Developmental sensitive periods and neurobiological mechanisms of stress resilience

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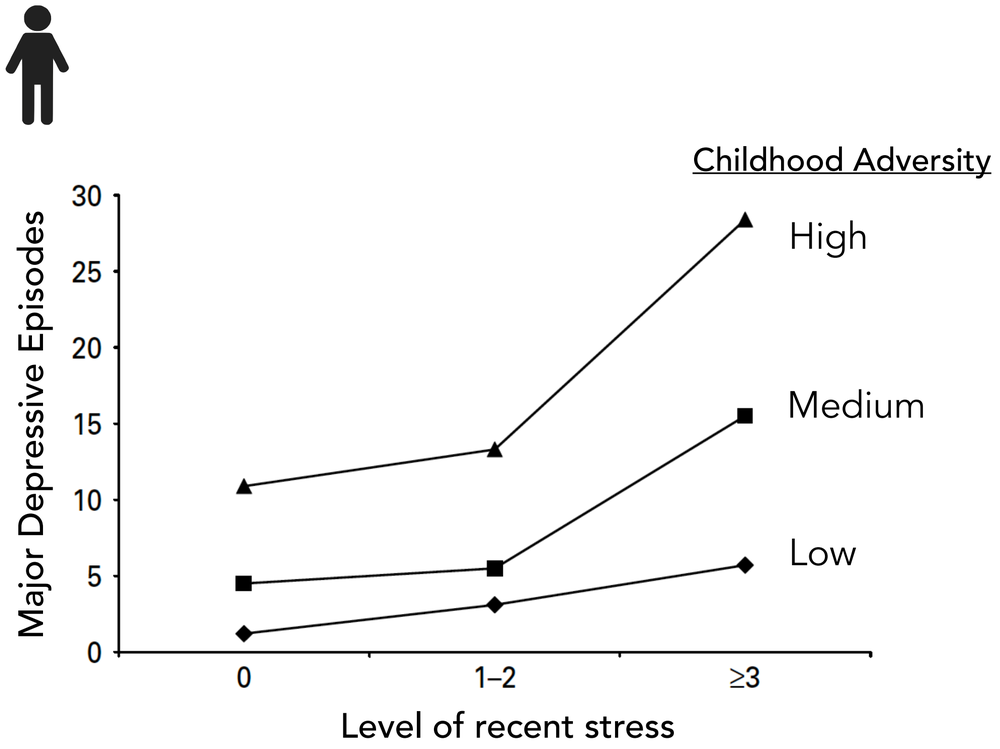
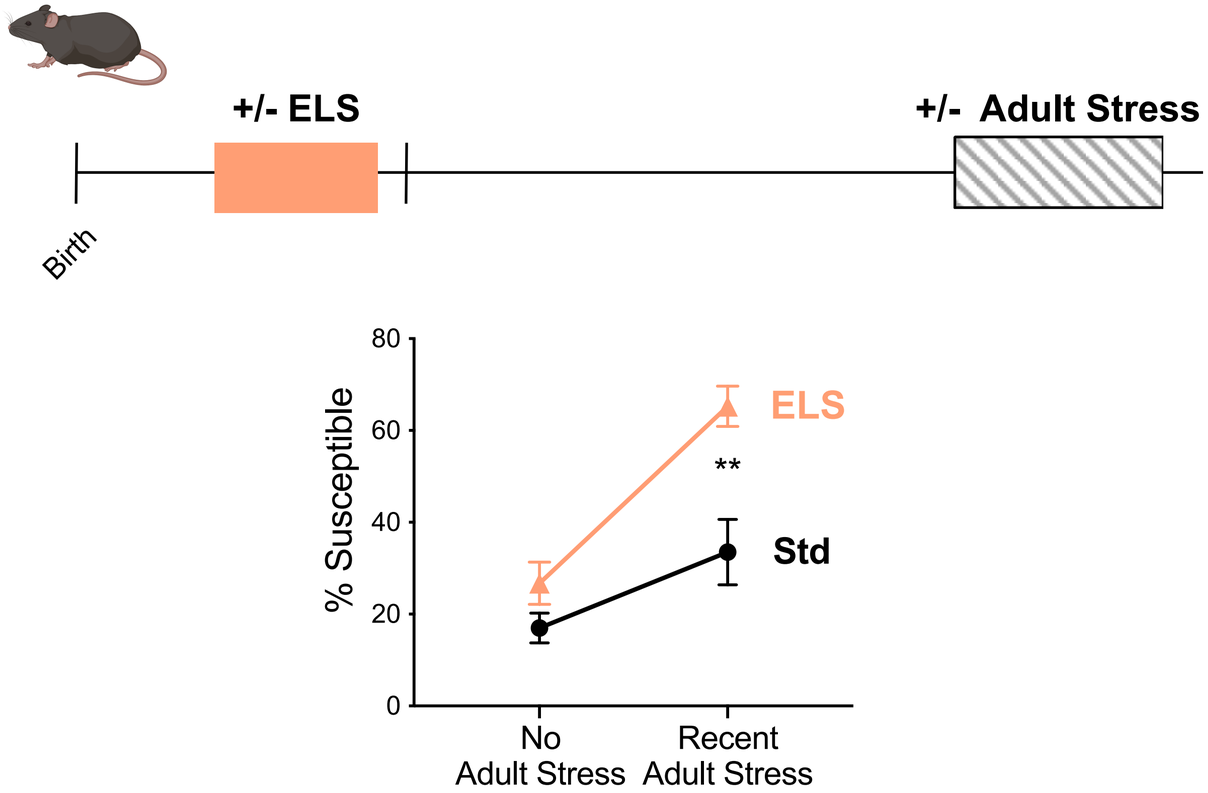
Early Life Stress (ELS) sensitizes response to future stress





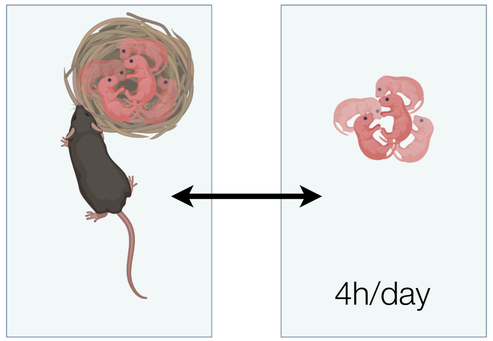
- *Adapted from* McLaughlin et al., 2010
- Sidamon-Eristoff, Cohodes, Gee, **Peña.** *Dev Psychobio* (2021)

- Peña et al., *Science* (2017)
- Peña et al., *Frontiers Behavioral Neuroscience* (2019)
- Peña et al., *Nature Communications* (2019)
- Peña, *Neurobiology of Stress* (2025)

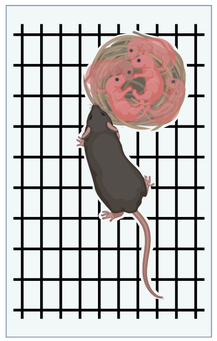
Rodent models of early-life stress and resilience

Standard Rearing

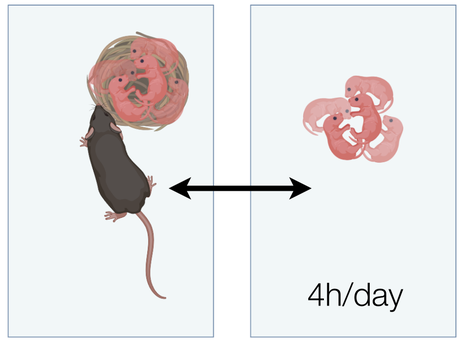
Maternal Separation



Limited Bedding & Nesting



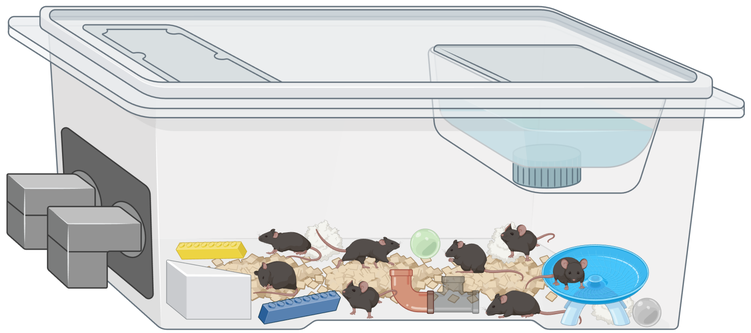
"Multiple ACES"



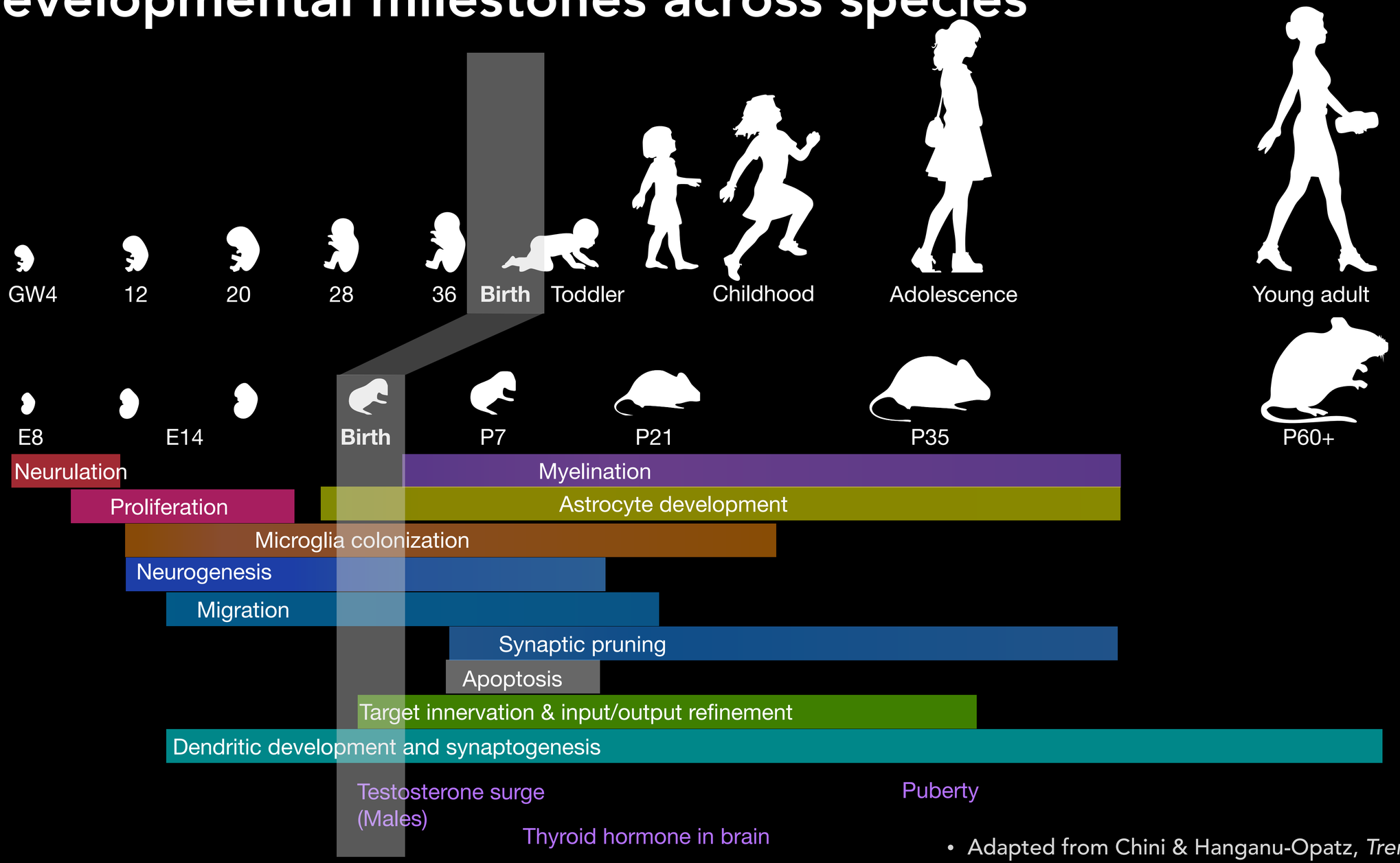
Stress Inoculation

predictable or controllable

Enrichment



Developmental milestones across species



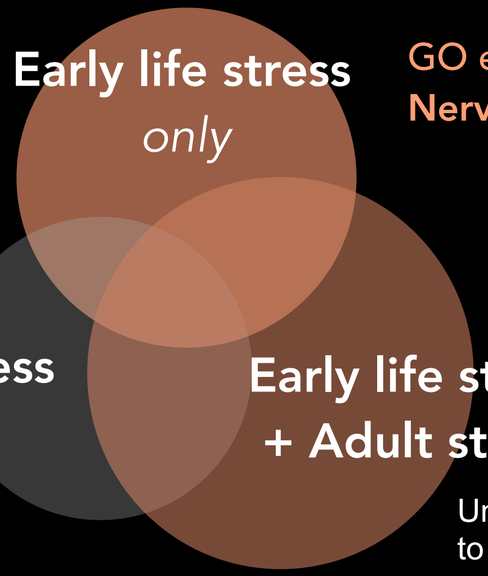
- Adapted from Chini & Hanganu-Opatz, *Trends in Neuro* (2021)
- Peña, *Neurobiology of Stress* (2025)

How does early-life experience prime later stress response?

- ➡ Cellular level
- ➡ Molecular level

Long-lasting molecular changes across brain regions

RNA-seq
Δ gene exp.



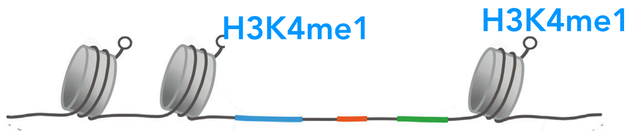
GO enrichment:
Nervous system development

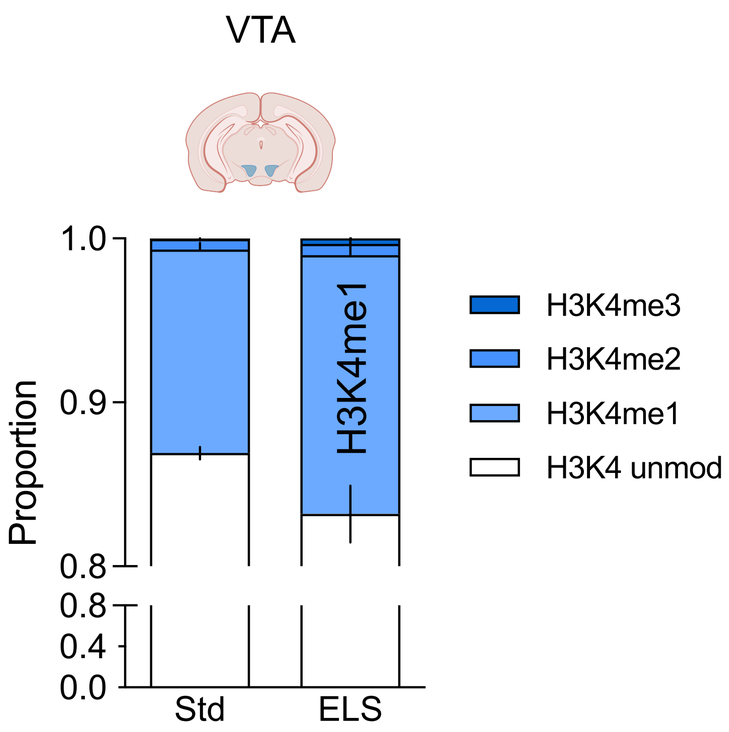
Unique response
to adult stressors

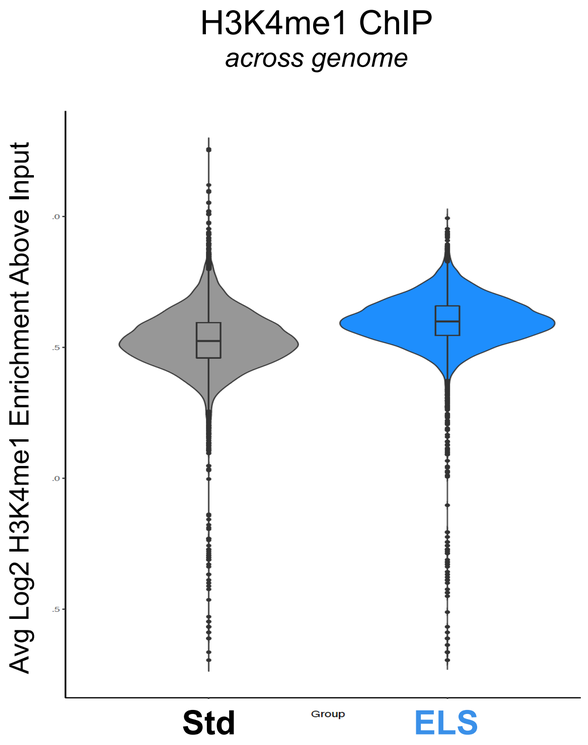
GO enrichment:
Response to stimulus

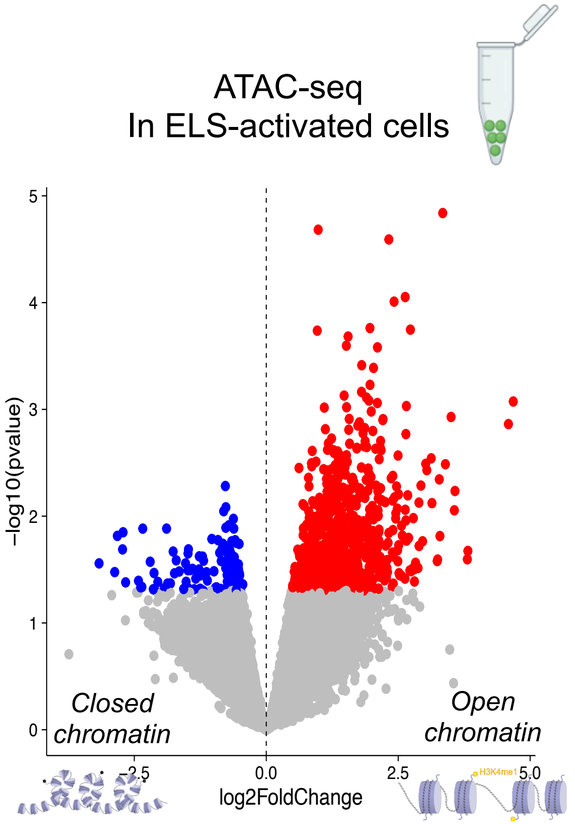
- Peña et al., *Science* (2017)
- Peña et al., *Nature Communications* (2019)

Early-life stress primes the epigenome



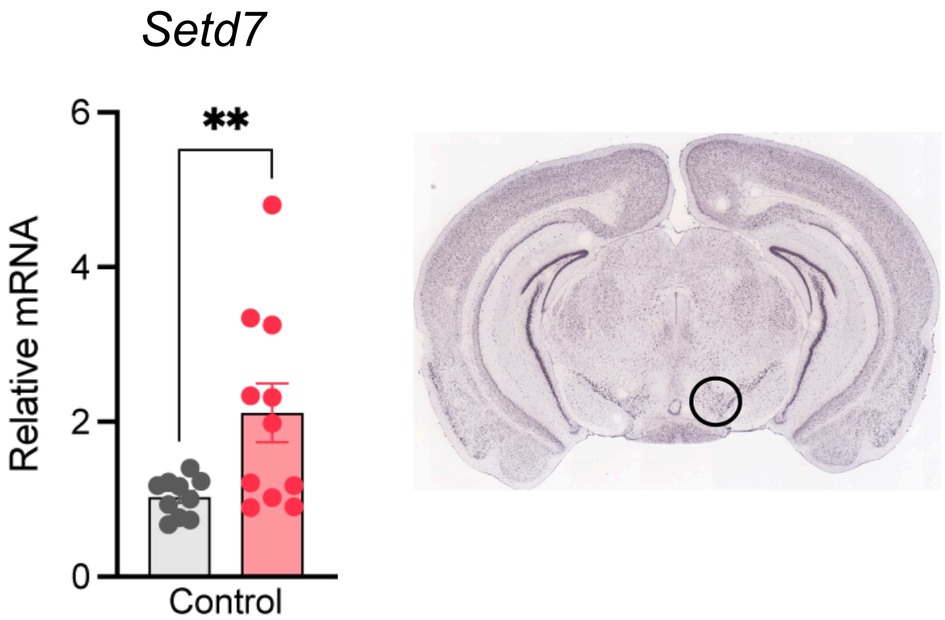


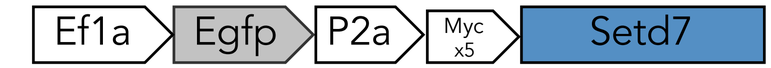


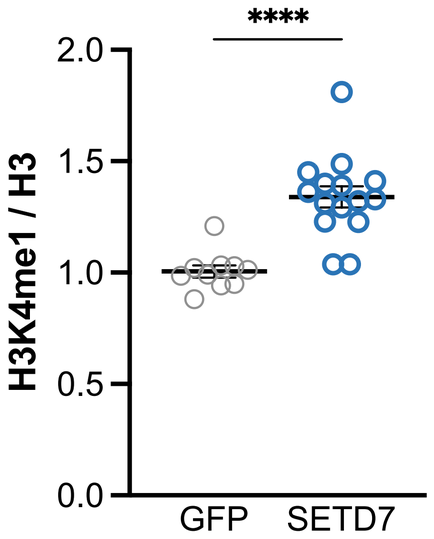


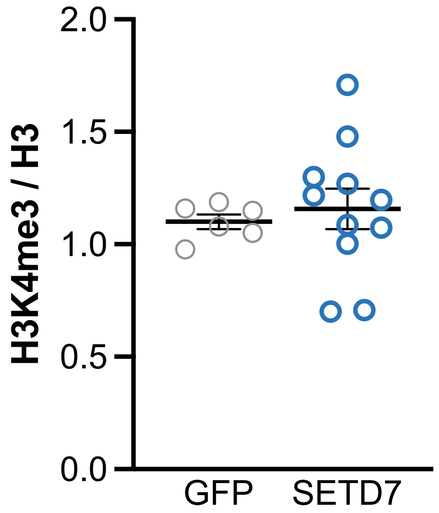
- Geiger, Balouek et al. *BioRxiv 2024*
- Rashford et al. *BioRxiv 2024*

Epigenome priming increases stress sensitivity





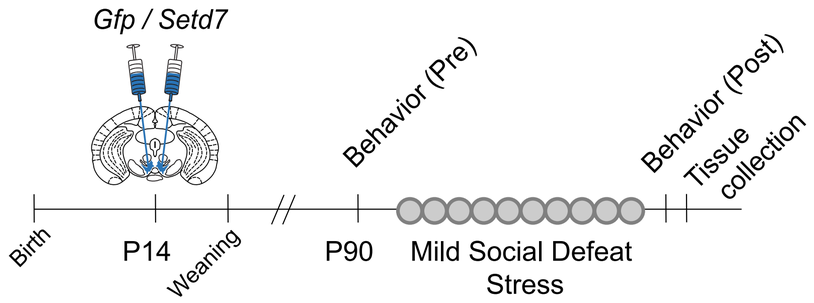




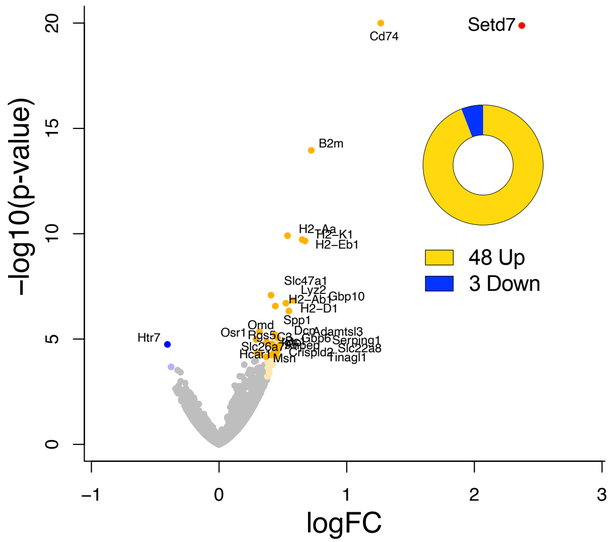
ELS elevates the enzyme that catalyzes H3K4 monomethylation

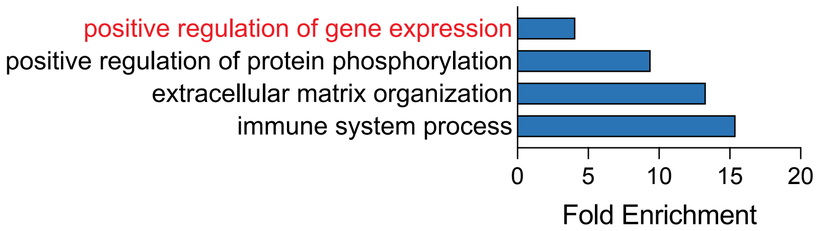
- Geiger, Balouek et al. *BioRxiv 2024*

Epigenome priming increases stress sensitivity

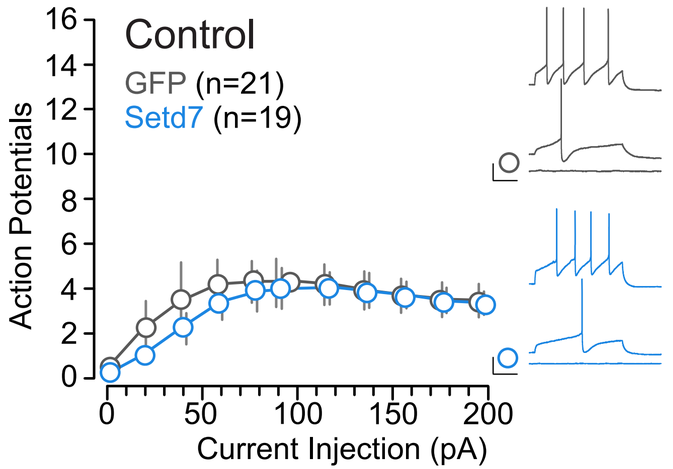


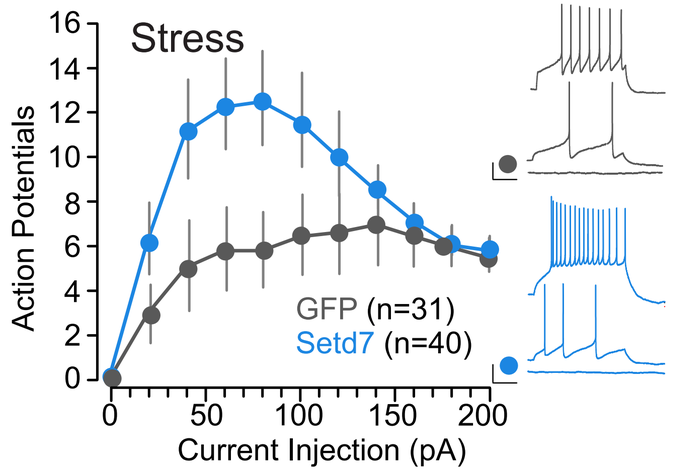
Transcription



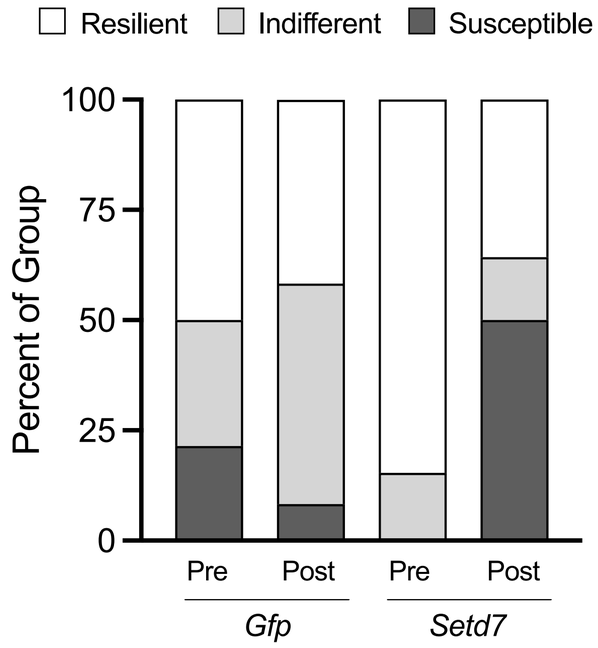


Physiology





Behavior

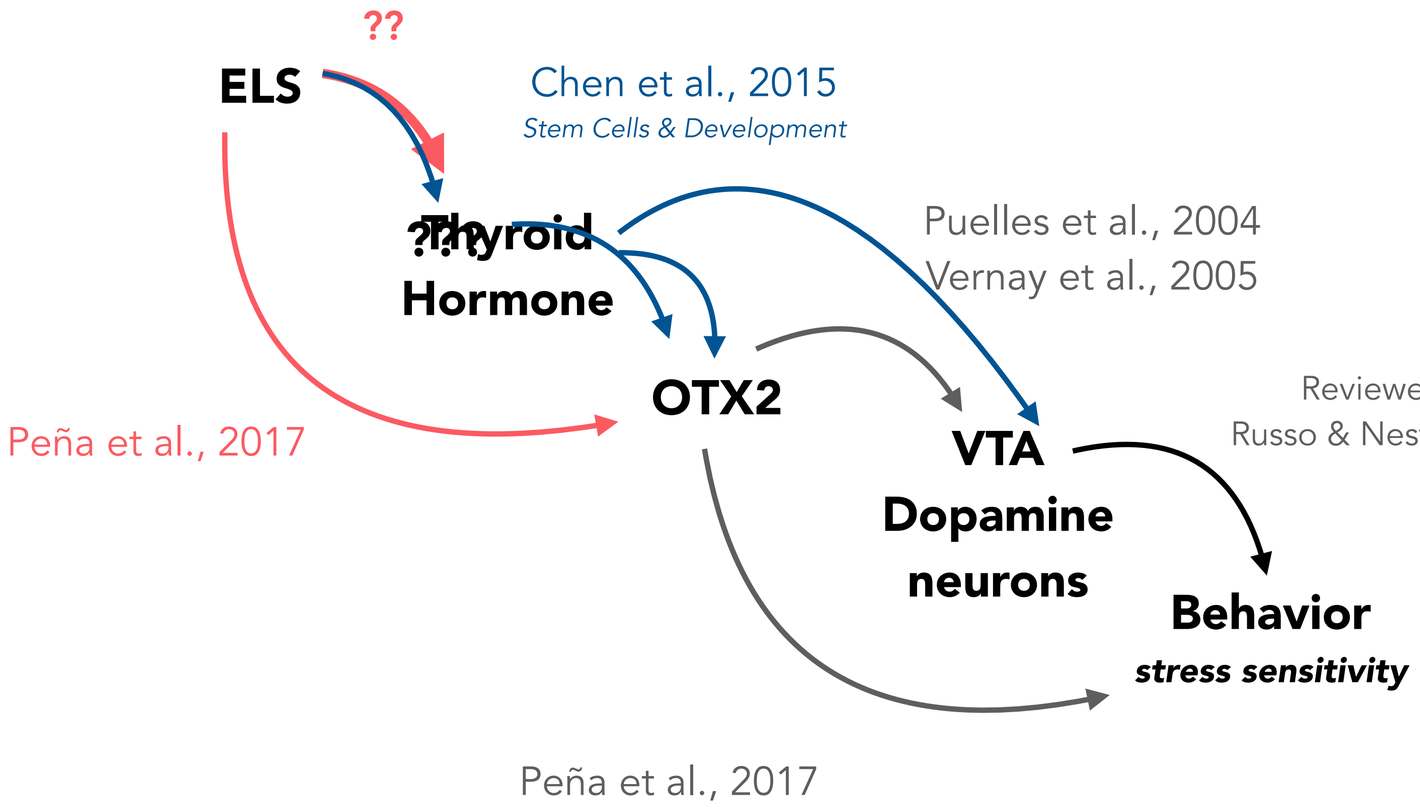


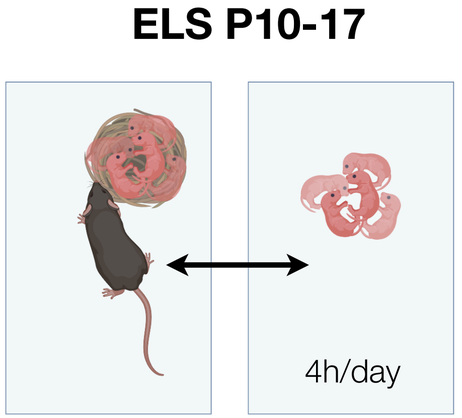
- Geiger, Balouek et al. *BioRxiv 2024*

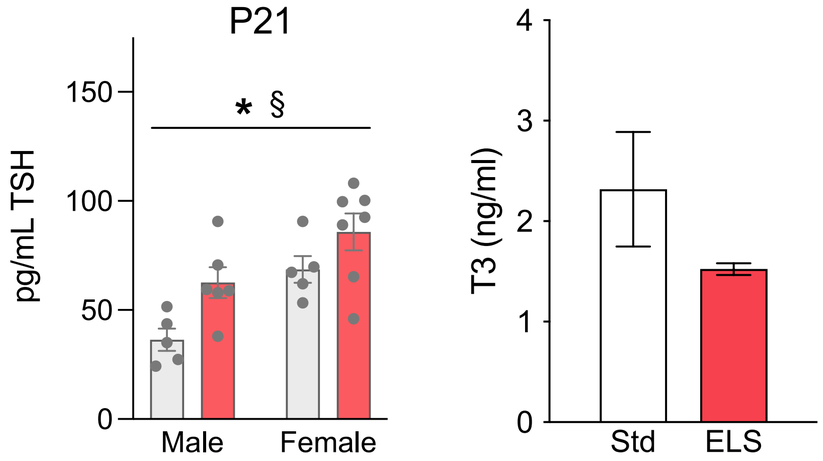
Epigenome priming: an opportunity for resilience?

- Can epigenome priming (by stress?) also prime response to enrichment and positive experiences?

Upstream regulation by thyroid hormones







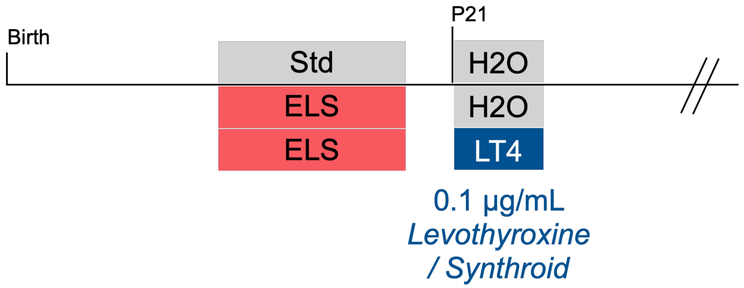
Early life trauma is associated with decreased peripheral levels of thyroid-hormone T3 in adolescents

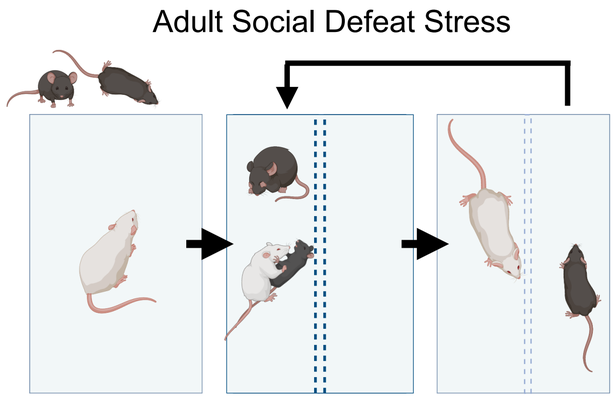
T.D. Machado[a,*], G.A. Salum[b], V.L. Bosa[a], M.Z. Goldani[a], M.J. Meaney[c,d], M. Agranonik[e], G.G. Manfro[b], P.P. Silveira[a]

Table 1
Characteristics distribution of the subjects for T3 and T4.

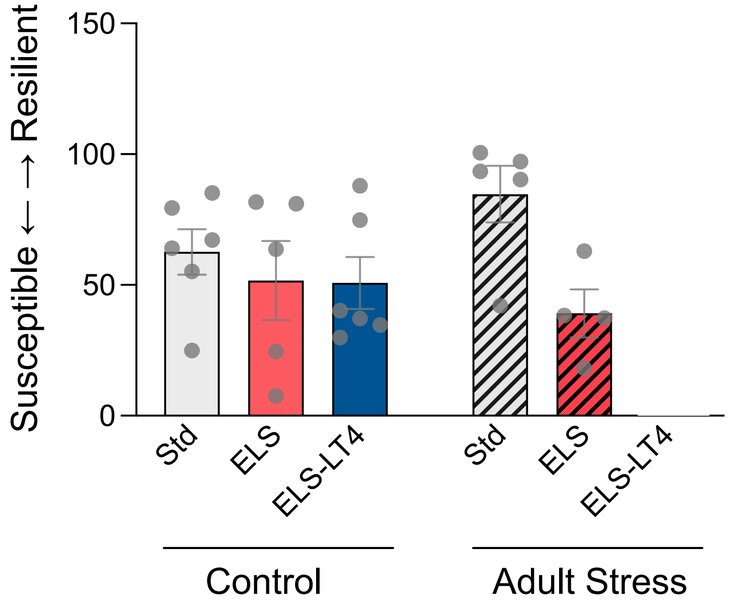
	T3			
	N	Mean	SD	*p*-Value
CTQ-physical abuse score				0.004**
Low	44	152.3[a]	30.38	
Intermediate	10	158.7[a]	27.95	
High	26	130.4[b]	24.75	
Pubertal status				0.002**
Pre-puberty	14	159.7[a]	28.31	
Puberty	31	154.2[a]	28.67	
Post-puberty	35	133.2[b]	27.77	
Gender				0.292*
Male	29	150.7	27.71	
Female	51	143.3	31.36	
Socioeconomic status				0.036*
Low	24	135.2	28.53	
High	56	150.6	29.85	
BMI	80	$r = 0.246$		0.028#

Promoting resilience after stress by restoring thyroid hormones





Behavior



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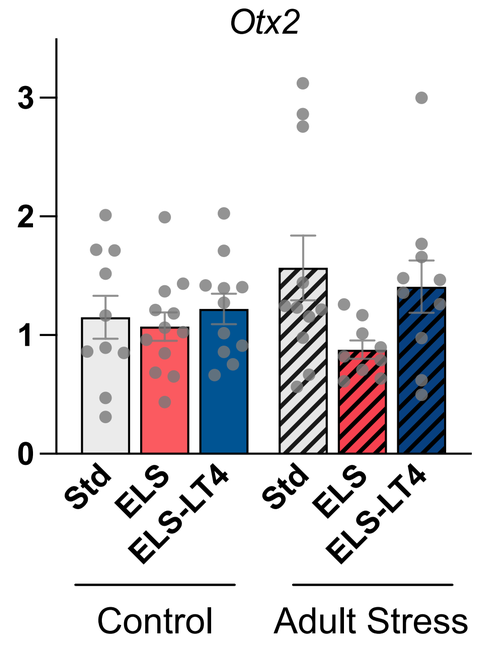
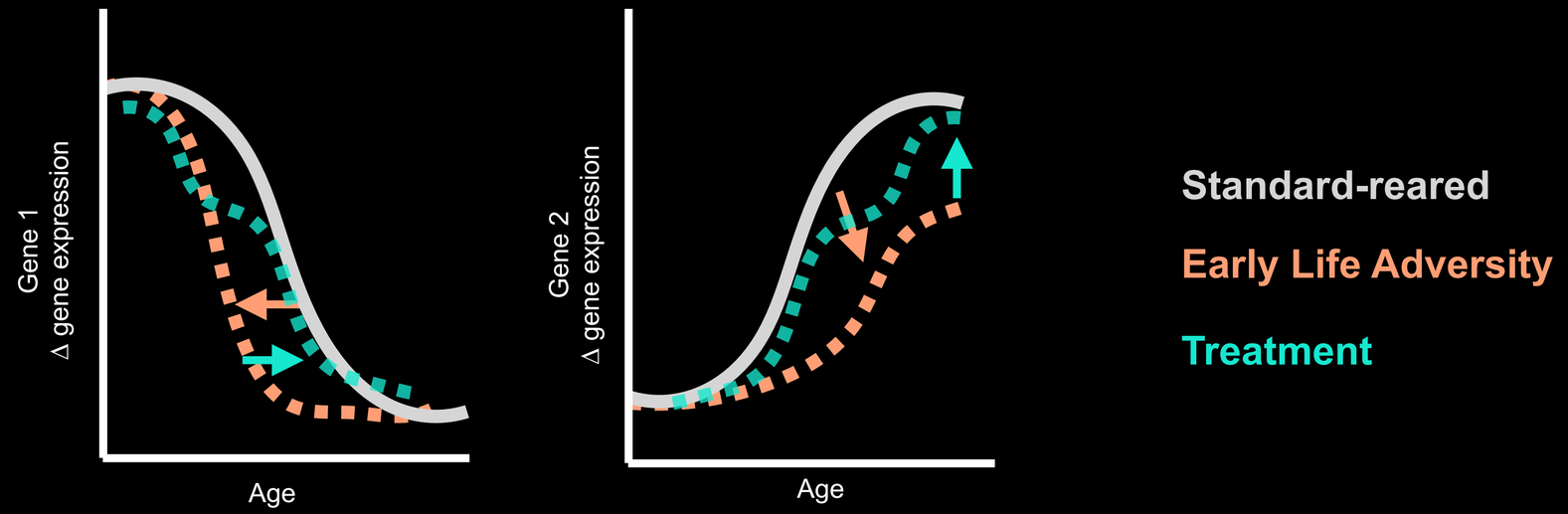


- Bennett, Chang et al., *Hormones and Behavior* (2024)
- And unpublished

Gaps: targeting brain development itself to restore resilience



- Can targeting upstream regulators of brain development (e.g., thyroid hormones) *re-align* these trajectories and prevent a plethora of risks?