Loss of VLDLR & ApoER2 Alters Circuit-Level Neural Activation in Response to Acute Stress

Aleah Ryan[1] · **Faculty mentor: Xuanmao Chen**[1,2]

[1] Neuroscience & Behavior, University of New Hampshire [2] BMCB / COLSA, Chen Lab, University of New Hampshire

Background & Rationale

Reelin signaling wires the developing brain and is linked to disease

- Wires the developing brain
- Active throughout life
- Linked to schizophrenia and Alzheimer's disease

Reelin

ApoER2 loss

IN DEVELOPMENT
Late-born neurons fail to migrate past earlier-born ones

IN THE ADULT BRAIN
Supports neuronal survival and plasticity

VLDLR loss

IN DEVELOPMENT
Neurons overshoot their stopping point

IN THE ADULT BRAIN
Role in the adult brain poorly understood

QUESTION:

Does this receptor divergence shape how the adult brain's stress circuits respond?

Key Terms

KO knockout: mice lacking that receptor

c-Fos marks recently active neurons

PVN hypothalamic hub that starts the stress response

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Key references

Trommsdorff et al. (1999) Cell 97:689
Hack et al. (2007) Development 134:3883
Beffert et al. (2006) Curr Biol 16:2446
Lane-Donovan & Herz (2017) J Lipid Res 58:1036
Sharaf et al. (2013) PLoS ONE 8:e71091
Sánchez-Hidalgo et al. (2022) Front Neuroanat 16

Methods

Acute footshock, then c-Fos mapping across four stress-relevant regions

Experimental design

	Baseline (unstressed)	90 min post-stress	~4–6 h post-stress
Wild-type	●	●	●
ApoER2 KO	●	●	●
VLDLR KO	●	●	●

Trace fear conditioning (mild footshock)

Acclimate	Tone	Wait	Shock	Interval
2–4 min	15 s	30 s	0.7 mA · 1 s	100–300 s

Tone–shock pair repeats 7 times

Regions imaged

1. Hippocampus
2. Amygdala
3. Prefrontal cortex
4. PVN

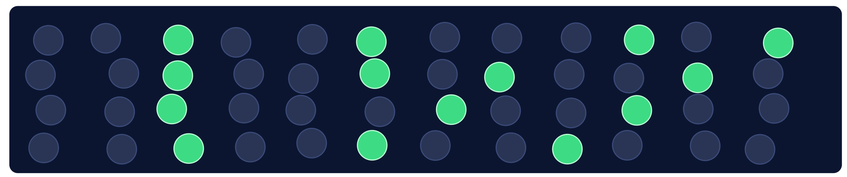
From tissue to data

1. Perfuse and section the brain
2. Stain for c-Fos (IHC) and GM130 (Golgi)
3. Image with confocal microscopy
4. Count c-Fos+ cells (manual + semi-automated)
5. Stats: two-way ANOVA, genotype × timepoint

Why c-Fos?

c-Fos marks recently active neurons, so we will use it to map the stress response

1. Footshock stress activates neurons
2. Active neurons rapidly make c-Fos protein
3. Stain + confocal: active nuclei glow, and we count them



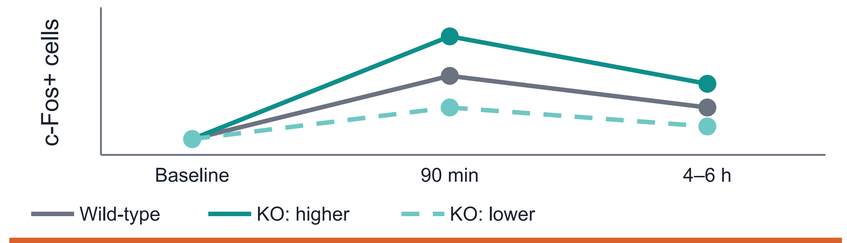
● c-Fos+ (recently active) ● c-Fos− (not labeled)

Illustration only, not data. Schematic of how c-Fos+ nuclei will appear in a stained section.

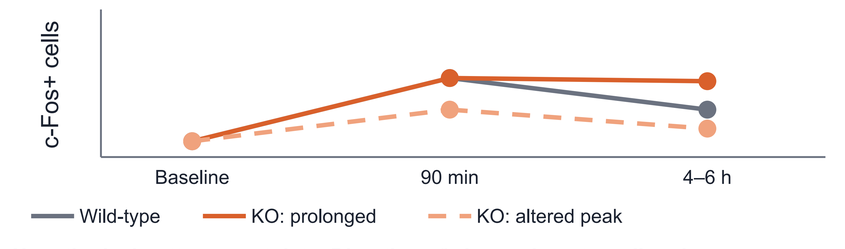
Hypotheses & Expected Results

Receptor loss changes how strongly or how long neurons respond to stress.

ApoER2 KO: altered magnitude



VLDLR KO: magnitude or persistence?



Hypothetical patterns, not data. Direction of change is not predicted.