A Developmental Reduction of the Excitation:Inhibition Ratio in Association Cortex during Adolescence

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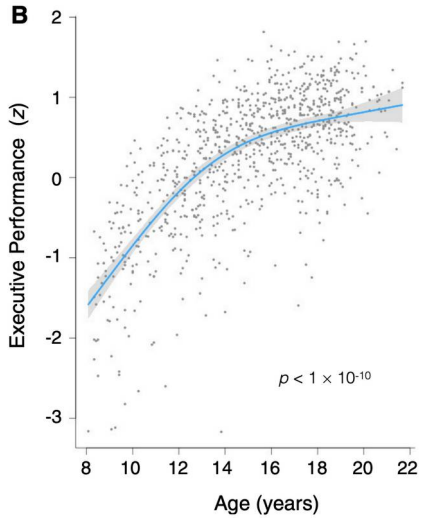
PennLINC Lab Meeting

Adolescence

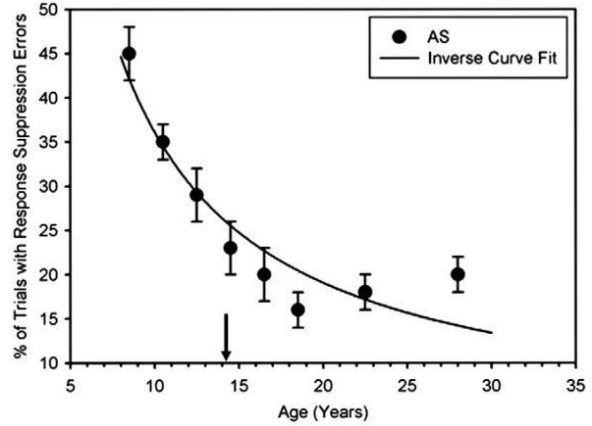
- Increased *consistency* and *reliability* of executive function
- Emergence of psychopathology that is characterized by executive dysfunction

Executive Function

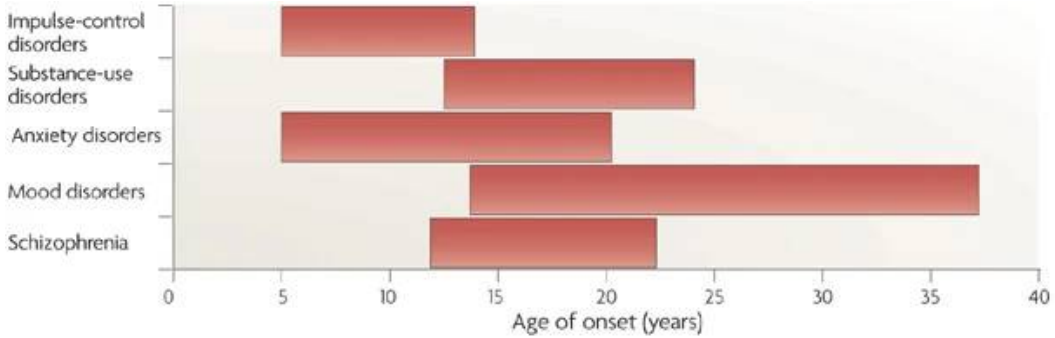


Baum et al. (2017). *Current Biology*

Inhibitory control error rate

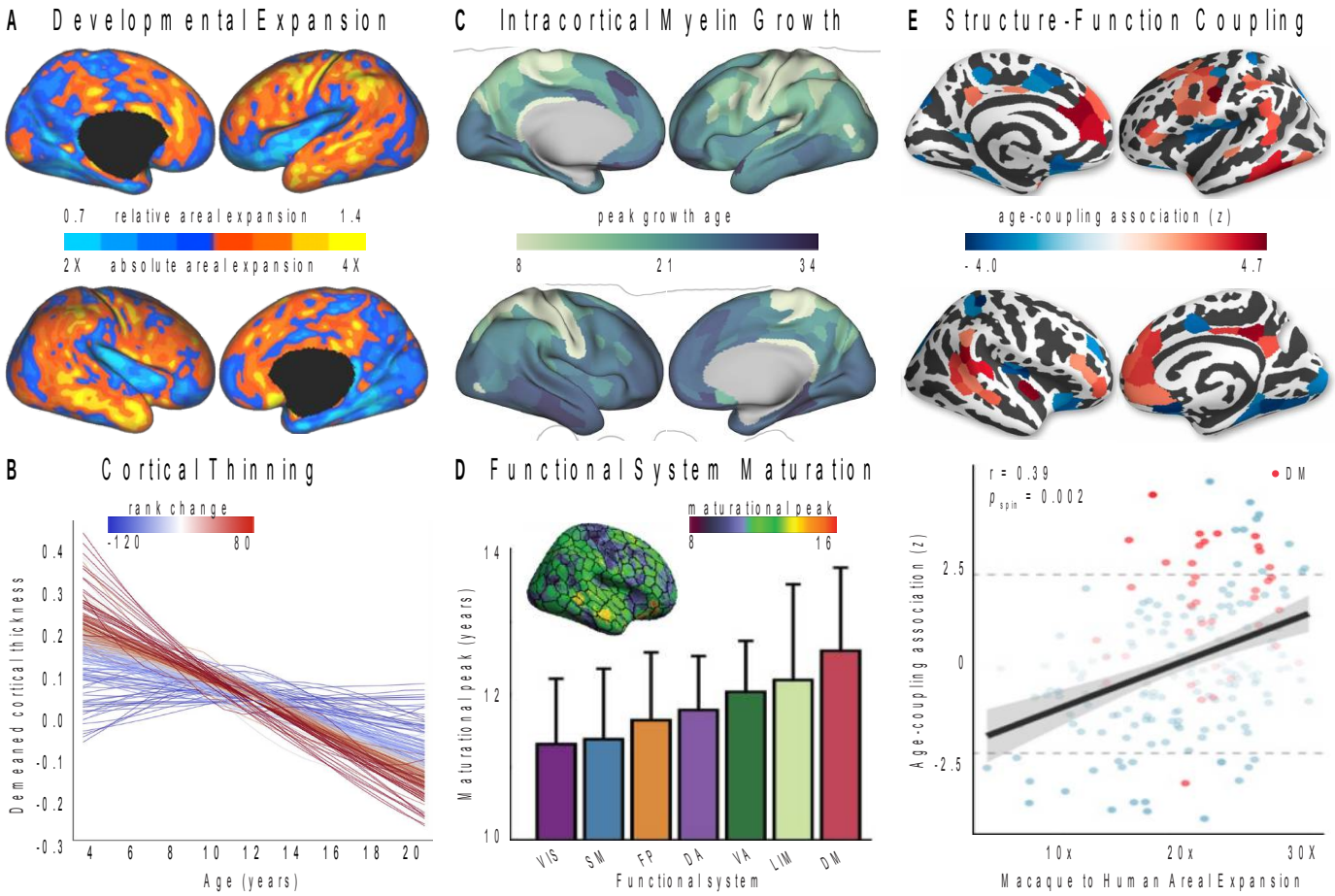


Luna et al. (2004). *Child Devel*



Paus, Keshavan, Giedd, 2008, *Nat Rev*

Adolescence is characterized by the development of association cortex



Sydnor et al. *Neuron*

What are the underlying mechanisms?

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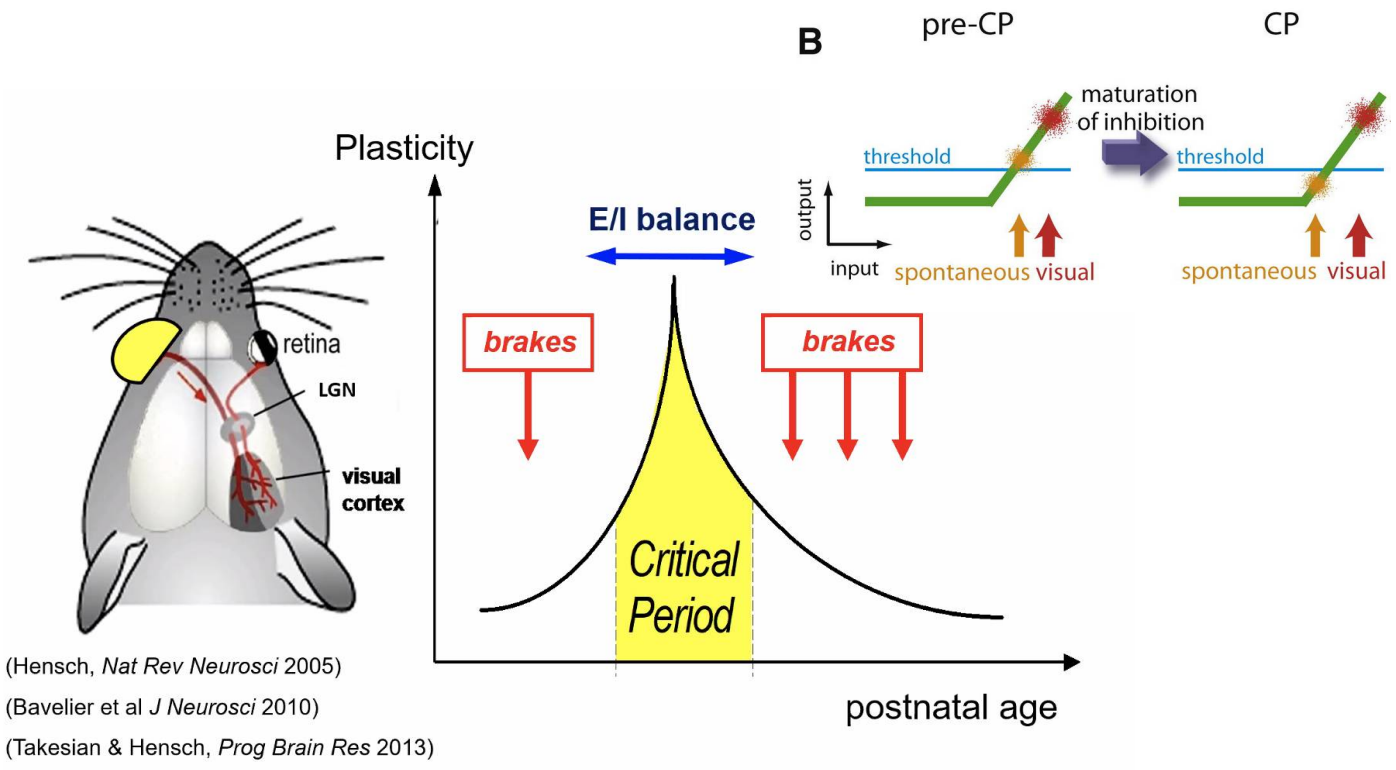
Critical period?

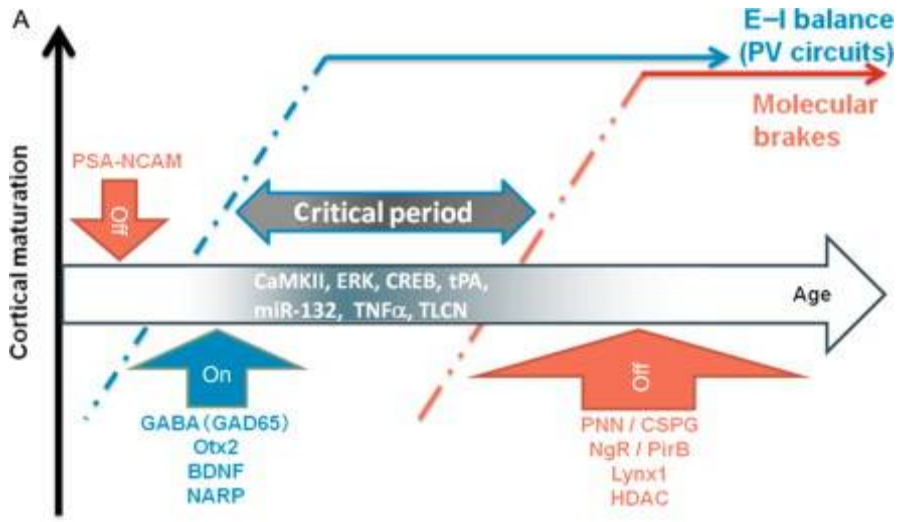
Shifting E:I balance is a hallmark of CP development



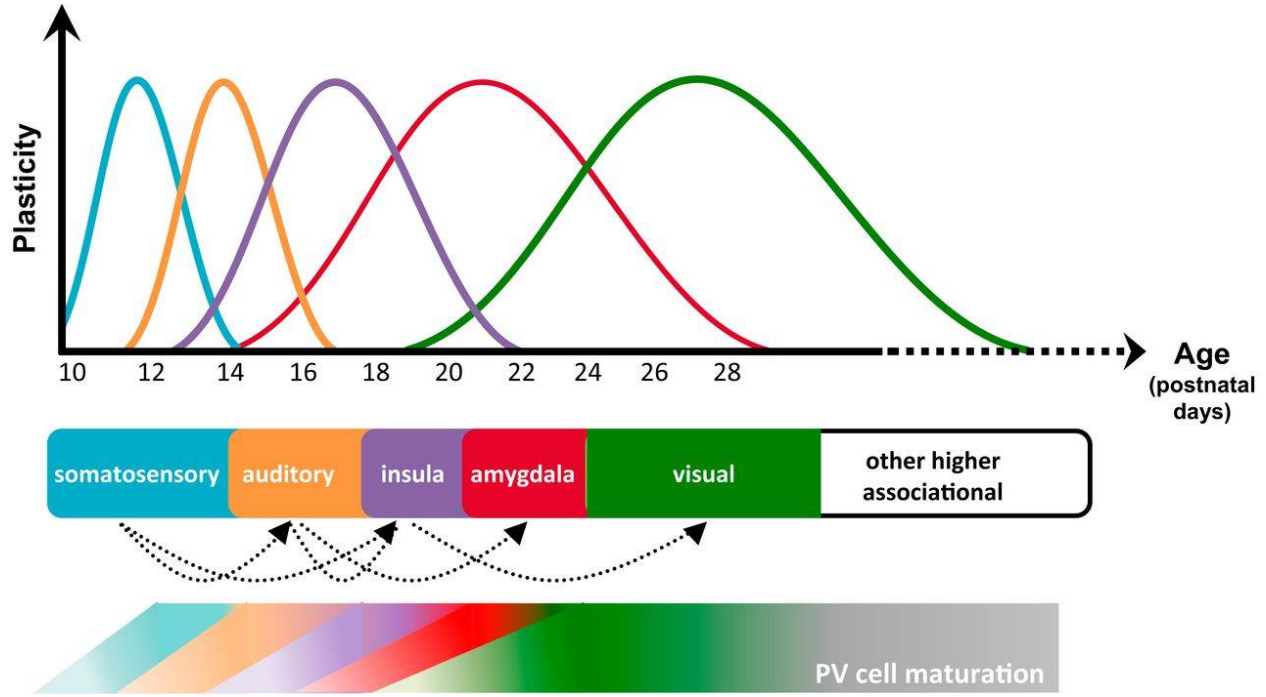
(Hensch, *Nat Rev Neurosci* 2005)

(Bavelier et al *J Neurosci* 2010)

(Takesian & Hensch, *Prog Brain Res* 2013)

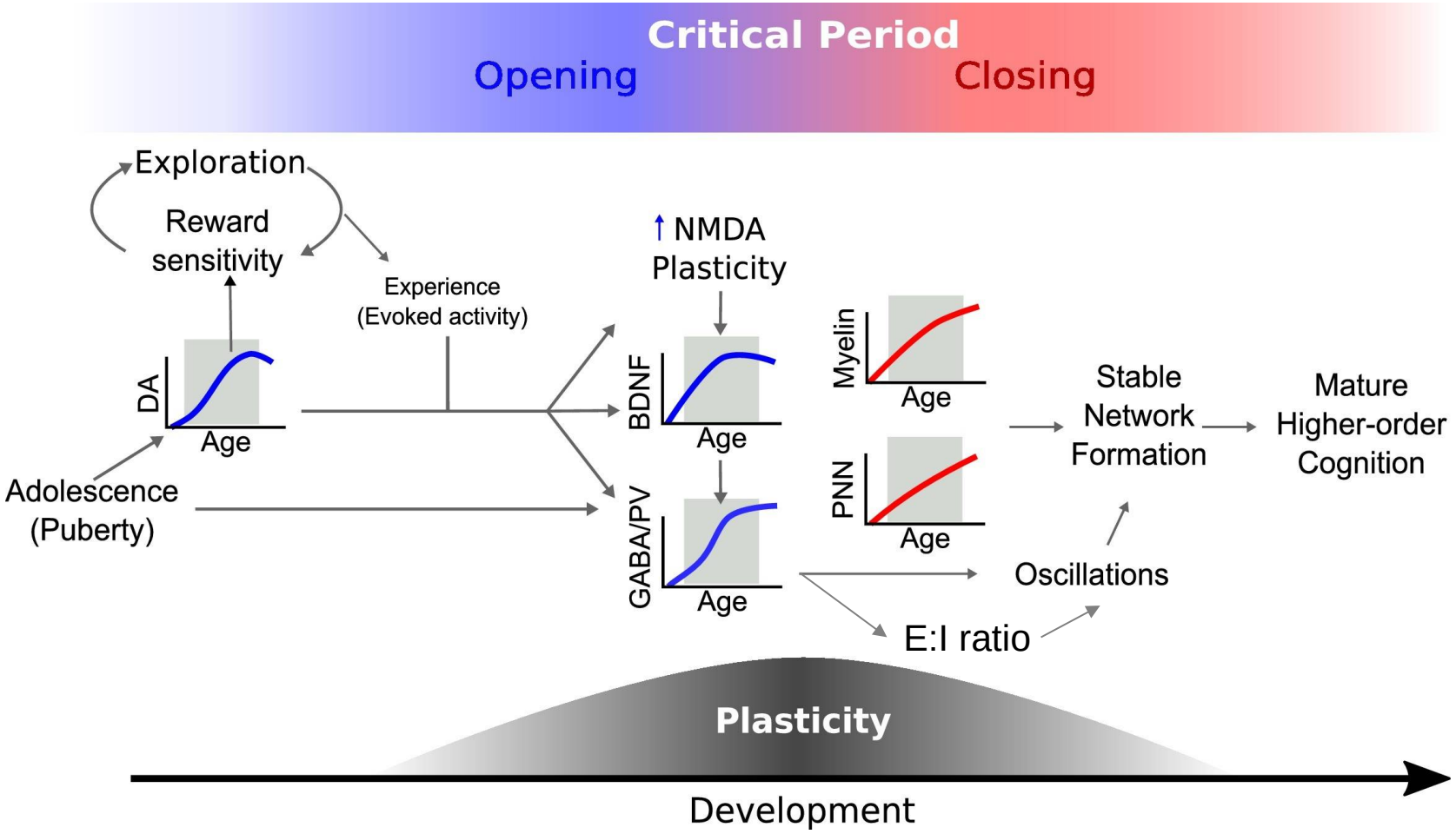


Critical periods progress hierarchically



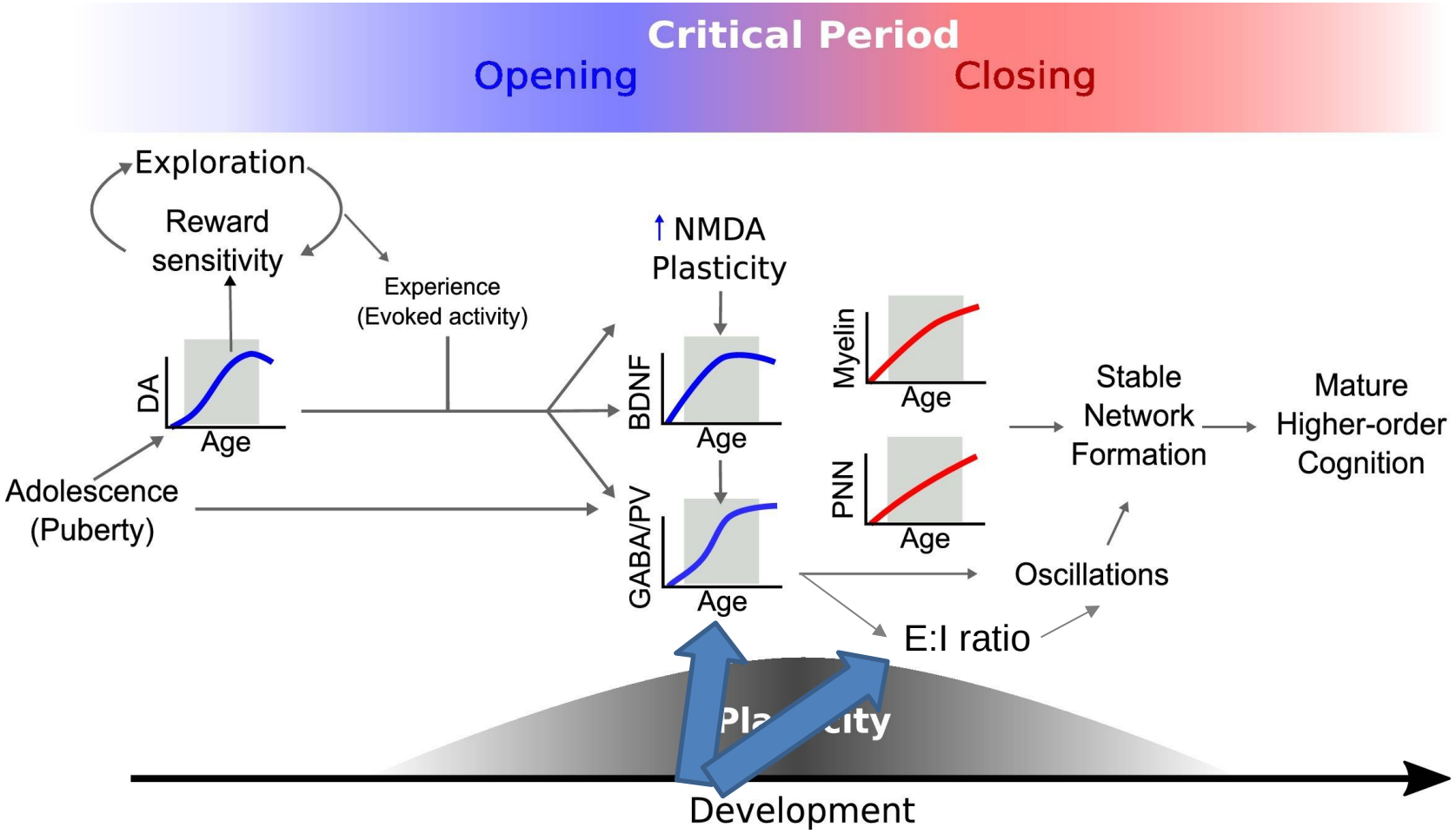
Reh et al. (2020). *PNAS*

Adolescence as a critical period for the development of association cortex



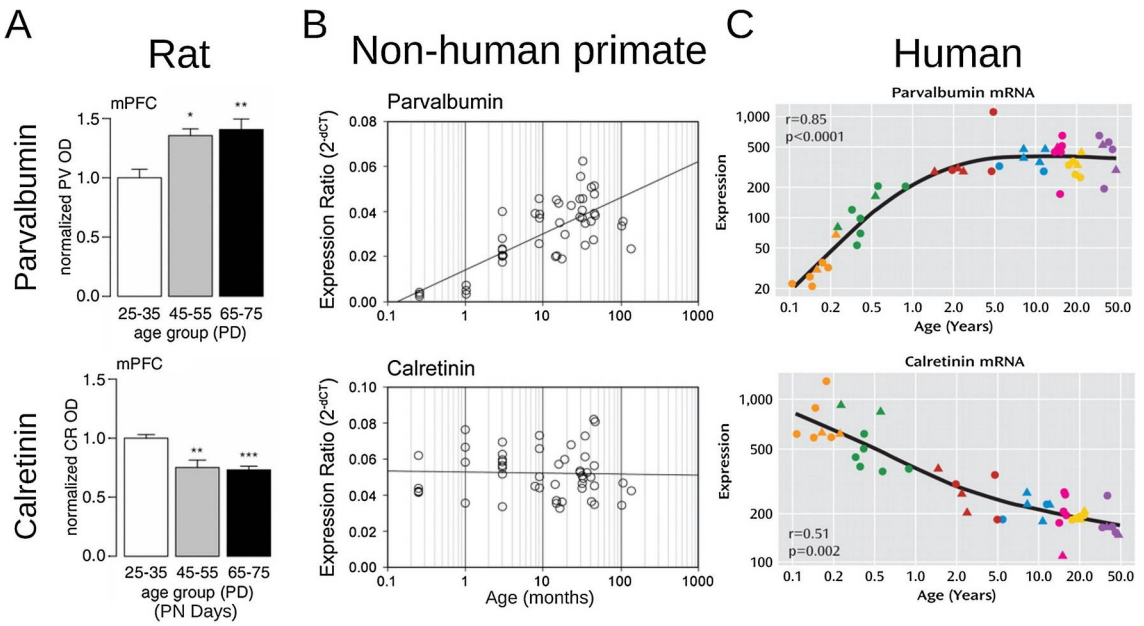
Larsen & Luna

Adolescence as a critical period for the development of association cortex



Larsen & Luna

Inhibitory development during adolescence



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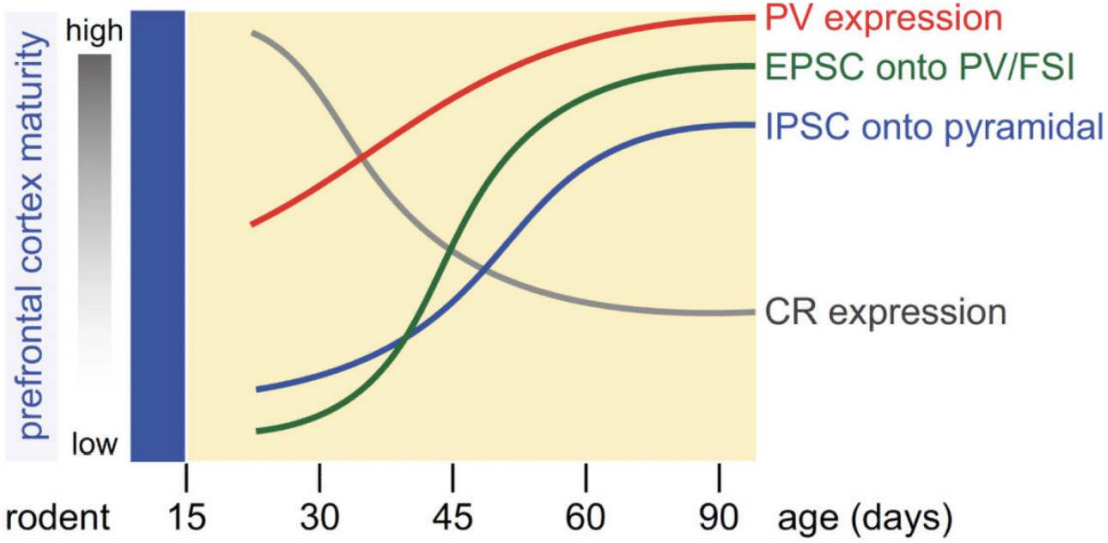
Species	Adolescent period
Human	8-20 years
Non-human primate	30-60 months
Rat	35-60 days

Larsen & Luna 2018.
Caballero et al. 2014
Hoftman et al. 2015
Fung et al. 2010



Caballero & Tseng 2016

Hypothesis

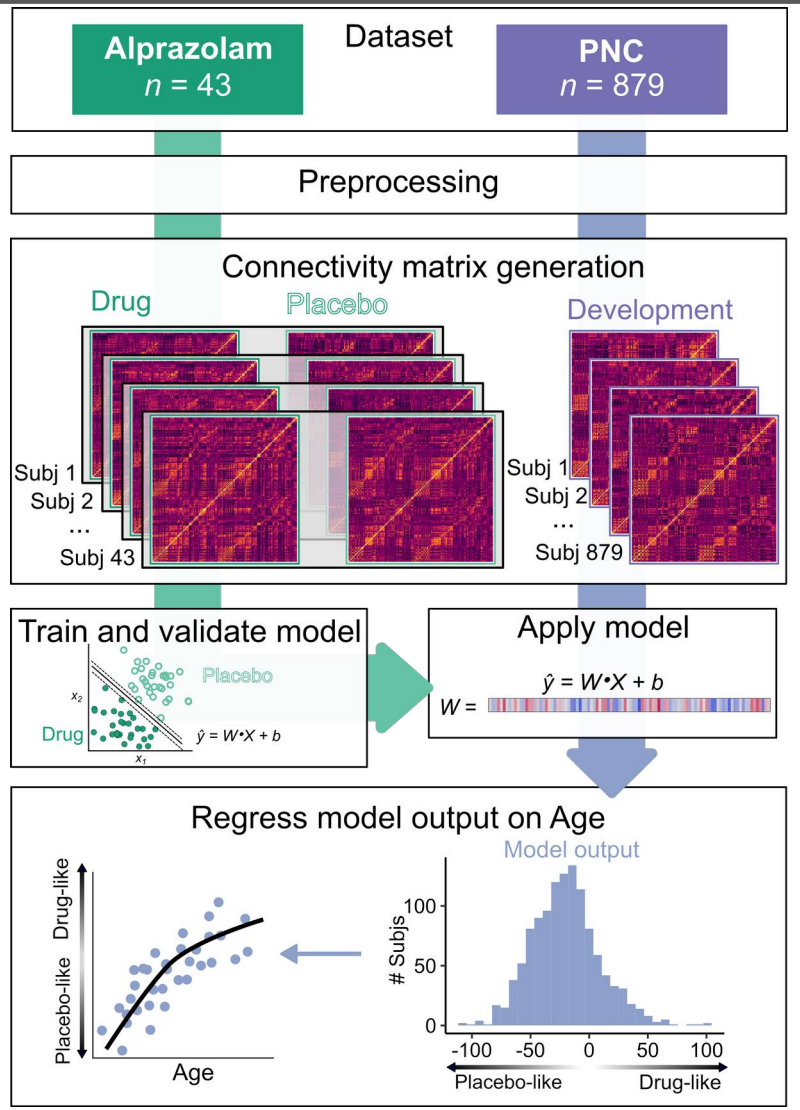
Inhibitory circuitry is maturing in association cortex during adolescence, leading to reduced E/I ratio.

Question

- How can we test this hypothesis in humans?
  - *How can we find evidence of reduced E:I ratio using neuroimaging*?

- Maybe we can create a model empirically

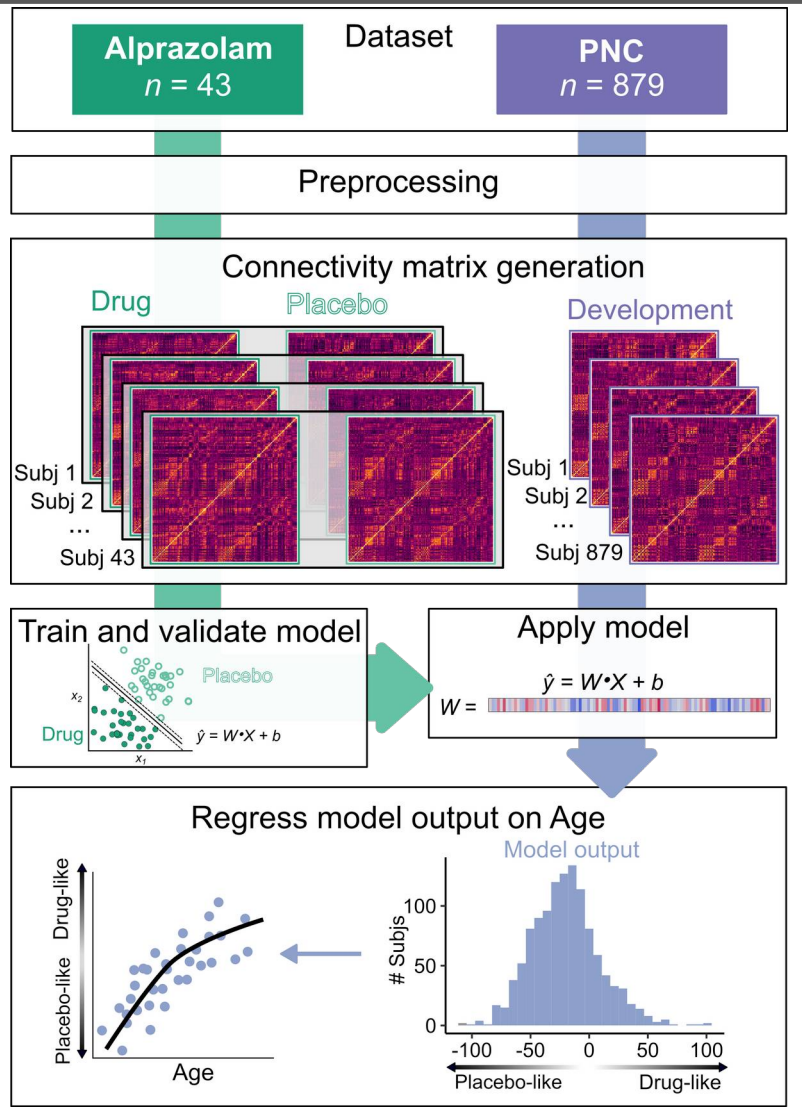
Study design



Study design

Alprazolam sample

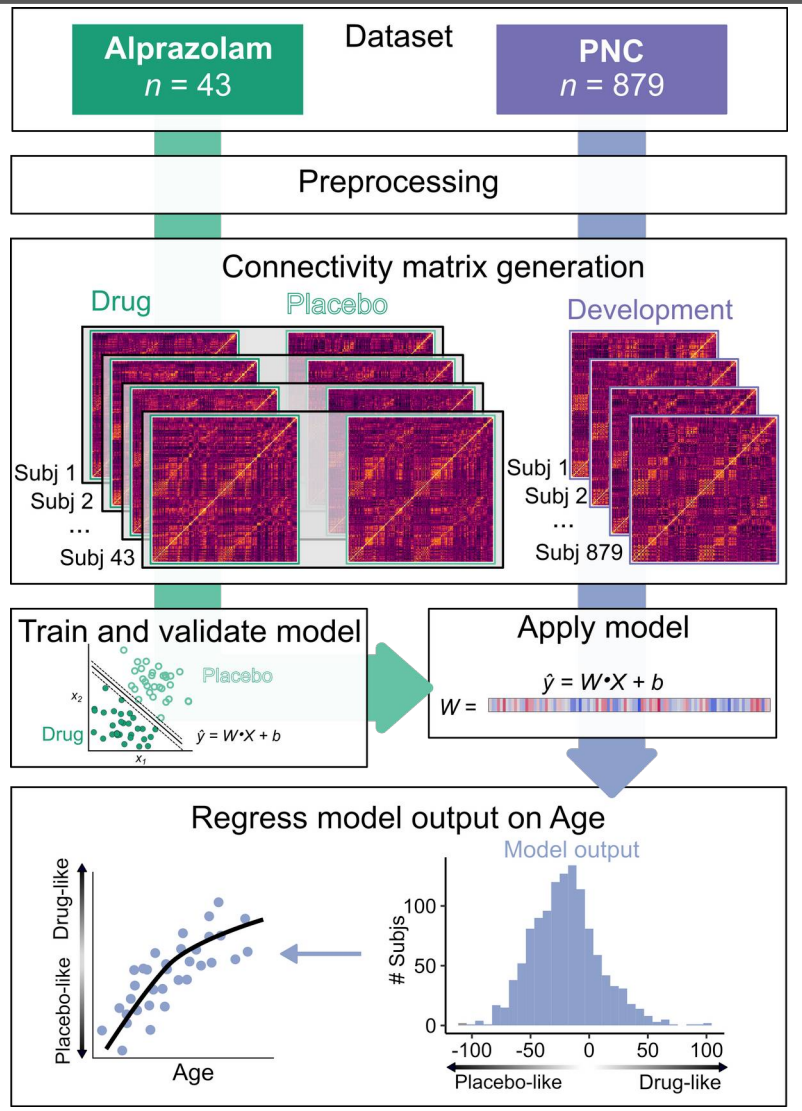
- 2 identical fMRI sessions (1 week apart)
- Alprazolam challenge
  - Alprazolam is a benzodiazepine that enhances GABAergic signaling at $GABA_A$ receptors
- Balanced double-blind within subject crossover design



Study design

fMRI data processing

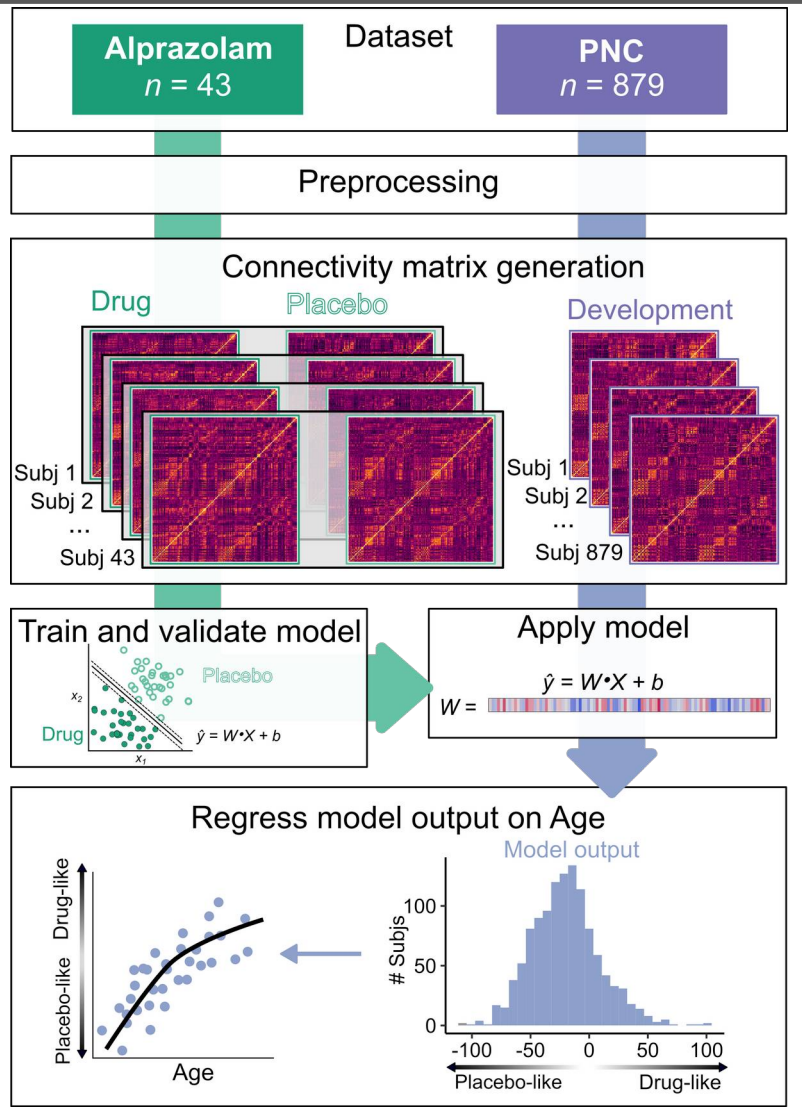
- Emotion identification task
- 204 volumes, 10.5 minutes
  - TR = 3s
  - 2x2x2 resolution
- Not whole brain coverage
- Task-regression and global signal regression applied
- Connectivity matrices generated from Schaefer400 + AAL subcortex



Study design

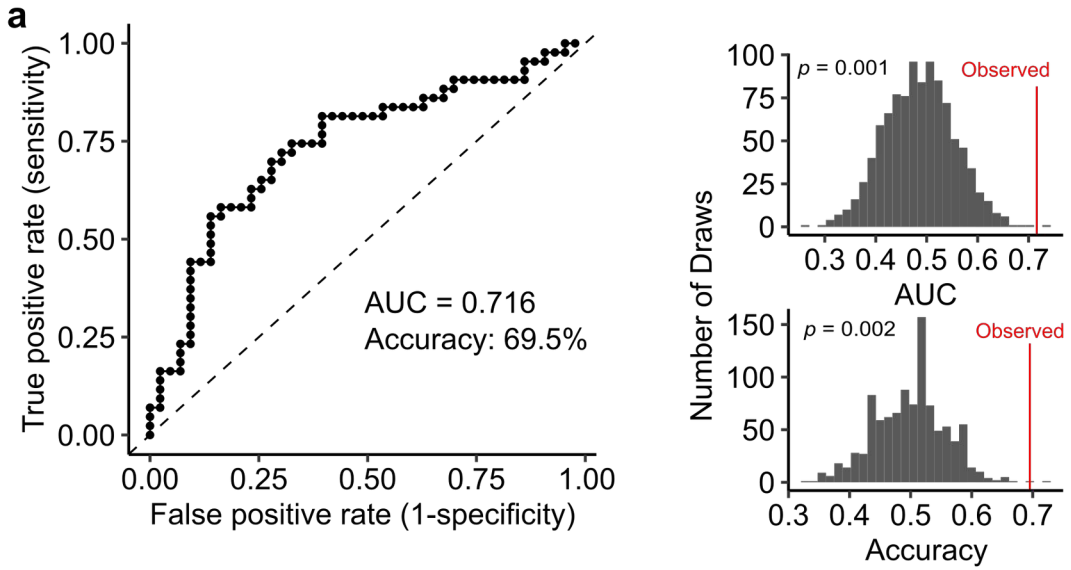
Linear SVM

- Train and validate in Alpraz sample
  - 10-fold CV
- Apply model to PNC sample
  - Model predicted distance from classification plane.

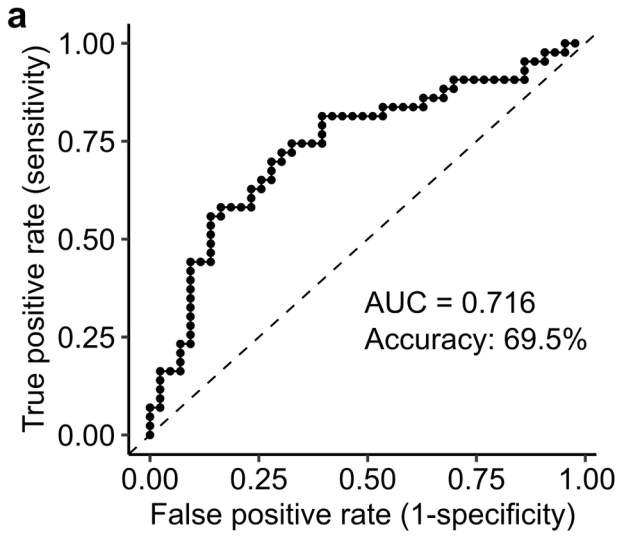


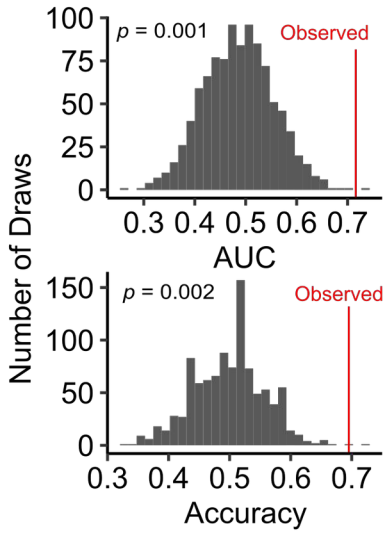
Results

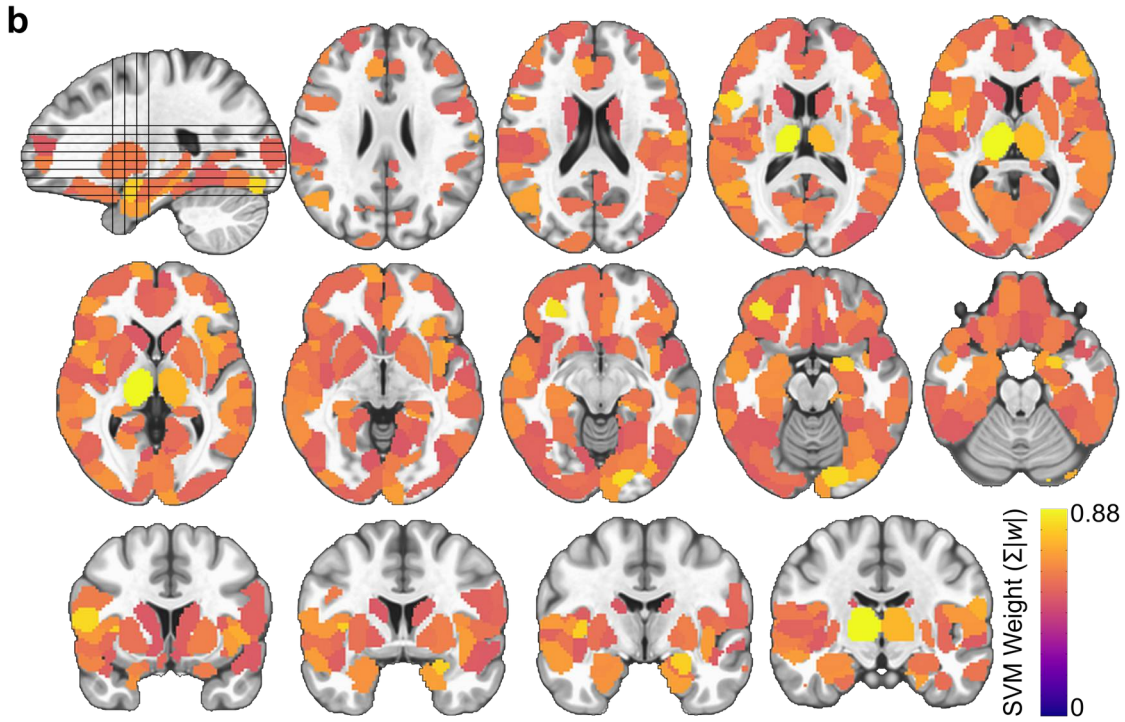
Model distinguishes alprazolam and placebo sessions



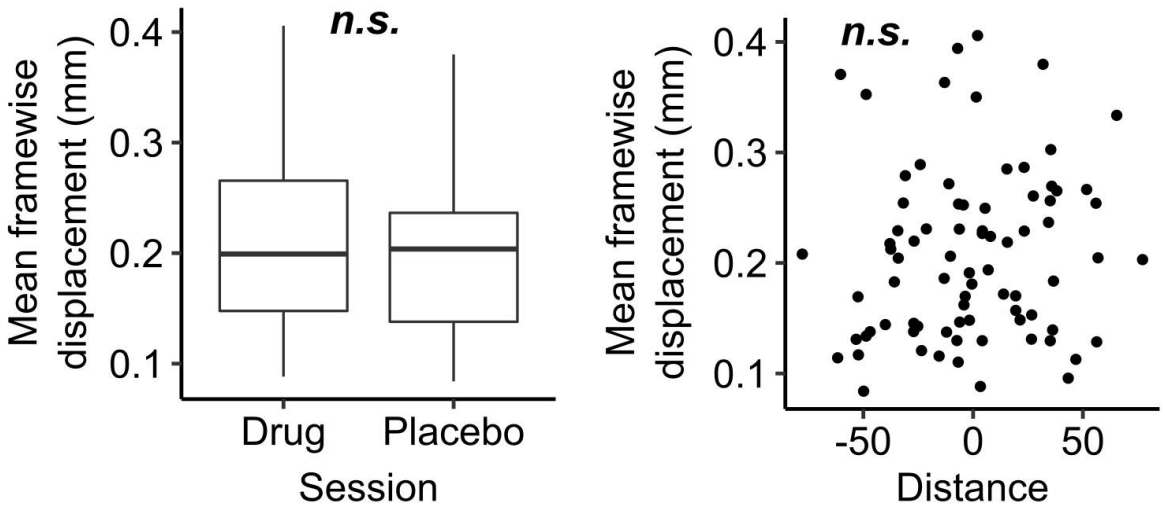
Model distinguishes alprazolam and placebo sessions



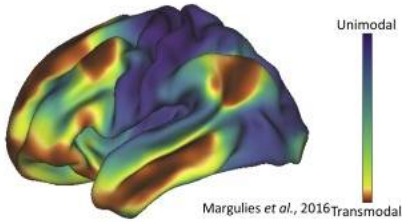


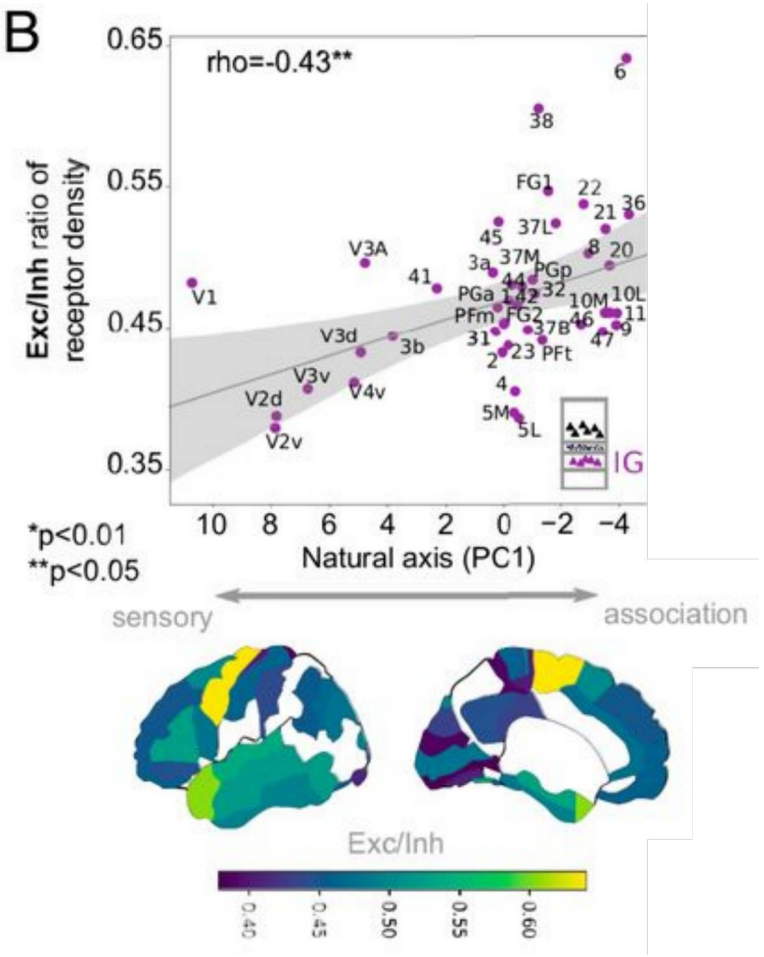


Model performance is not driven by motion



Biological validity of the E:I model





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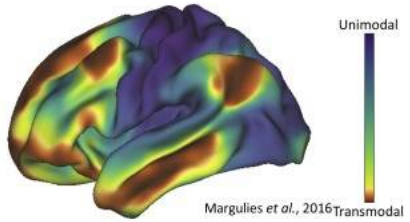

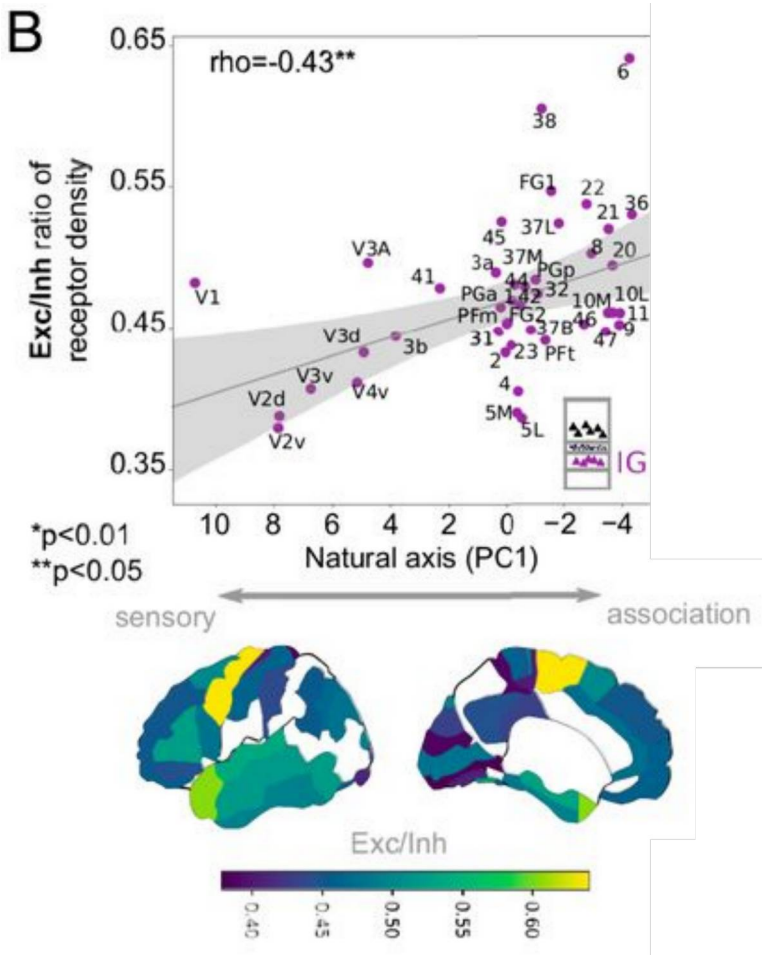

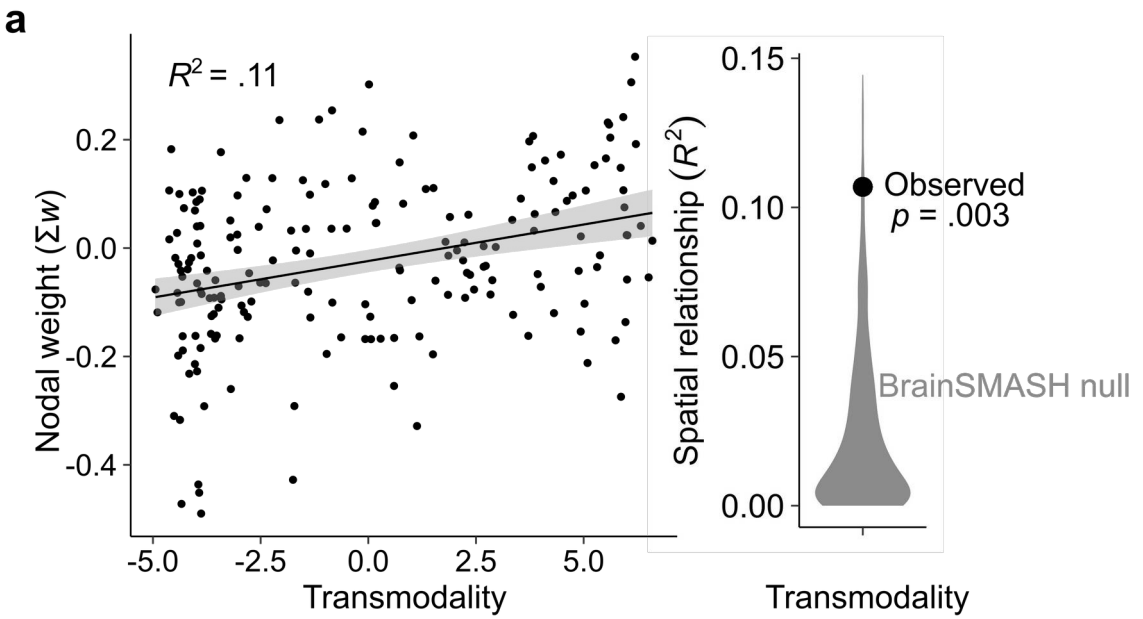

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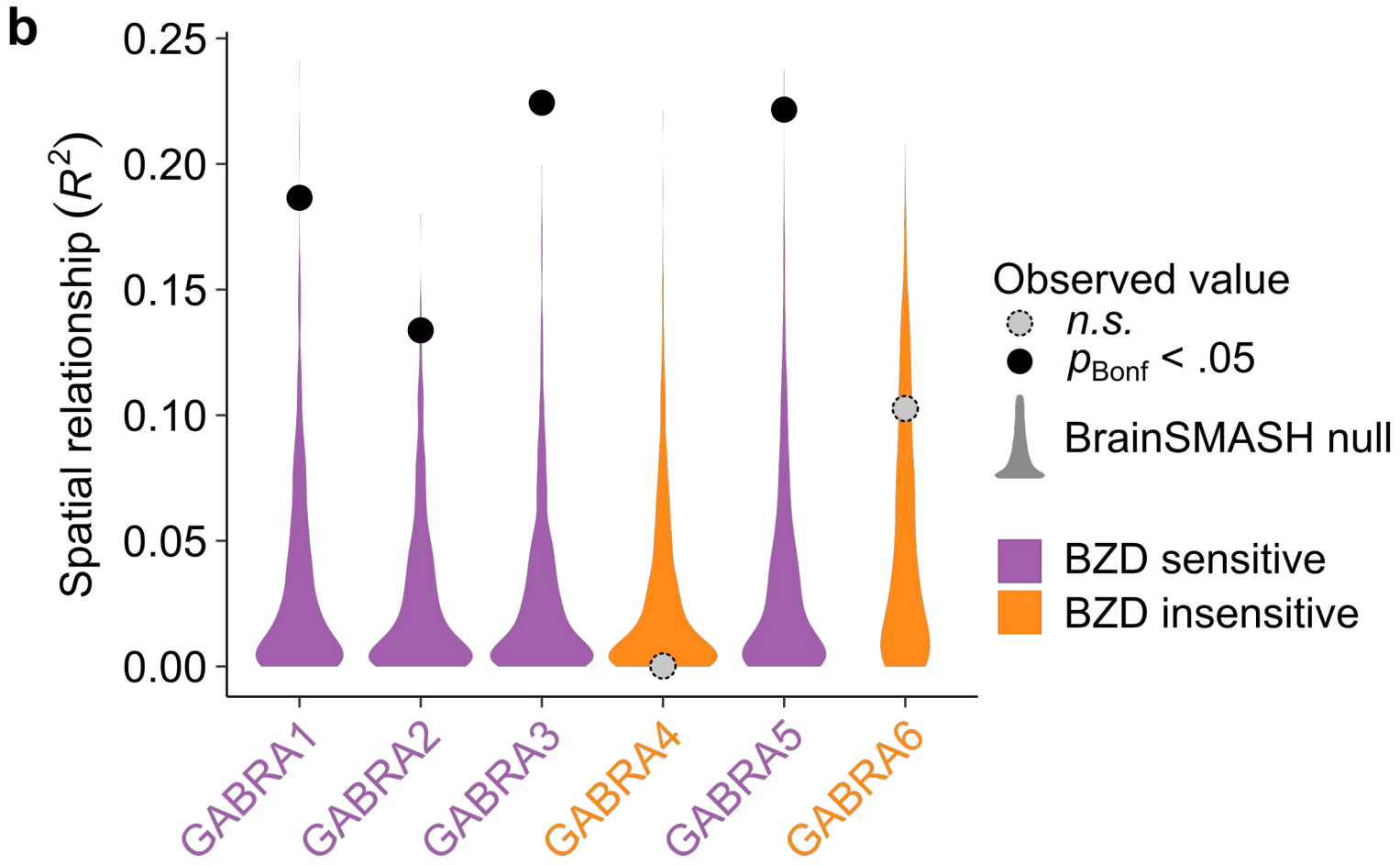
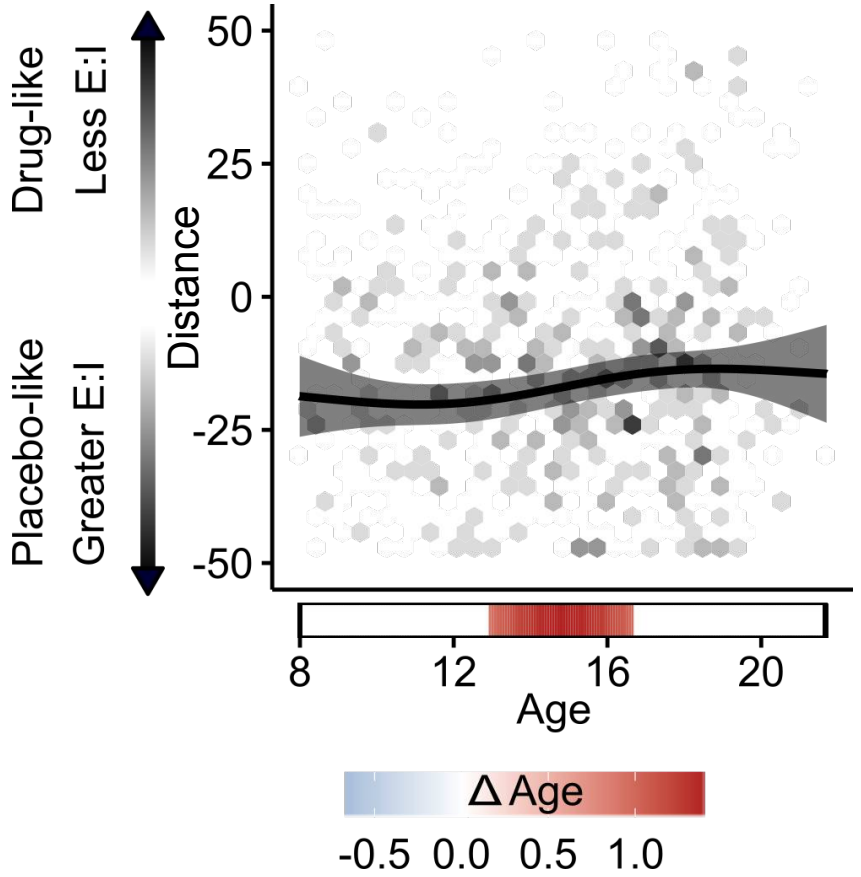


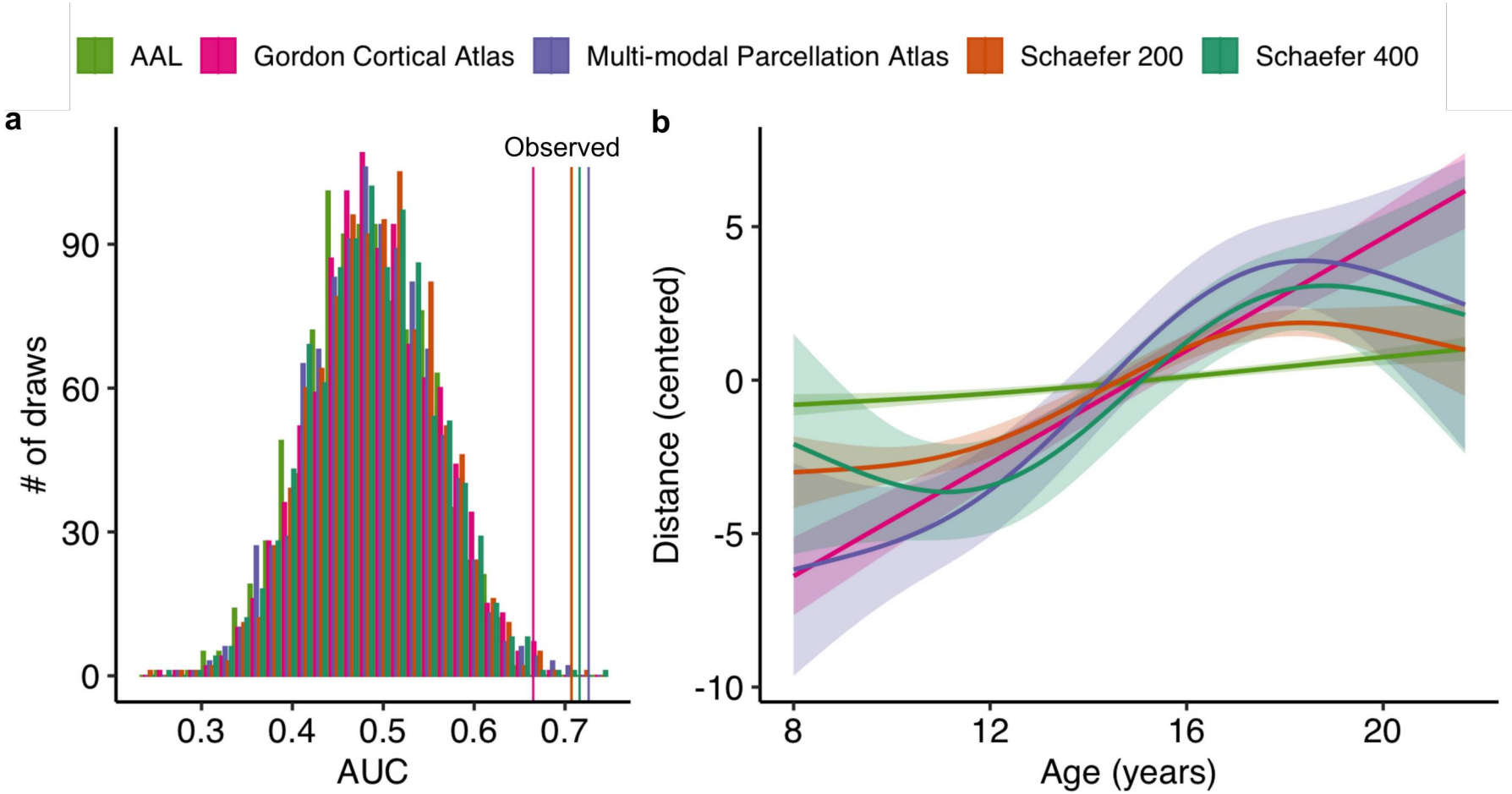
The α1-, α2-, α3- and α5-subunits contain an amino acid residue, histidine, that is vital to the benzodiazepine binding site (Sieghart,

Model predicted E:I decreases with age

- Significant increase from ages 12.9 – 16.7y

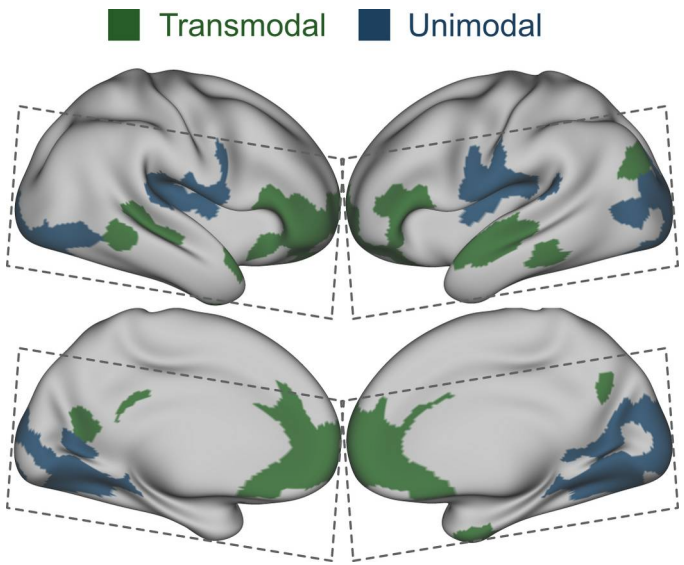


Effects are consistent across alternative parcellations

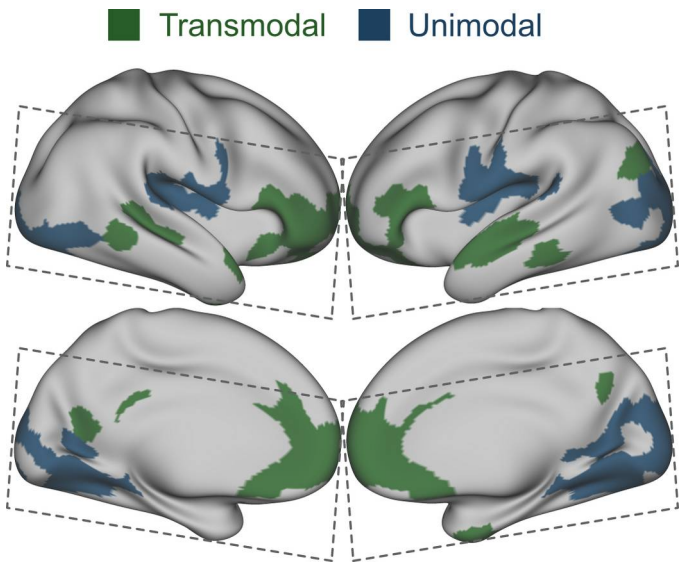


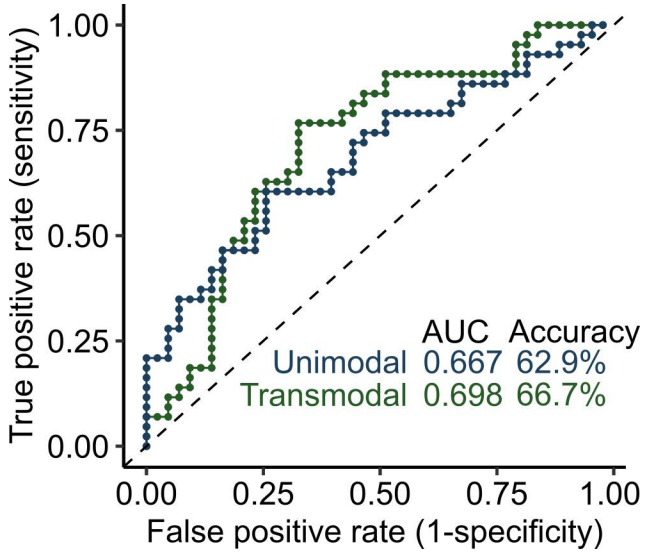
Are age-related reductions in E:I specific to association cortex?

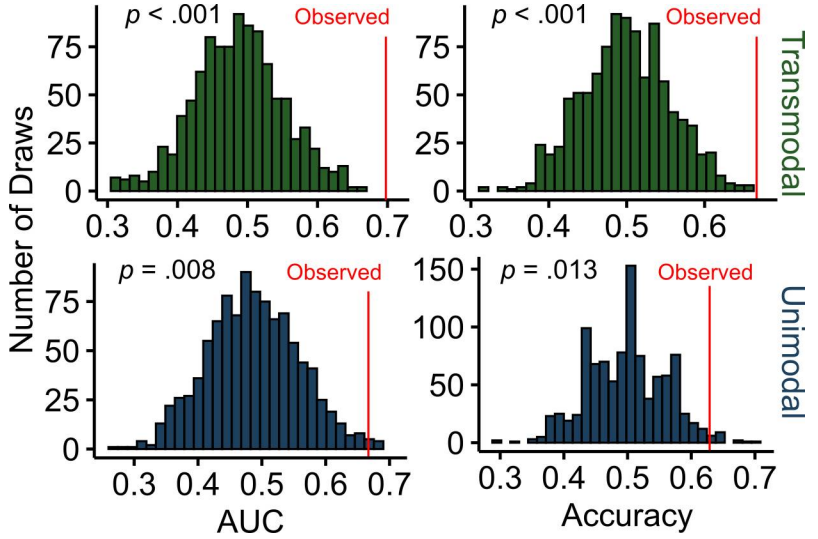
E:I reductions are specific to association cortex



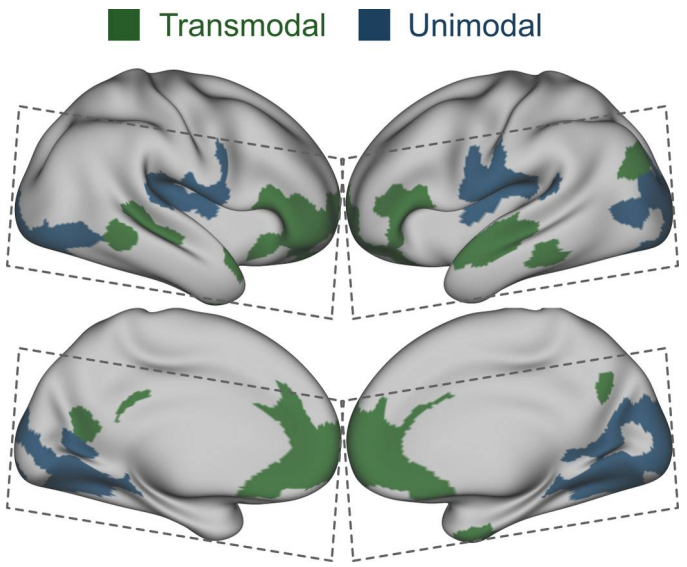
E:I reductions are specific to association cortex

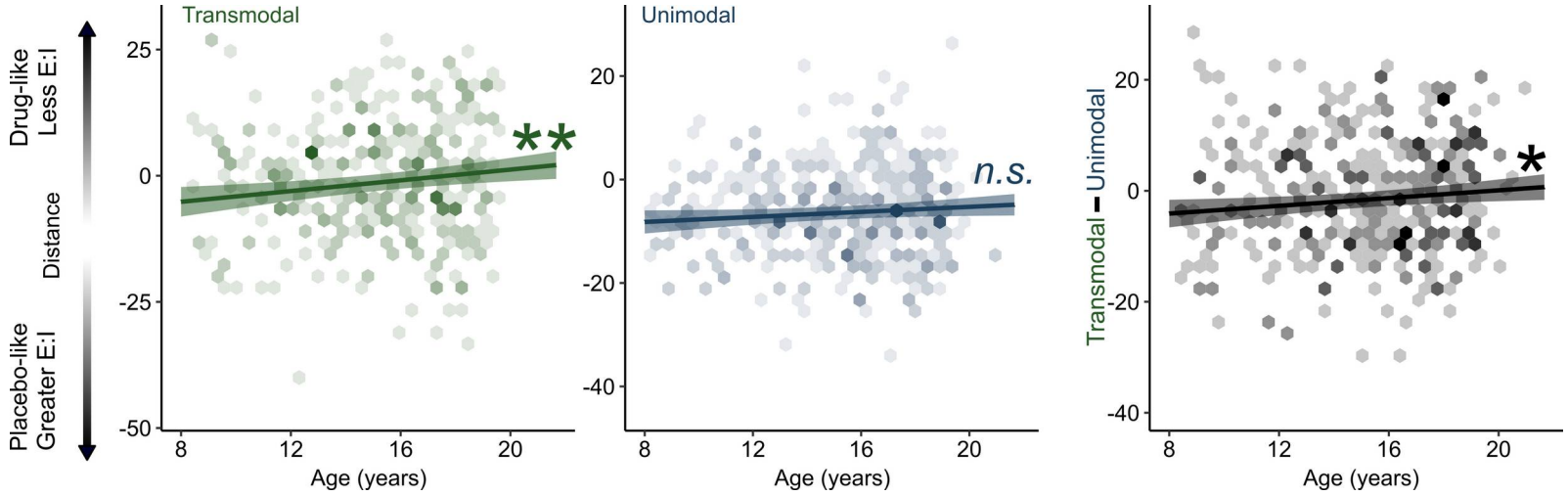






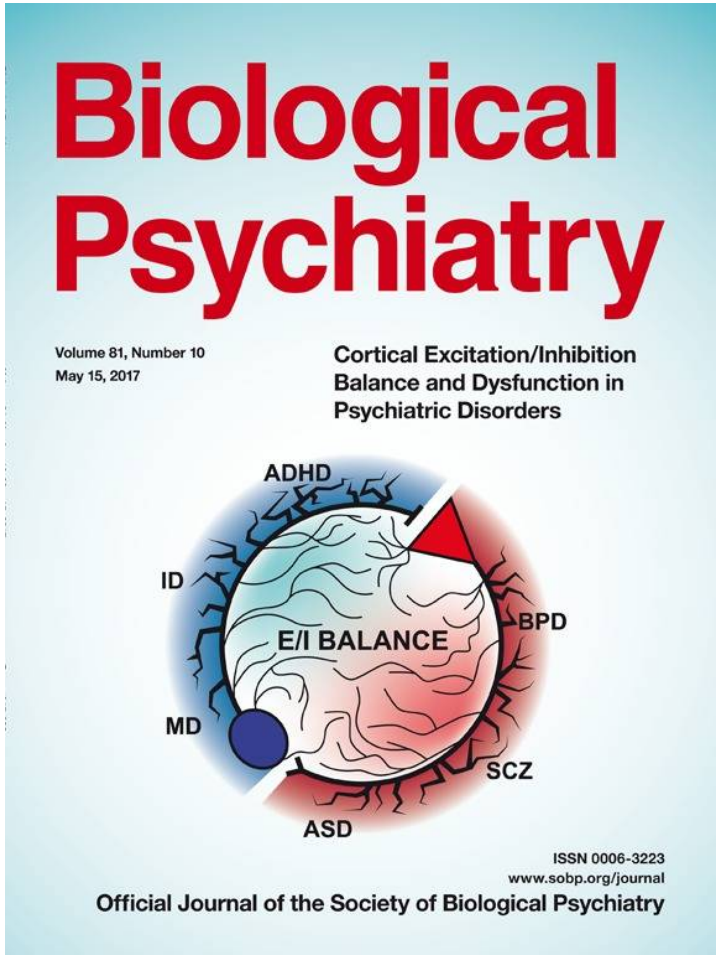
E:I reductions are specific to association cortex





Do differences in E:I explain differences in psychopathology?

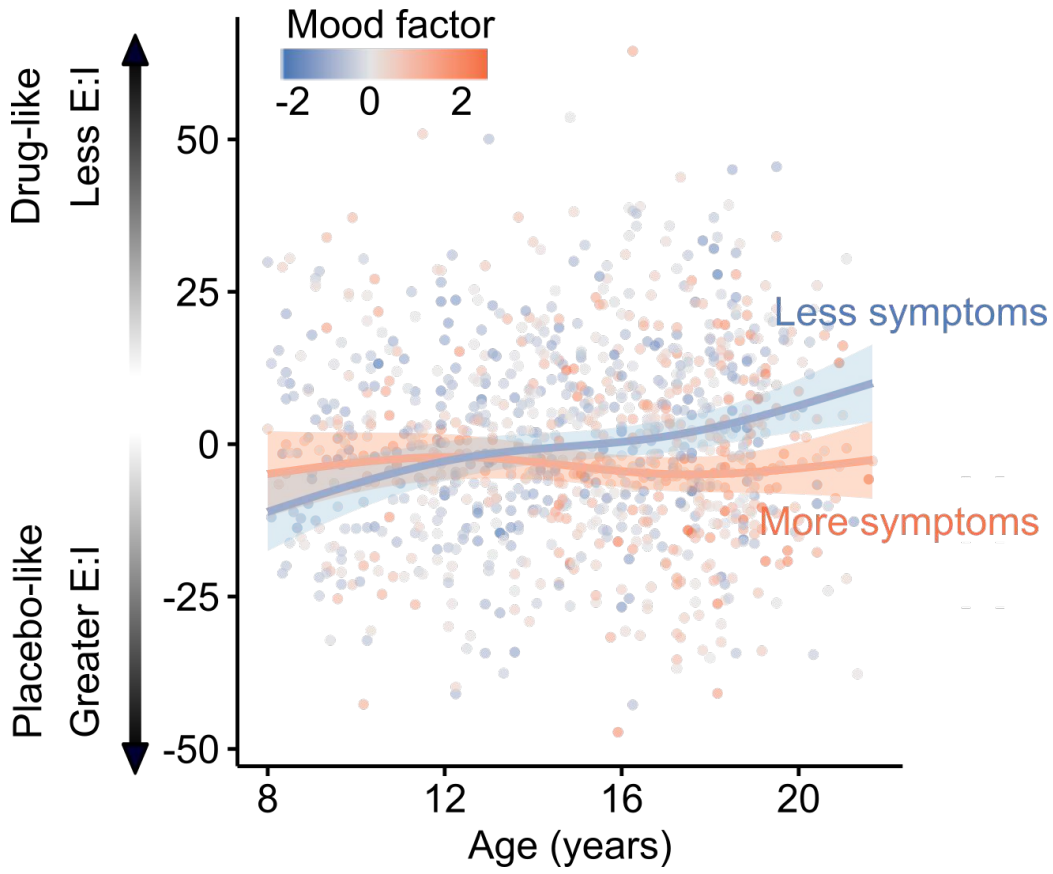
E:I imbalance underlying neuropsychiatric disorders



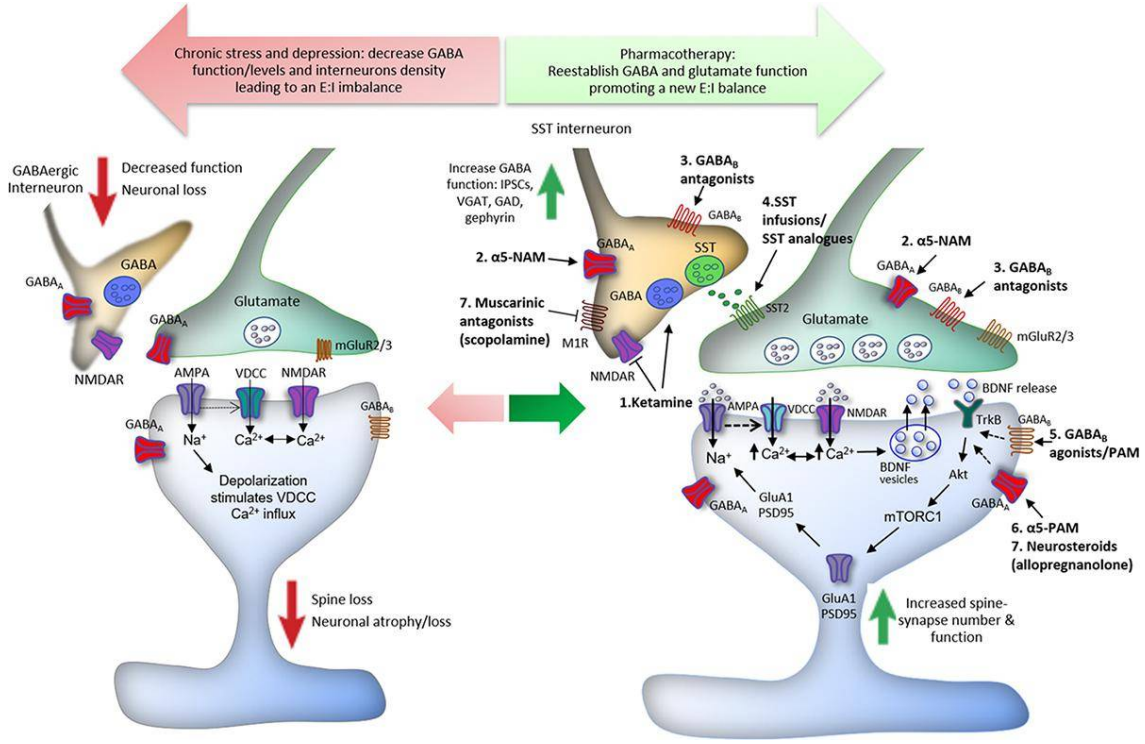
Volume 81, Issue 10. Eds. Anticevic &. Murray

Clinical effects

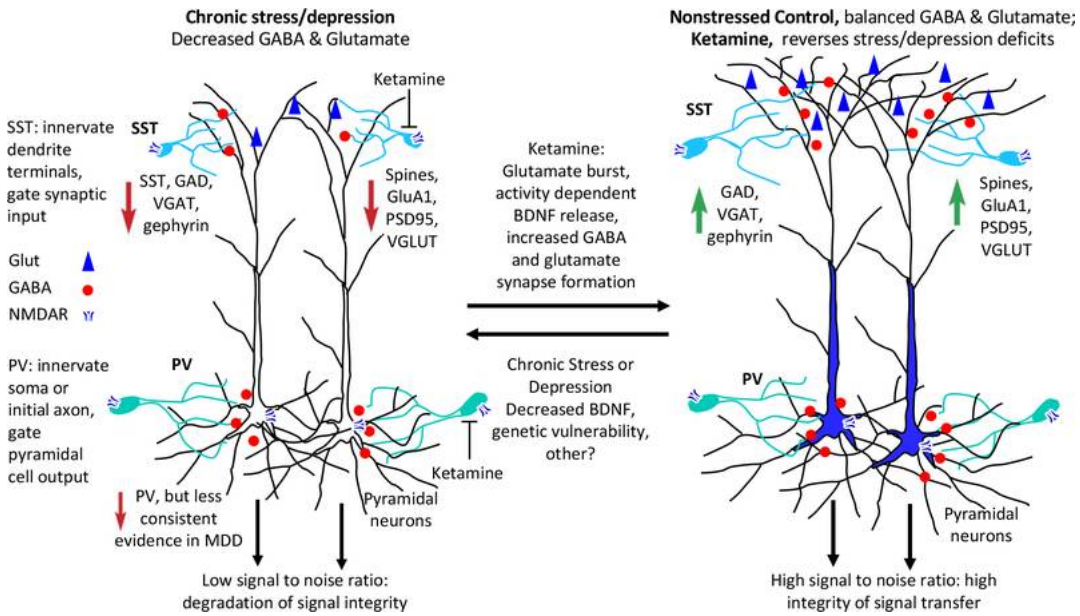
- Developmental reductions of E:I in association cortex are moderated by mood disorder symptom load
  - (Age*mood interaction)



E:I imbalance underlying depression



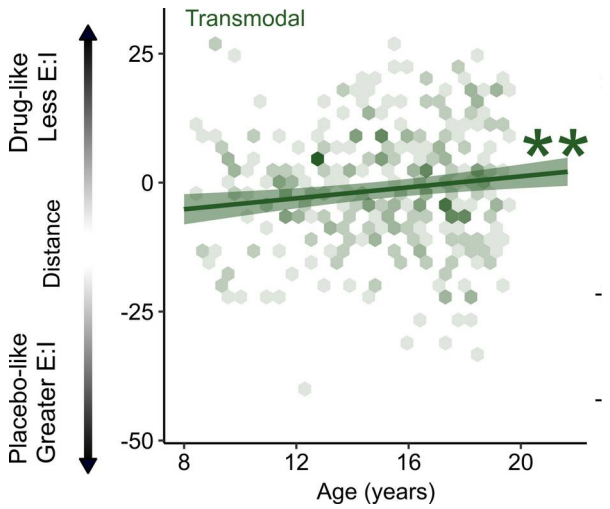
Fogaça & Duman. *Front Cell Neurosci.* (2019)

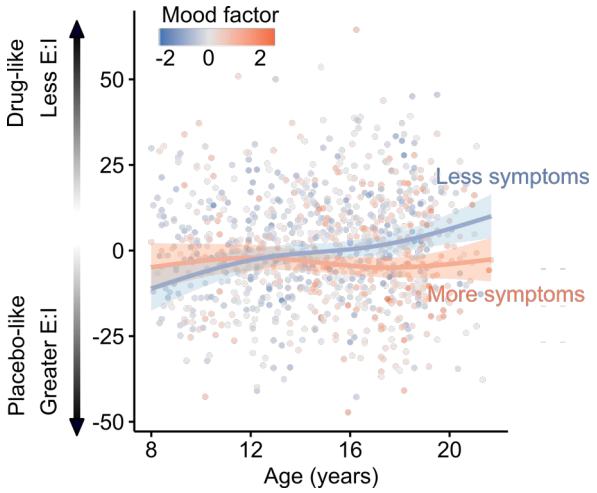


Duman et al. *Neuron* (2019)

Summary

- We observed age-related reductions in model-predicted E:I ratio during adolescence that were specific to association cortex
  - Supports a critical period model of adolescent cortical development
- Greater dimensional mood disorder severity is associated with atypical E:I development
- Using pharma-fMRI to generate neurobiologically relevant models that can be applied to new datasets may be a promising methodological approach





“Drugness” of thalamus connectivity