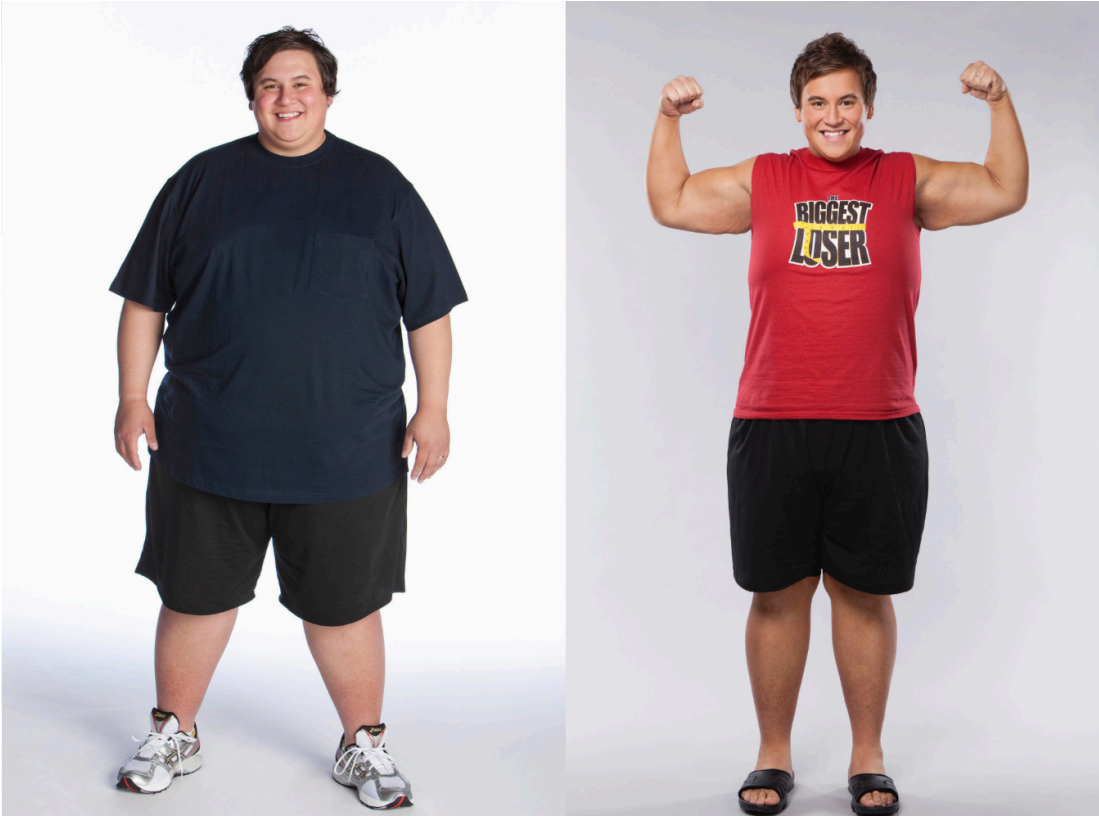


# Dieting is really, really hard

Sean Algaier, *The Biggest Loser*, 2009



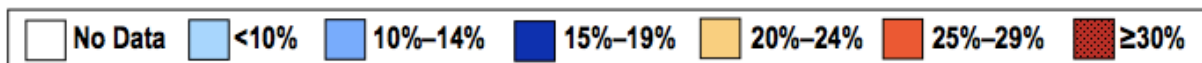
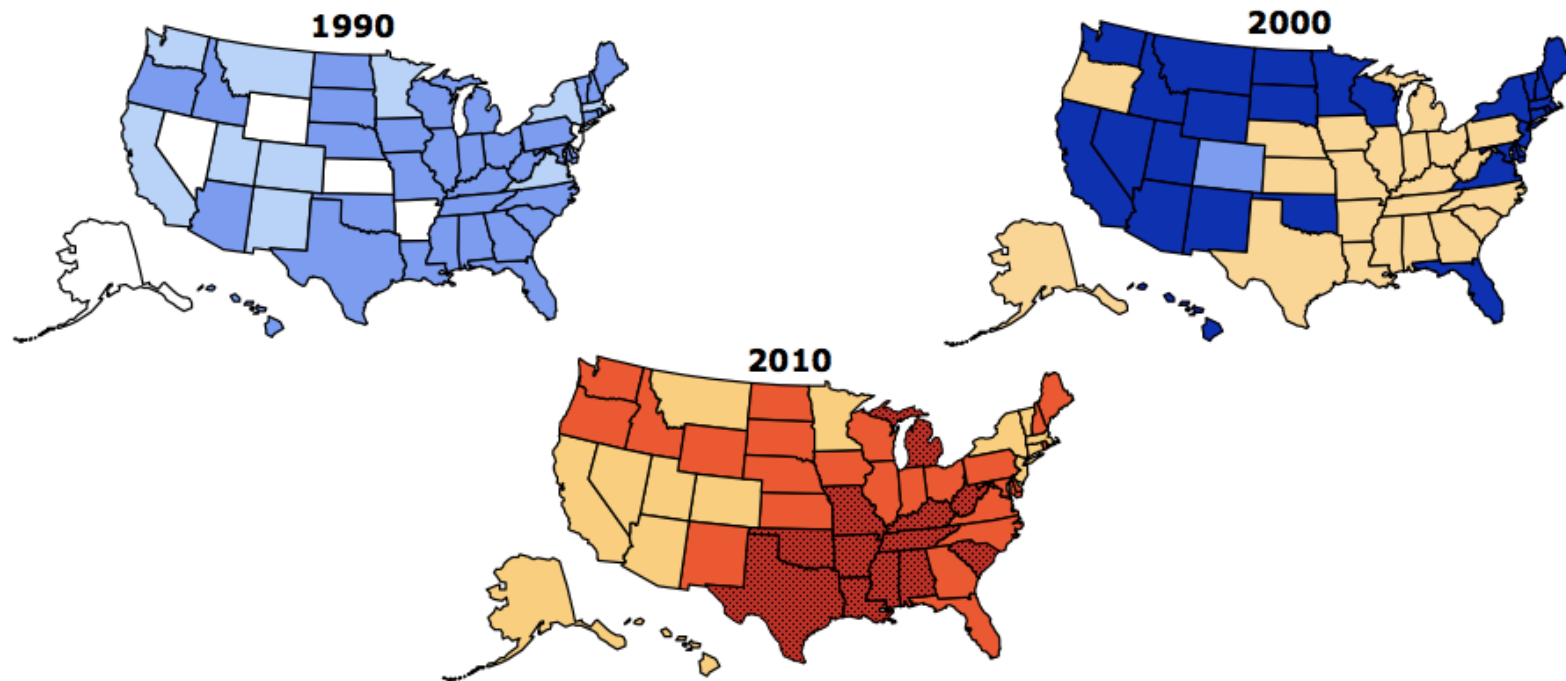
**Start:**  
**444 lbs**

**End:**  
**289 lbs**

# Obesity rates have risen dramatically

## Obesity Trends\* Among U.S. Adults BRFSS, 1990, 2000, 2010

(\*BMI  $\geq 30$ , or about 30 lbs. overweight for 5' 4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

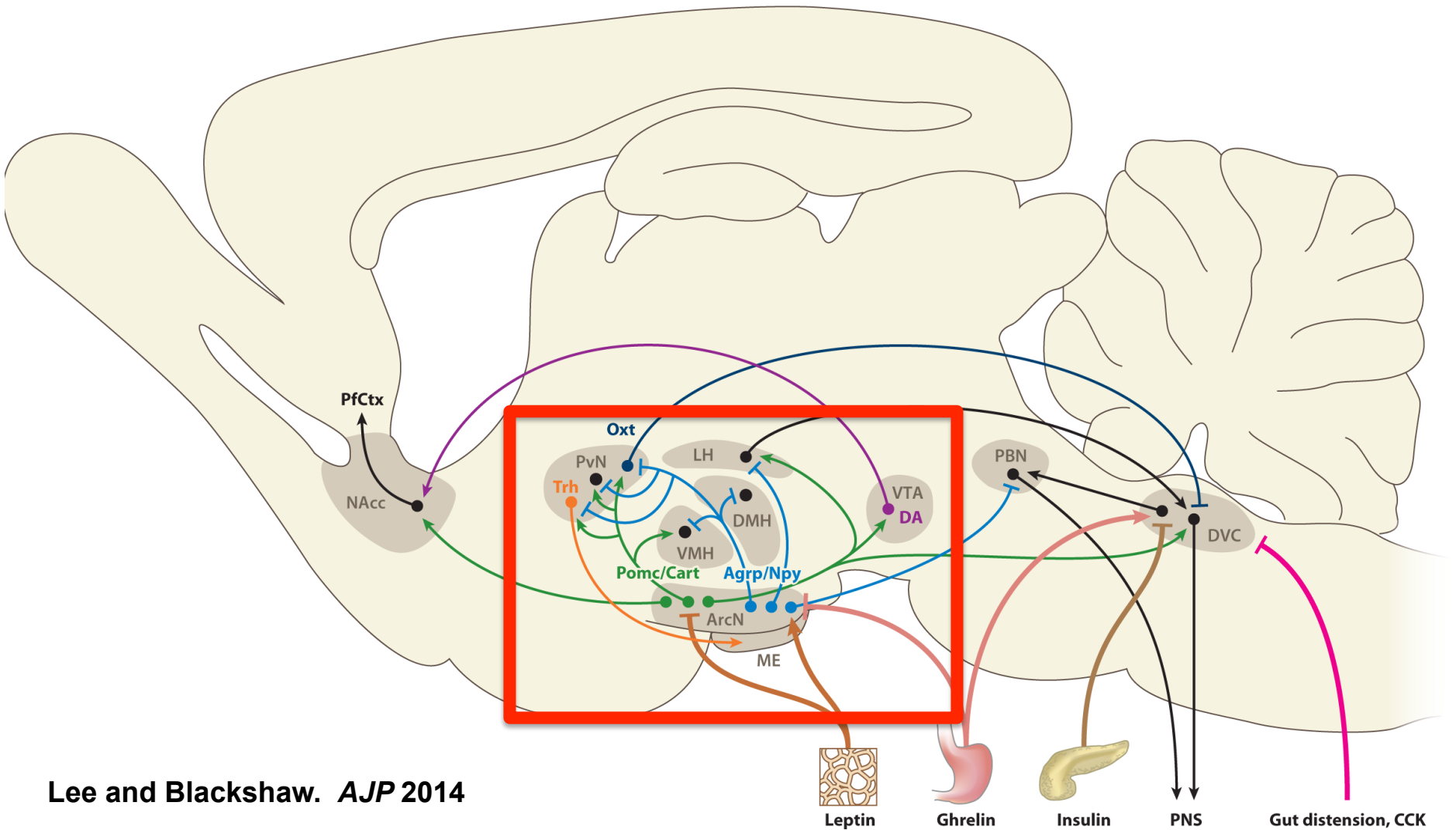
# Early postnatal diet can have life-long effects on metabolism

Underfeeding

Overfeeding

High fat diet

# Rewiring neural circuitry that regulates body weight



Lee and Blackshaw. *AJP* 2014

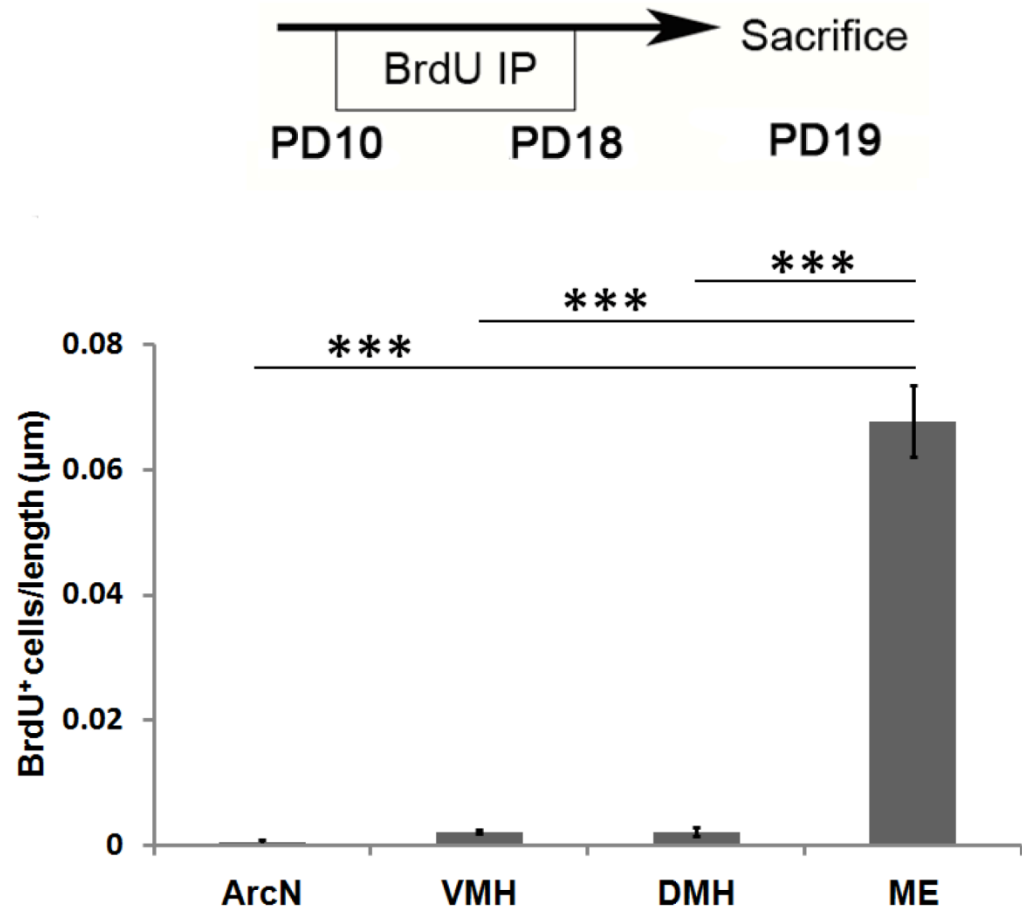
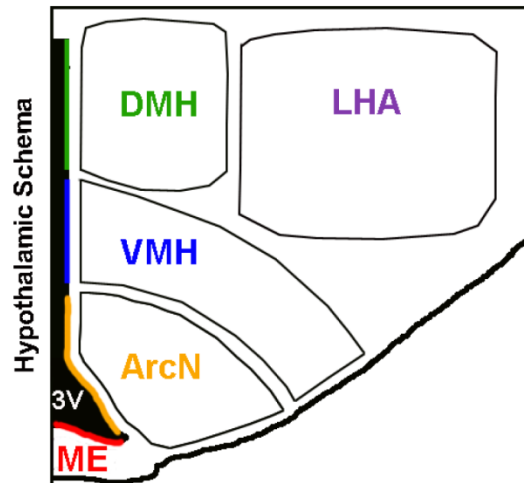
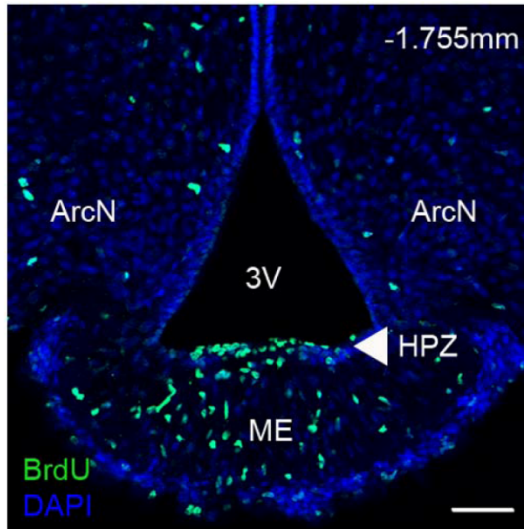
Altered neuronal activity

Selective neuronal death

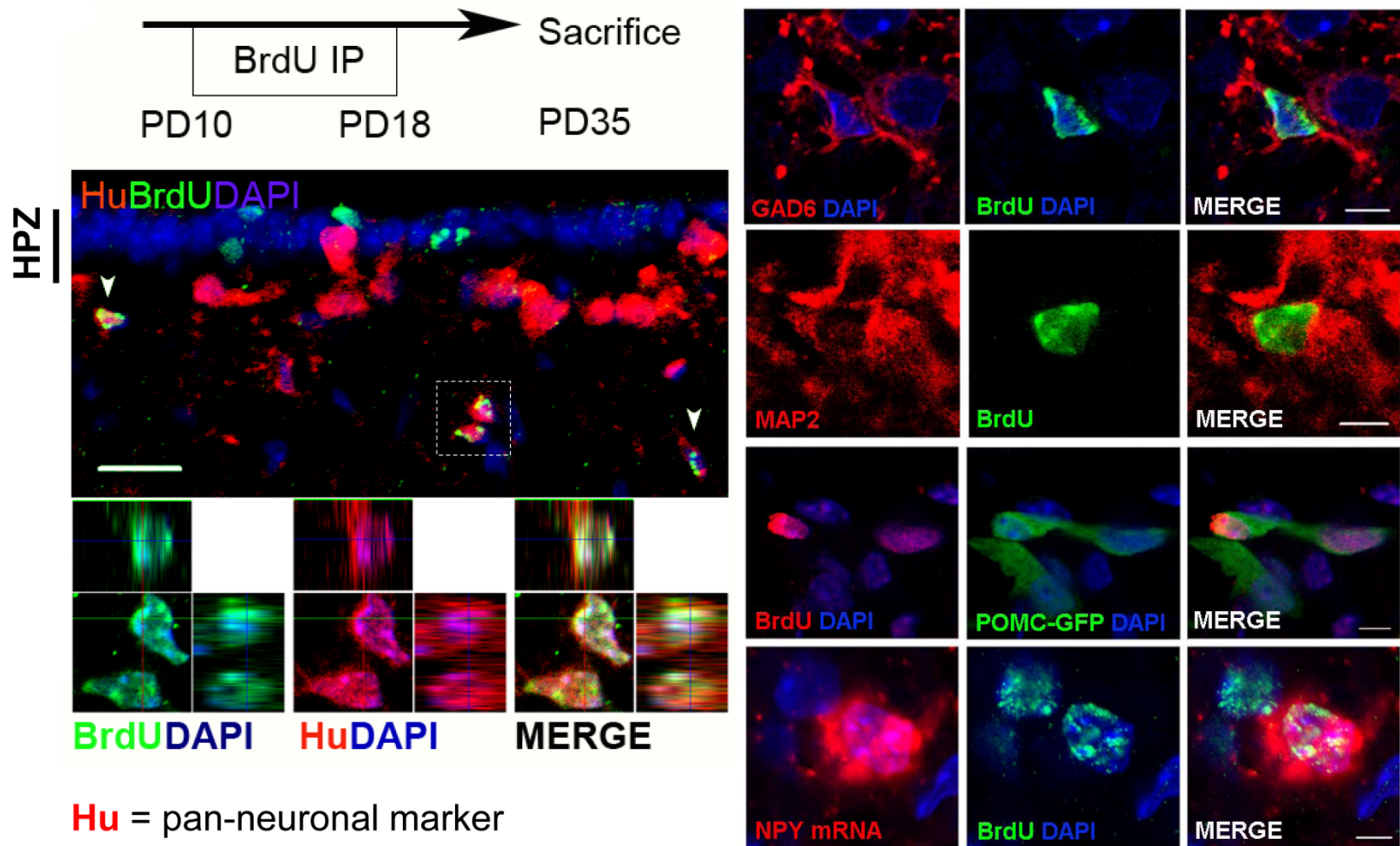
Altered neural connectivity

Postnatal neurogenesis

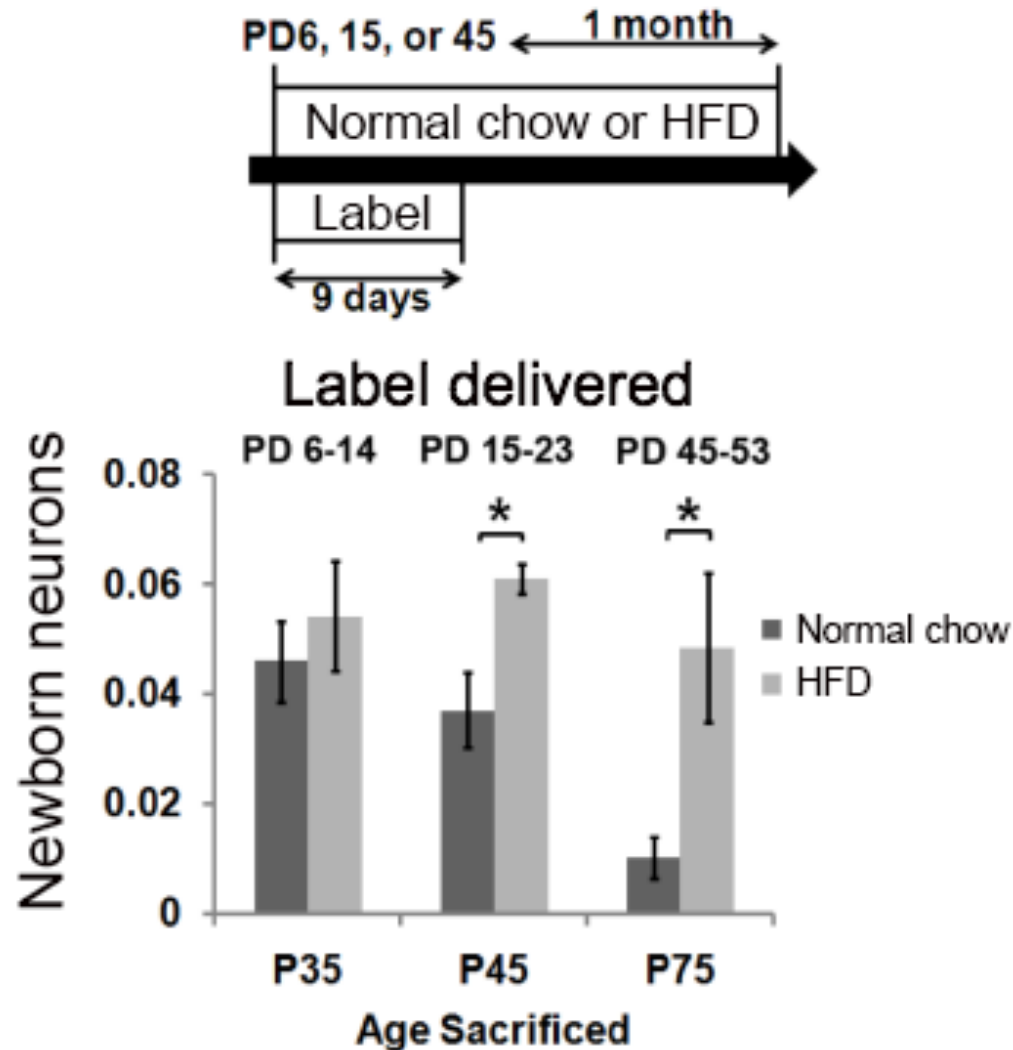
# Robust cell proliferation in hypothalamic median eminence



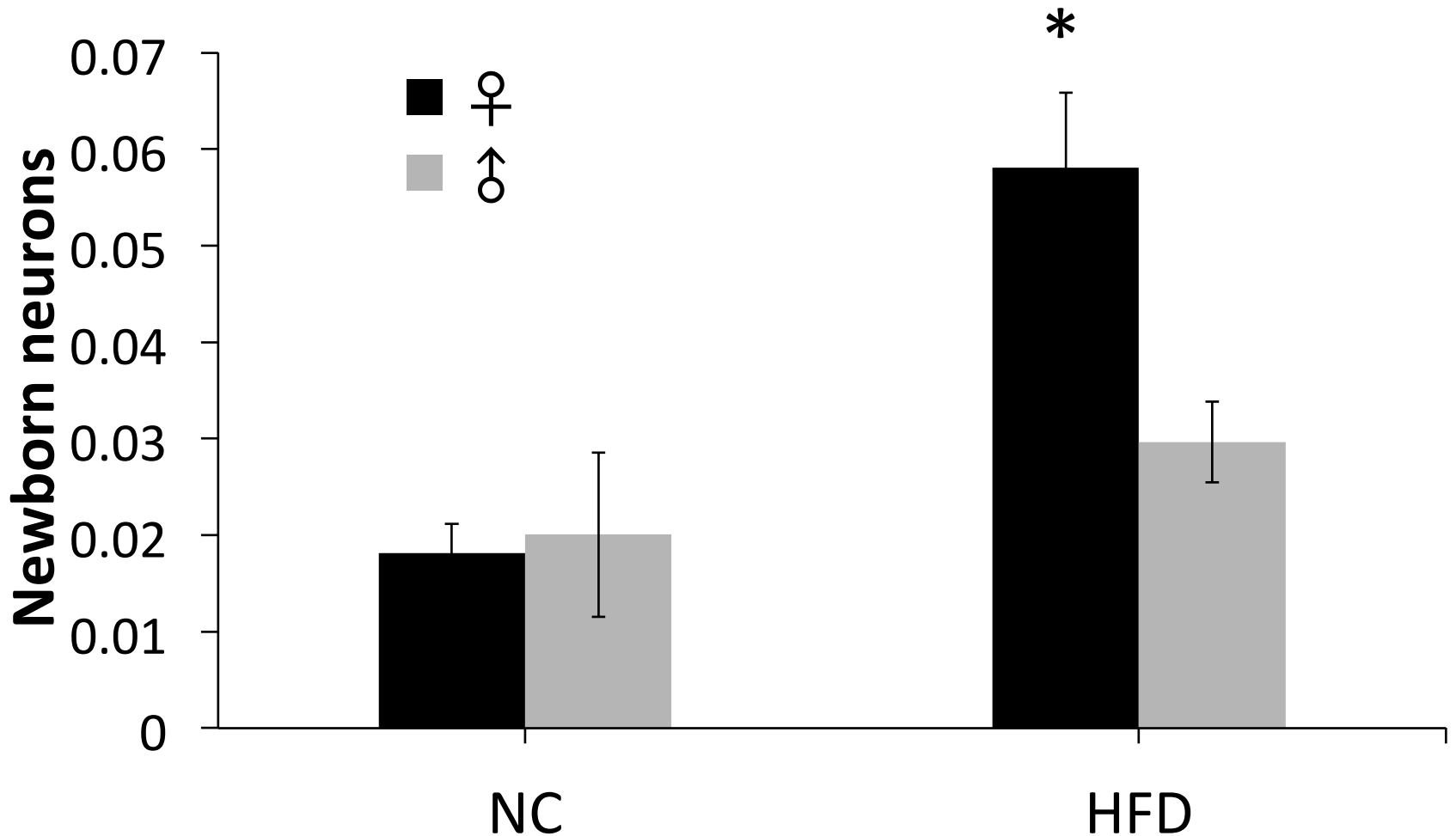
# Different classes of neurons are generated in postnatal ME



# Neurogenesis ends after weaning, but can be reactivated by high fat diet

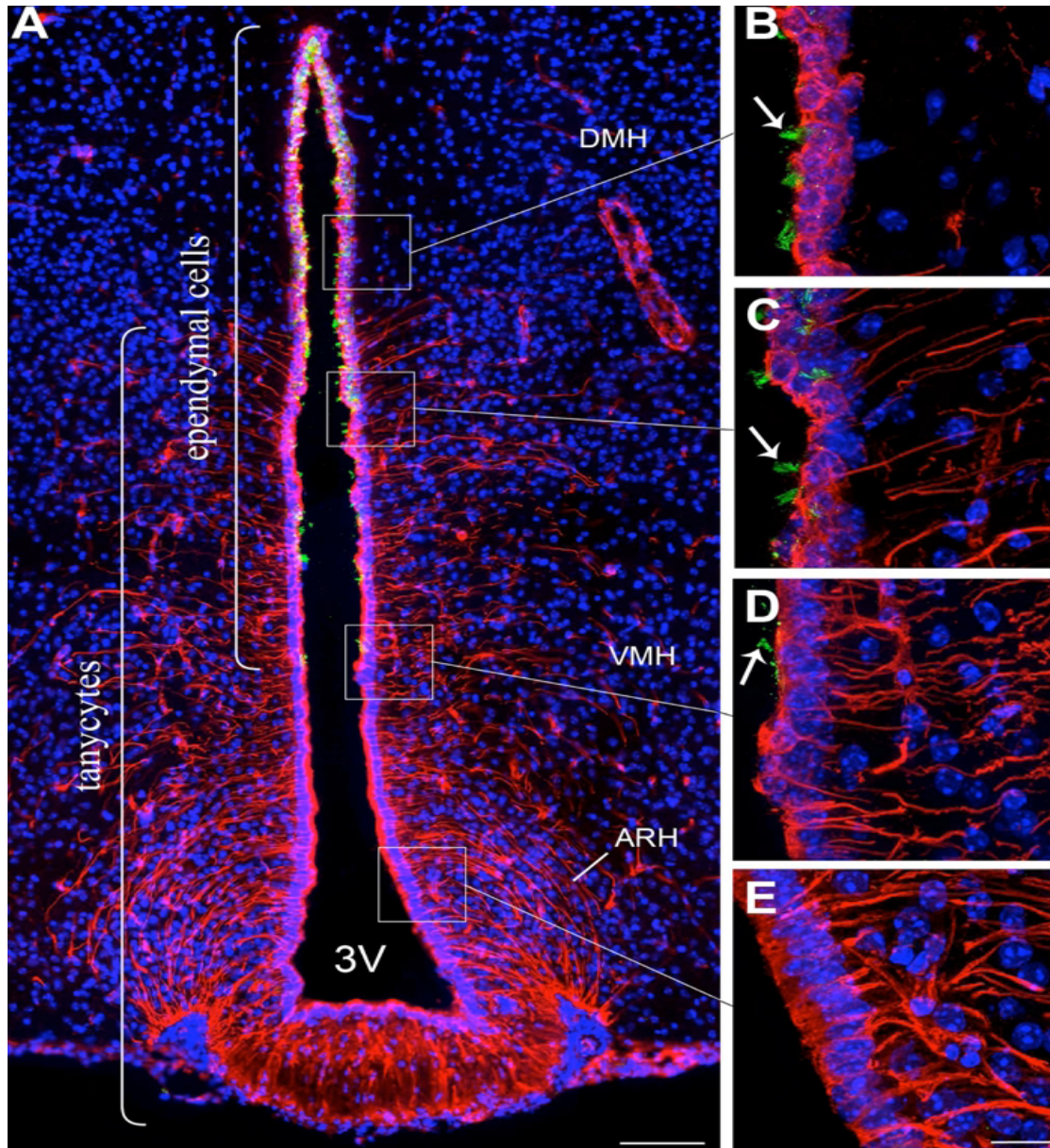


# HFD stimulates neurogenesis in young adult female, but not male, ME

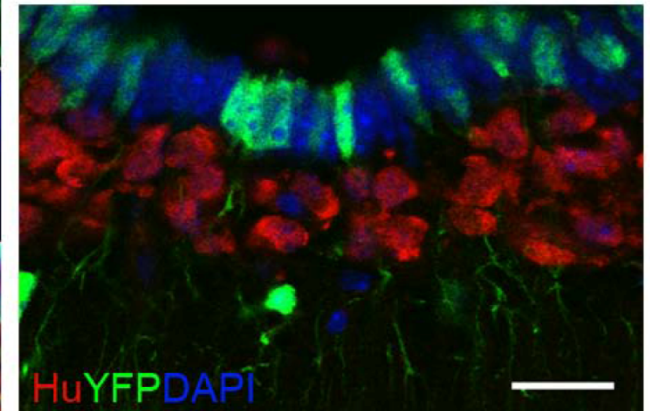
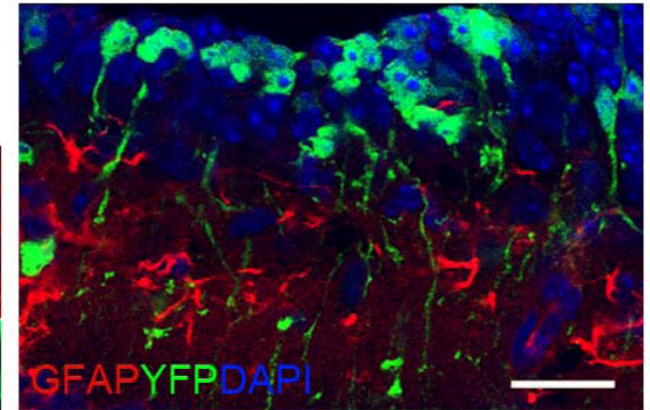
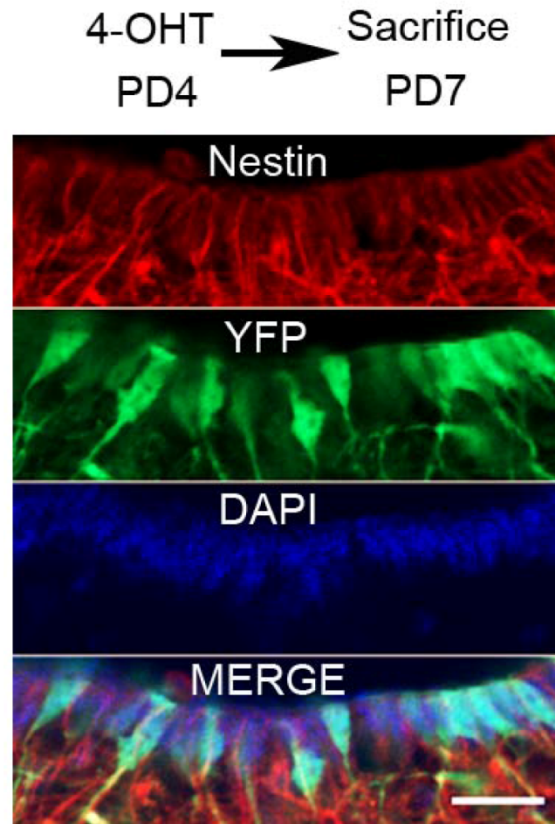
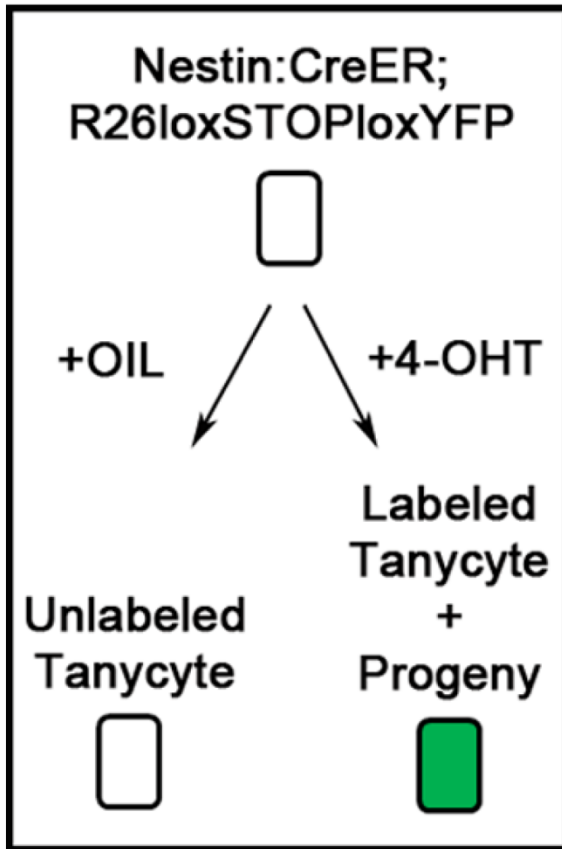




# Hypothalamic tanycytes

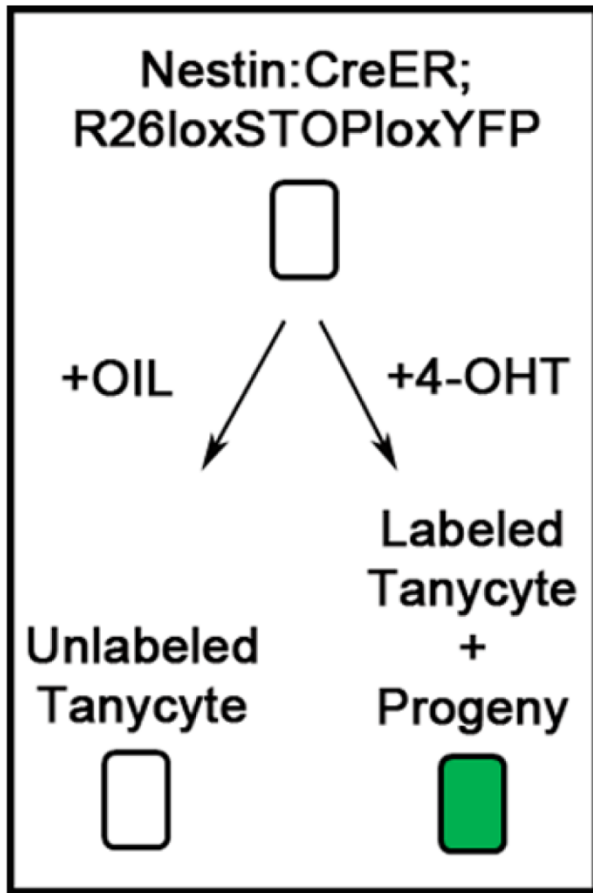


# Tanycytes can be selectively genetically labeled

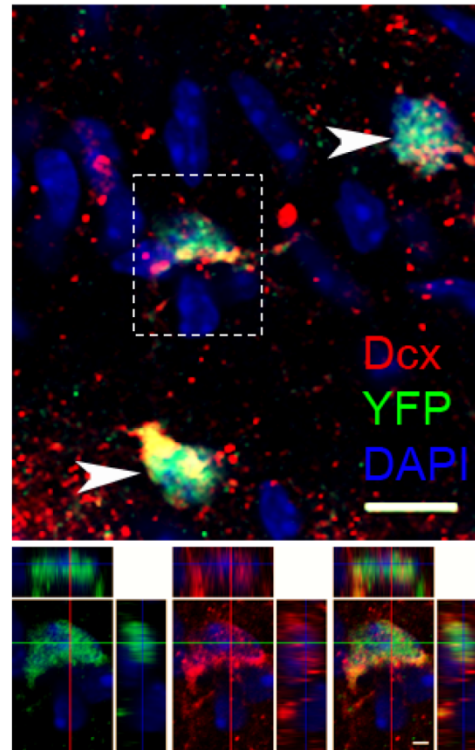


18.09% of Sox2  $\beta$ 2 Tanycytes labeled with YFP

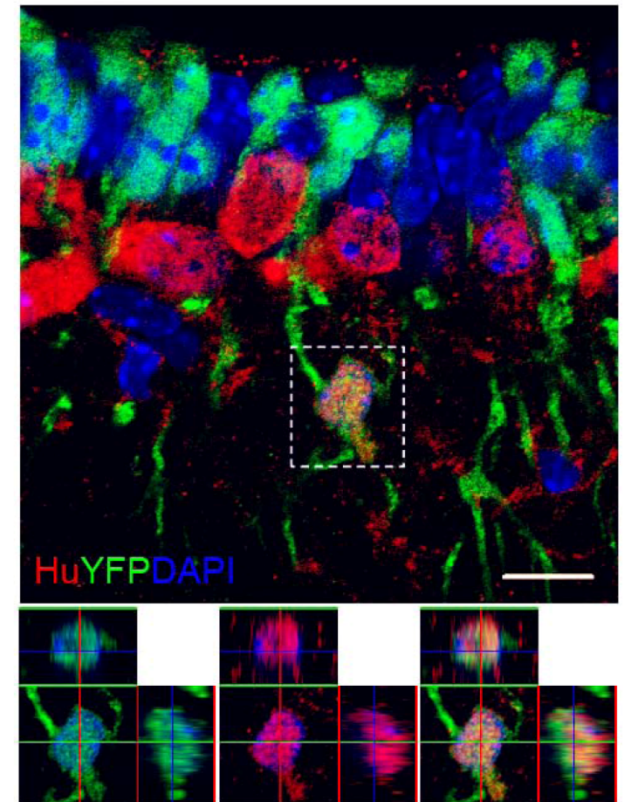
# Tanycytes of the medial eminence (ME) generates neurons in postnatal hypothalamus



4-OHT PD4 → Sacrifice PD21

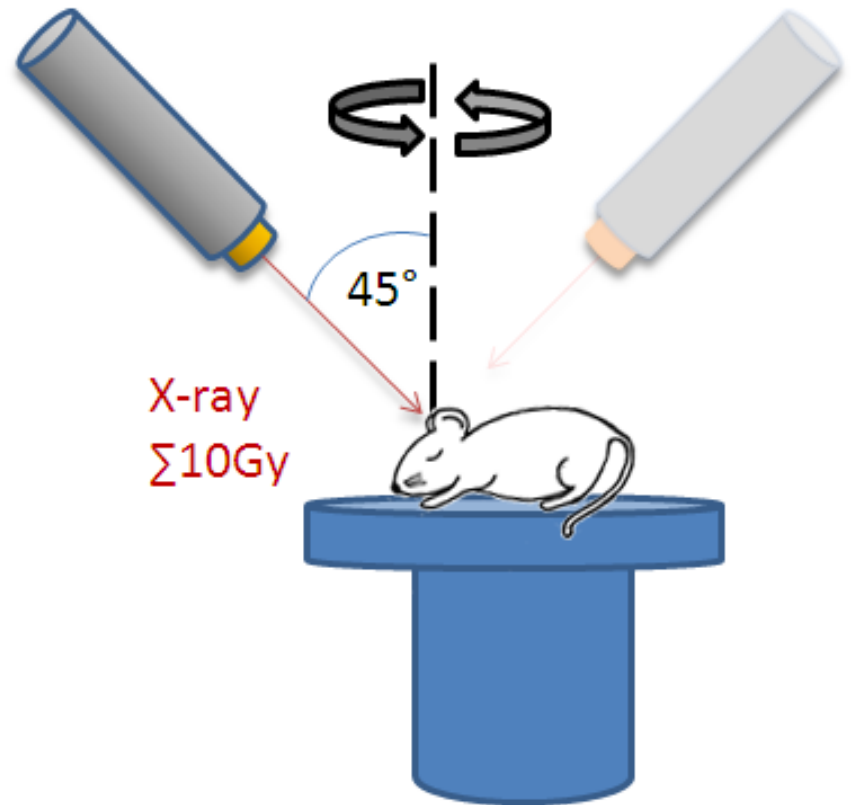
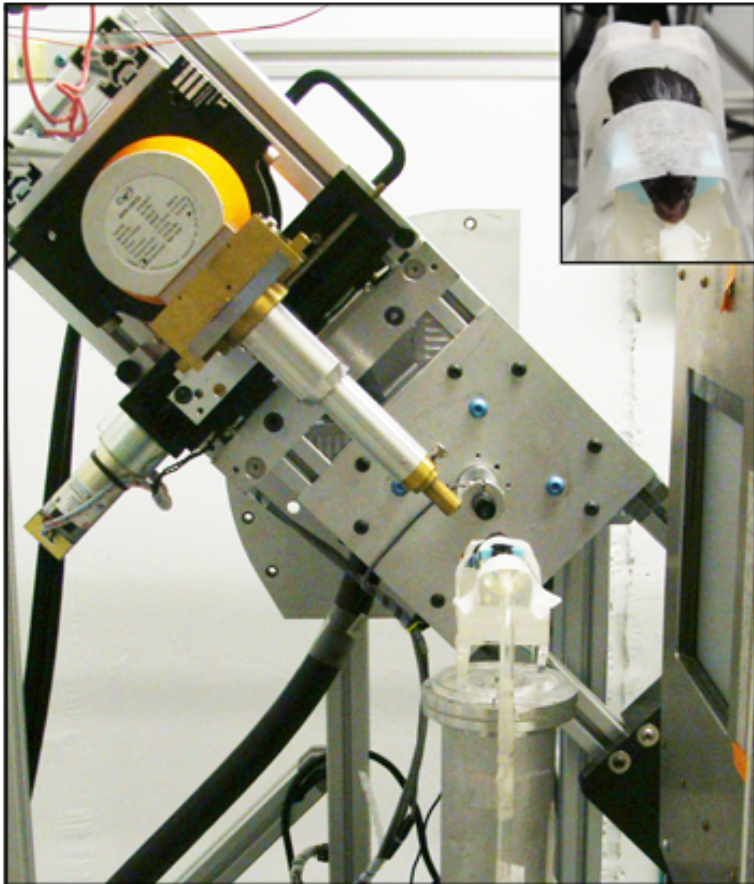


4-OHT PD4 → Sacrifice PD35



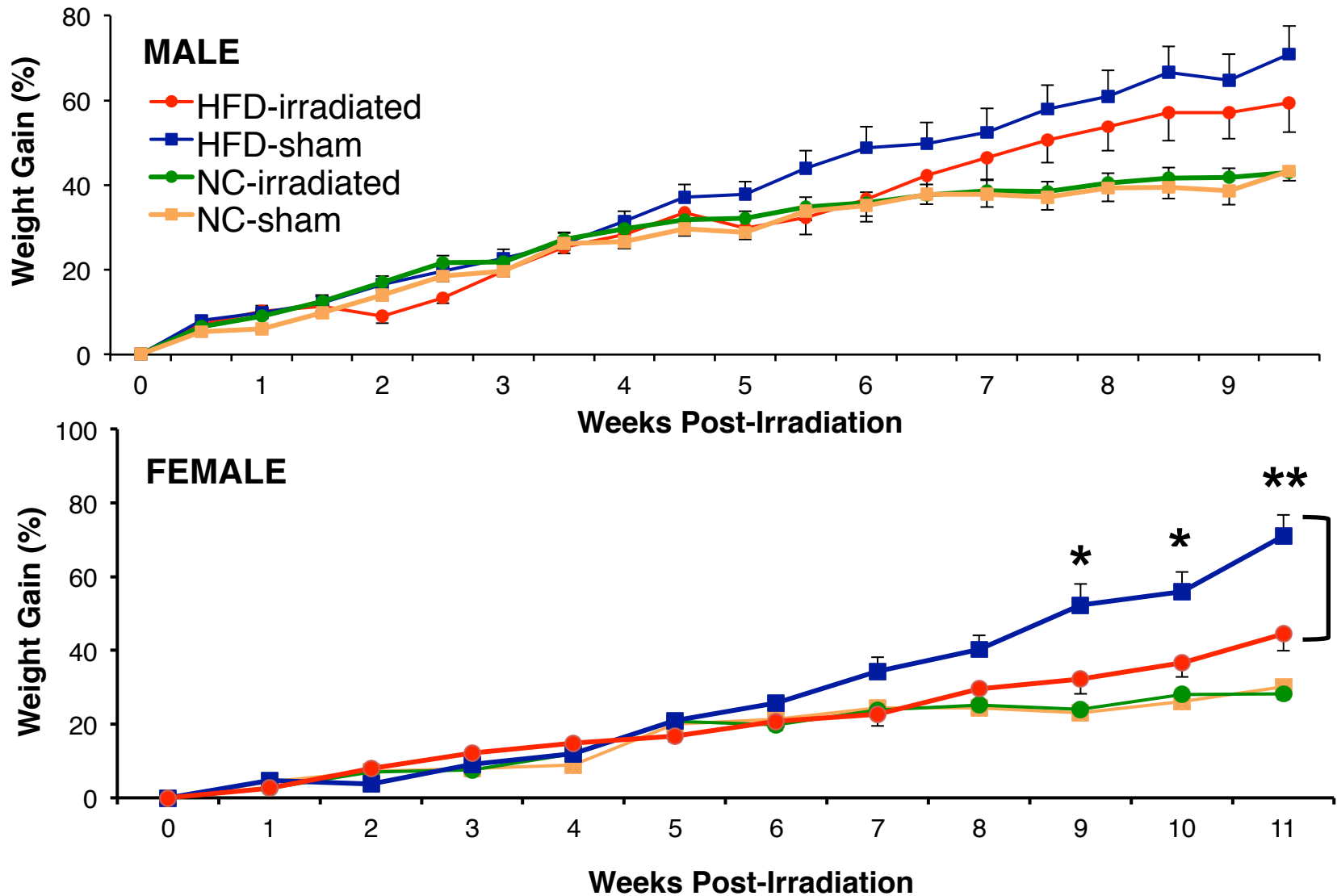
(8.1%±0.4 of Hu<sup>+</sup> neurons were YFP<sup>+</sup>; n=4)

# Localized CT-guided irradiation to inhibit ME neurogenesis in young adults

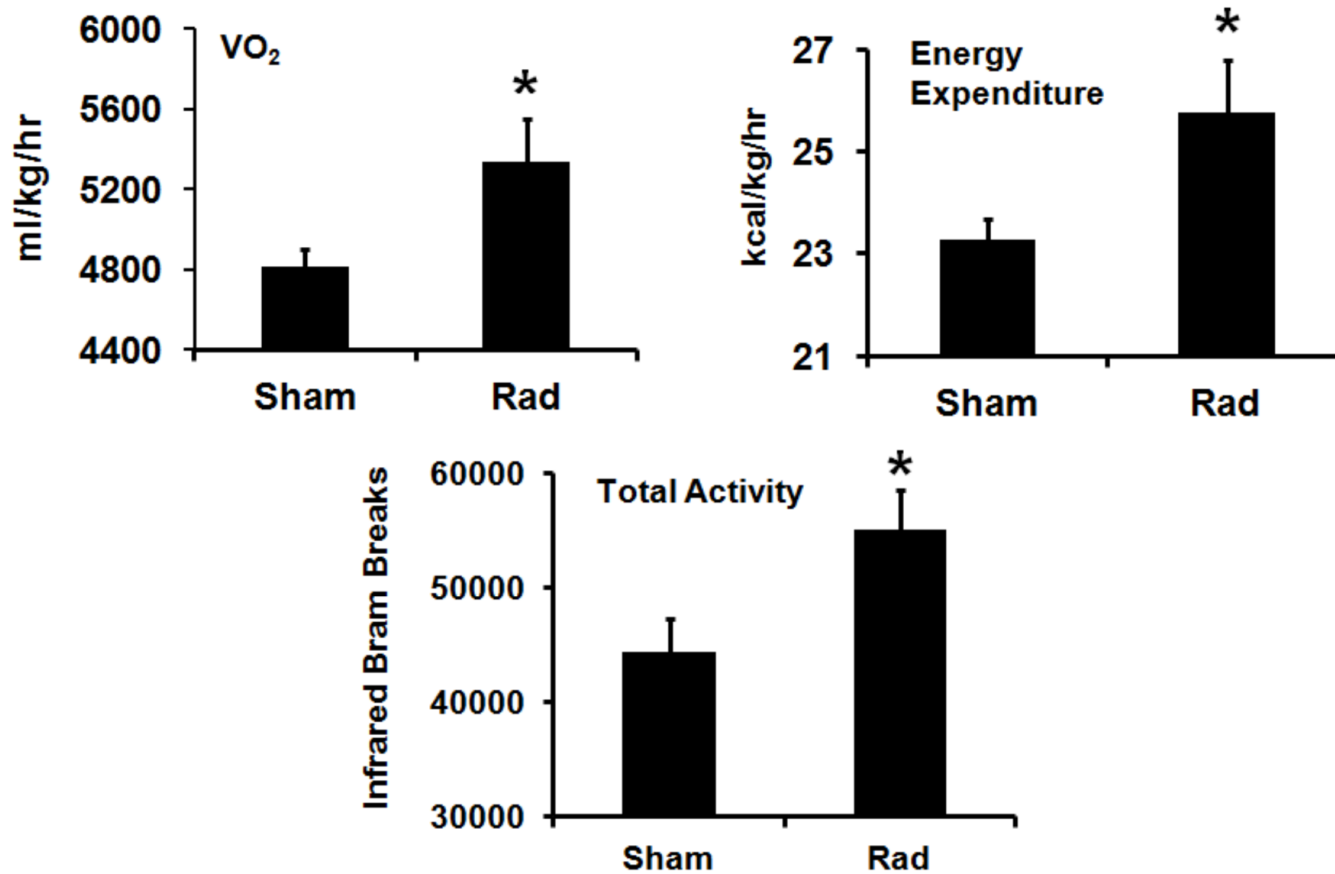


Lee, et al. *Nat Neurosci* 2012  
Lee, et al. *JoVE* 2014

# Focal irradiation of ME decreases weight gain in females but not males



# Focal irradiation of ME enhances activity levels and energy expenditure



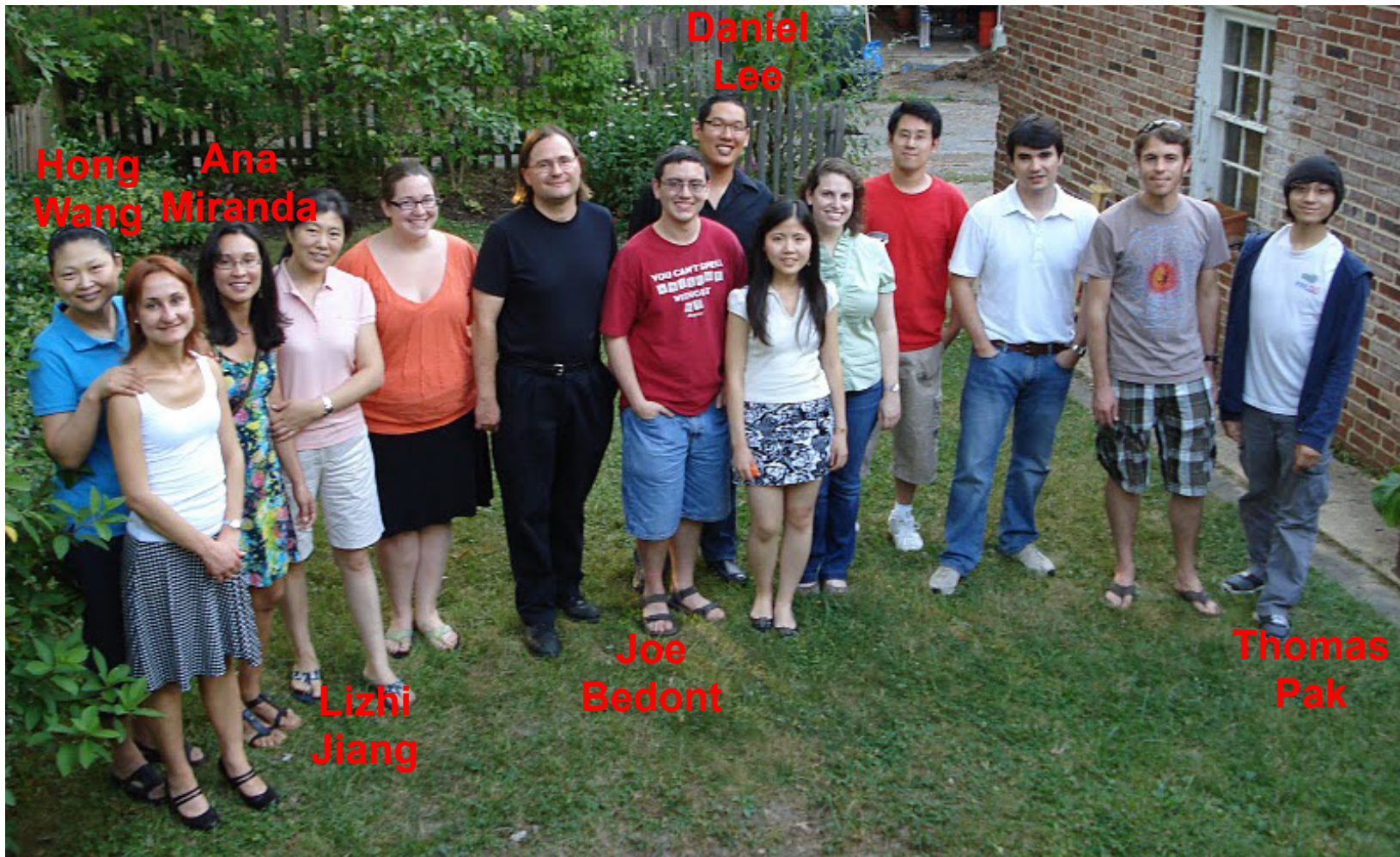
# What we now know

1. New neurons are born in juvenile hypothalamic median eminence.
2. Neurogenesis can be triggered by high fat diet in young adult females, but not males.
3. These neurons are generated from tanycytes.
4. Inhibiting cell proliferation in ME in females reduces weight gain and increases activity.

## What we don't yet know

1. Do the effects of focal irradiation in ME result from blocking neurogenesis?
2. What molecular signals induce tanycyte-derived neurogenesis?
3. Do signals other than diet control hypothalamic neurogenesis?
4. Do dietary signals also induce neurogenesis in human hypothalamus?





Daniel  
Lee

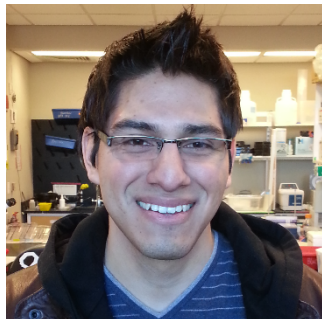
Hong Wang  
Ana Miranda

Lizhi  
Jiang

Joe  
Bedont

Thomas  
Pak

Juan Salvatierra



Sooyeon Yoo



Why should long-term weight gain be selectively adaptive for females?





# Median Eminence (ME)



Tanycyte



Blood Vessel



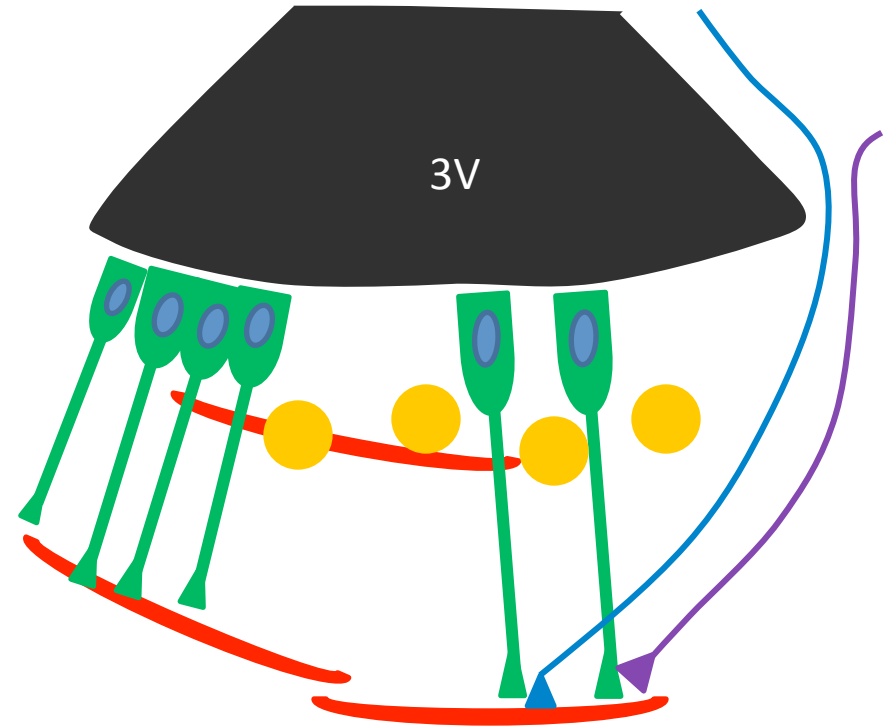
Neurons



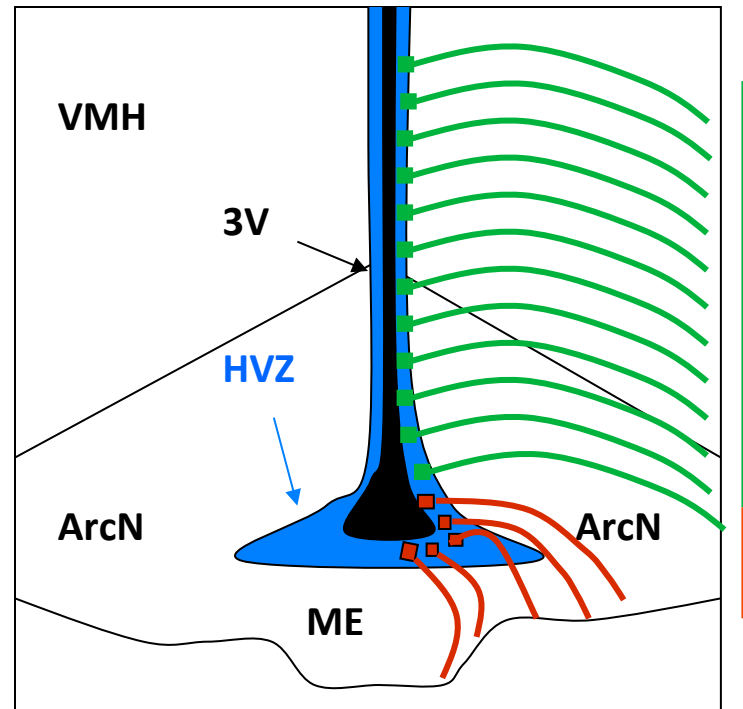
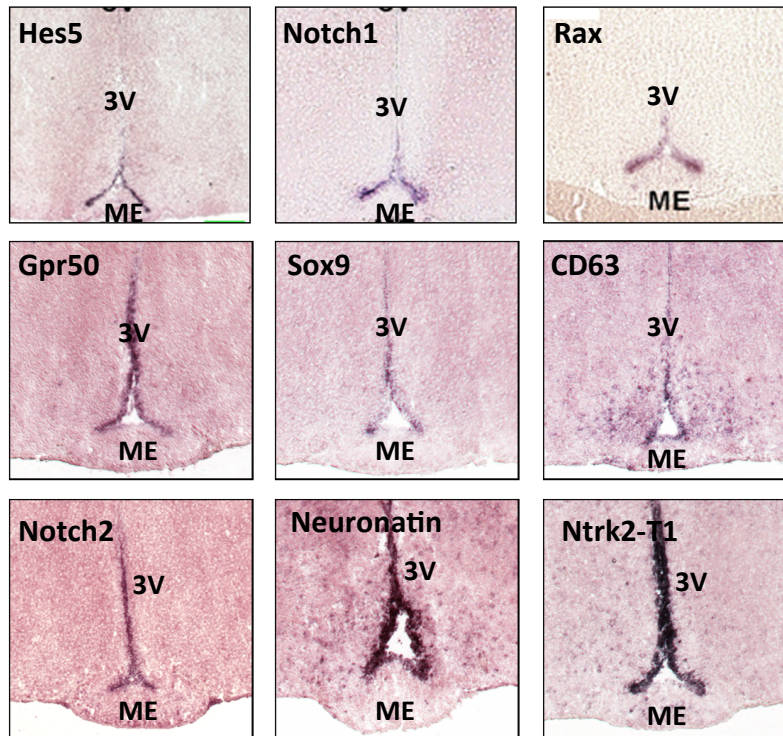
TRH Axon



GnRH Axon



# Tanycytes express stem and progenitor-specific markers



Nestin

GFAP

Vimentin

Sox2

