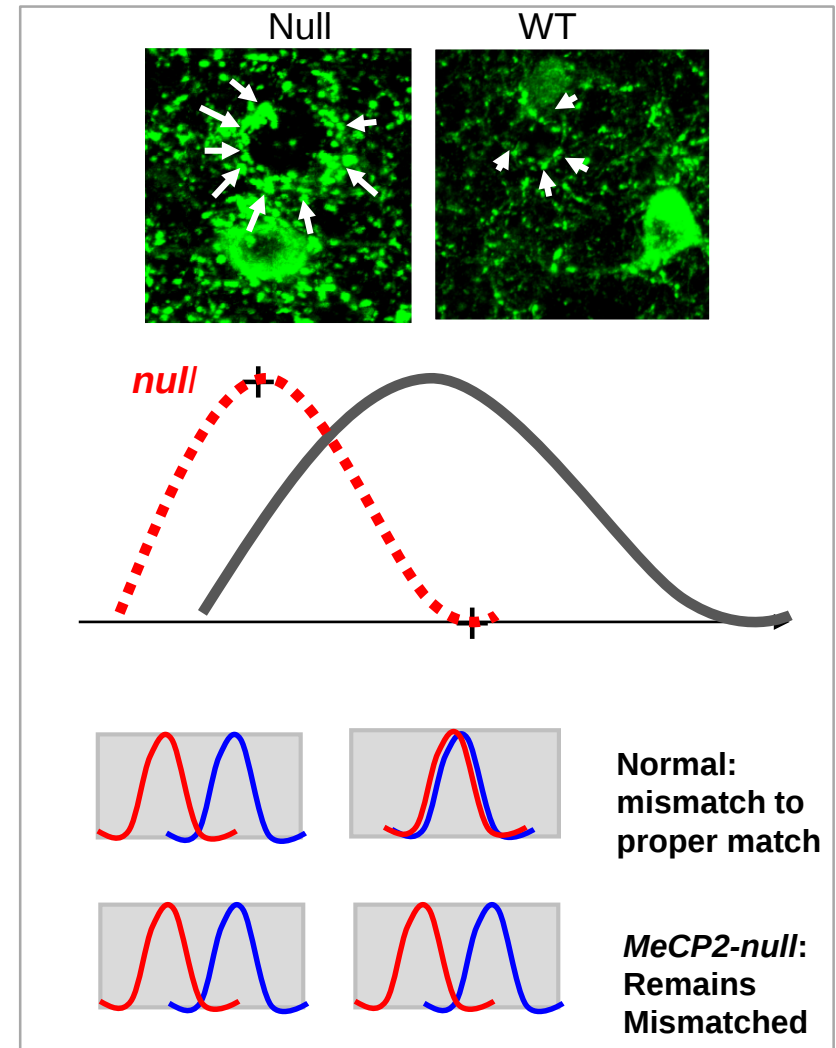
Orientation tuning of inputs from two eyes onto individual binocular cells remains mismatched in Null V1



MECP2 regulates timing of critical period plasticity

In Visual cortex of *MeCP2-null*:

- Precocious increase in key components of GABA transmission, mainly in PV+ neurons
- Precocious onset and termination of critical period
- Aberrant visual function, measured by binocular matching of orientation tuning of inputs
- Reducing GAD67 levels rescues onset of the precocious of critical period plasticity



Model

MeCP2-null male mice

MeCP2-heterozygous female mice

Context

Developing visual cortex

Adult auditory cortex

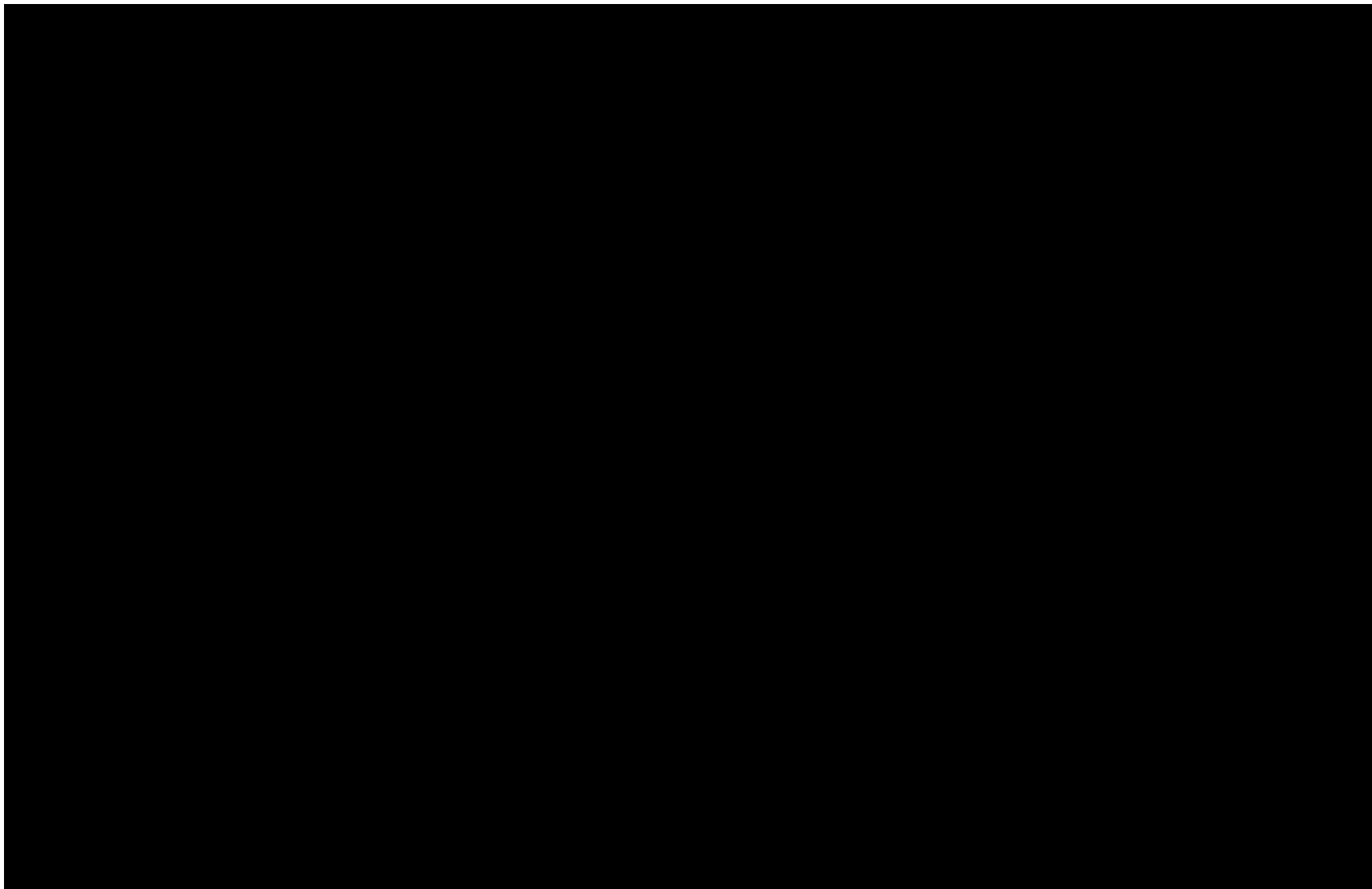
Cell type

Parvalbumin (PV⁺) GABAergic interneurons

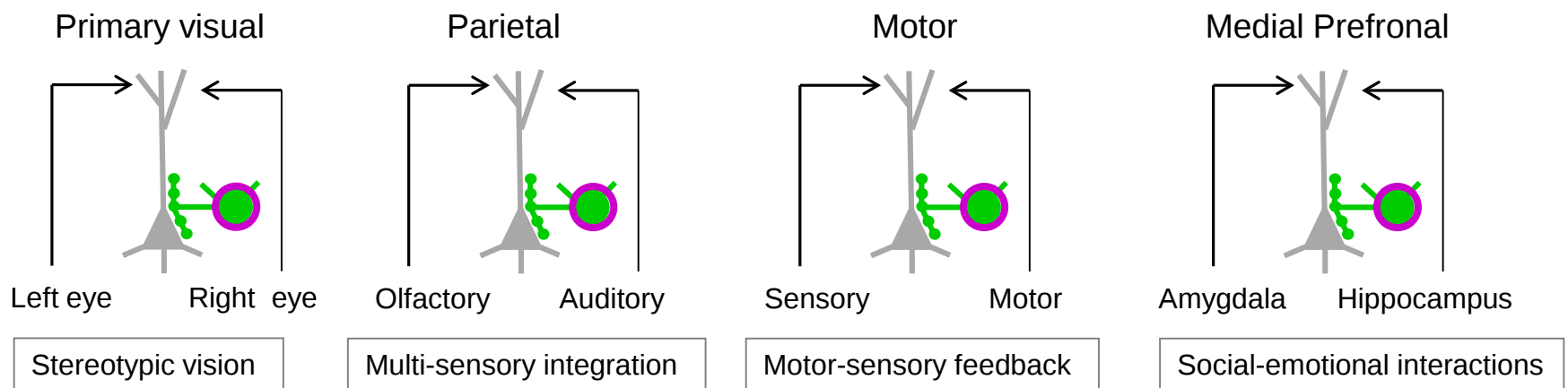
Concept

Timing of Experience-dependent plasticity





Speculation: Role of MECP2 in regulating timing of experience-dependent plasticity may apply to other brain systems

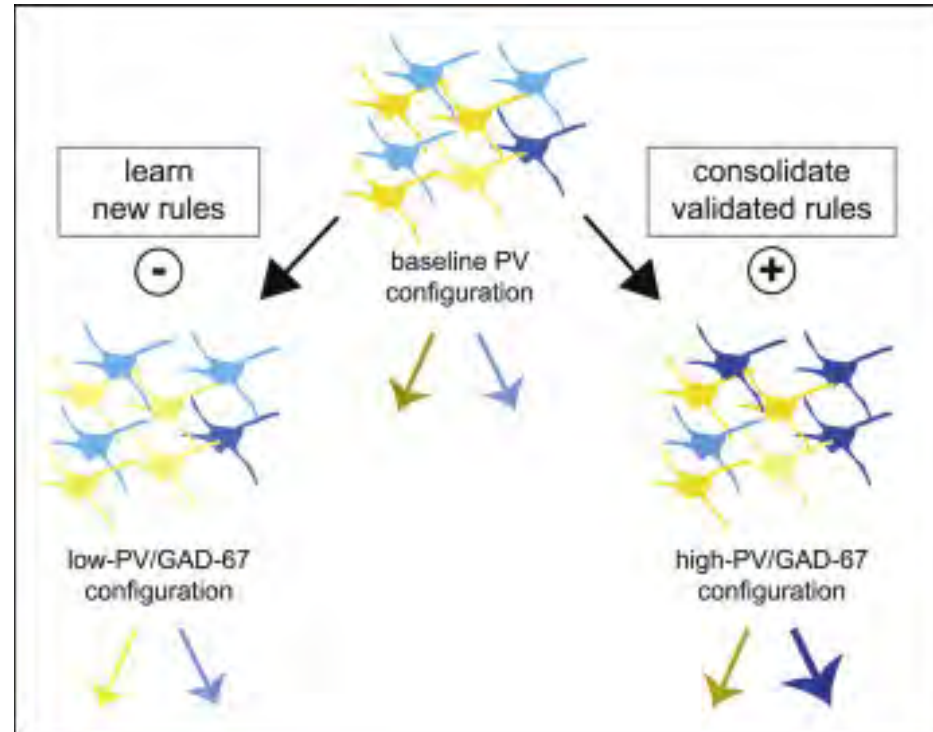


Sensory processing in RTT and ASD patients is affected

Speculation

In RTT and ASD,

- specific cells and networks involved in consolidating skills might be prematurely closed.
- Similar mechanisms involving PV⁺ network (PV/GAD67/PNNs) might be involved in regression
- These markers can be used to study and perhaps “rescue” regression phenotype (once identified) in animal models.



Caroni, 2015

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Billy Lau

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Arianna Maffei, SUNY



Awarding **NARSAD** Grants

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