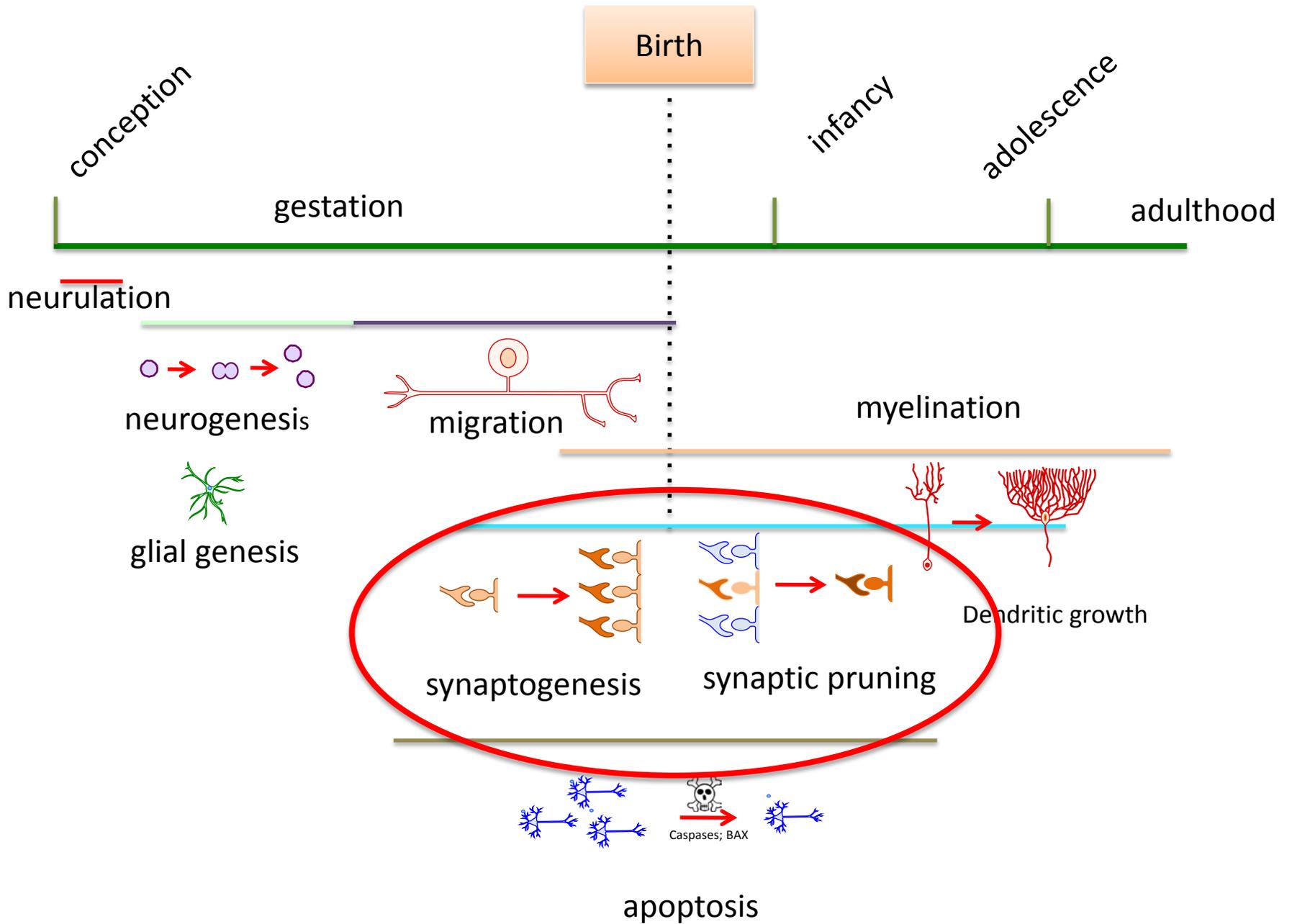
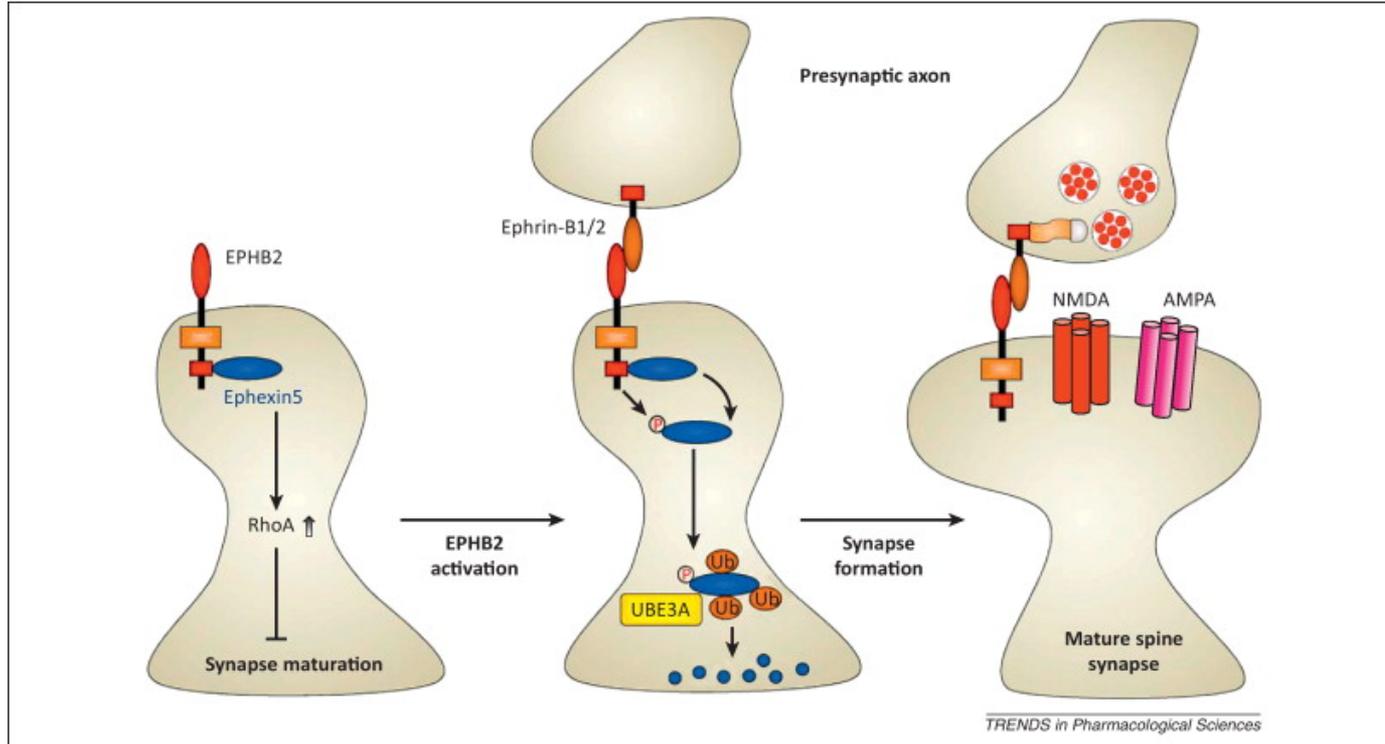


**MISUNDERSTANDINGS**  
and  
**LOST OPPORTUNITY**  
are the cost  
of not including both sexes in  
preclinical research

Margaret M. McCarthy, PhD  
University of Maryland School of  
Medicine

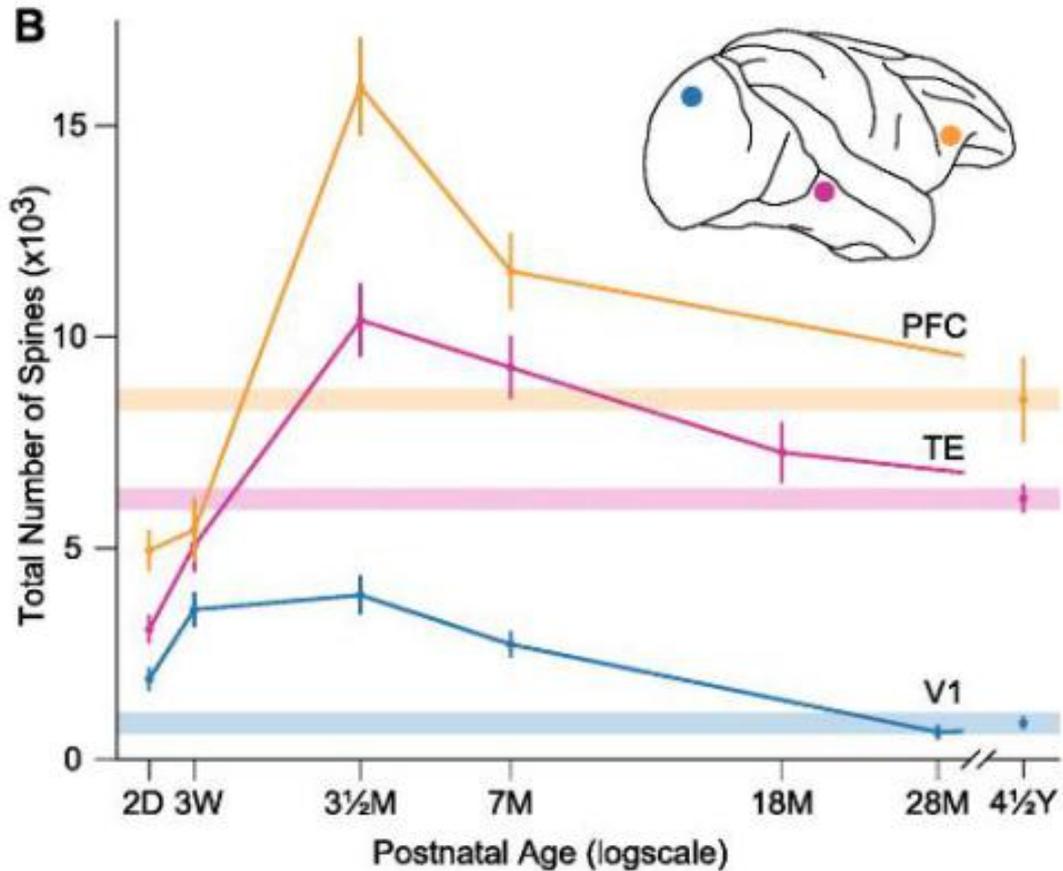


# Synaptogenesis



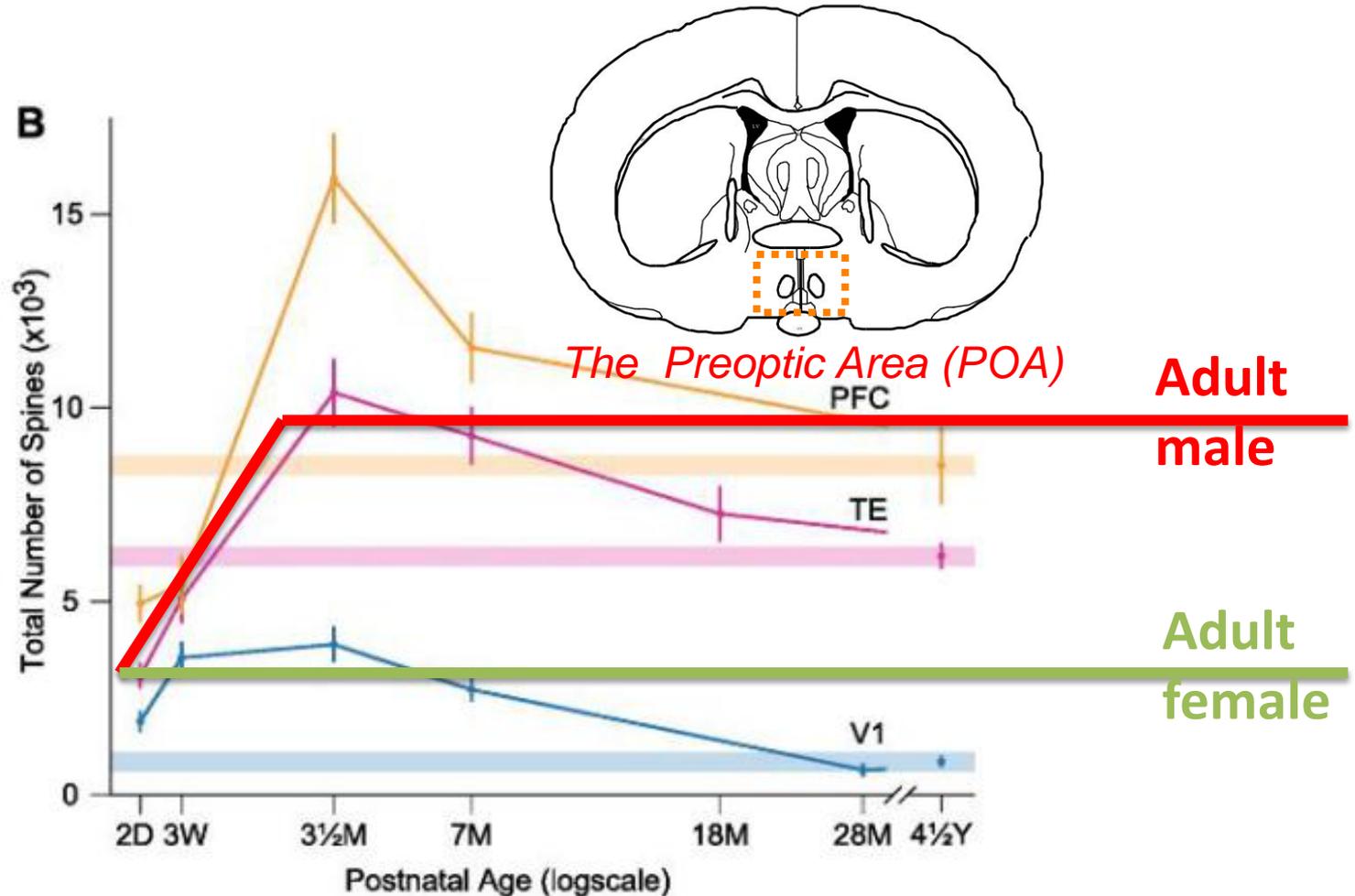
Prevailing view that synapses are formed by physical contact with axons and that glutamate receptors then follow – *Spooren et al., TIPS 2012*

# Synaptic patterning is then established by pruning

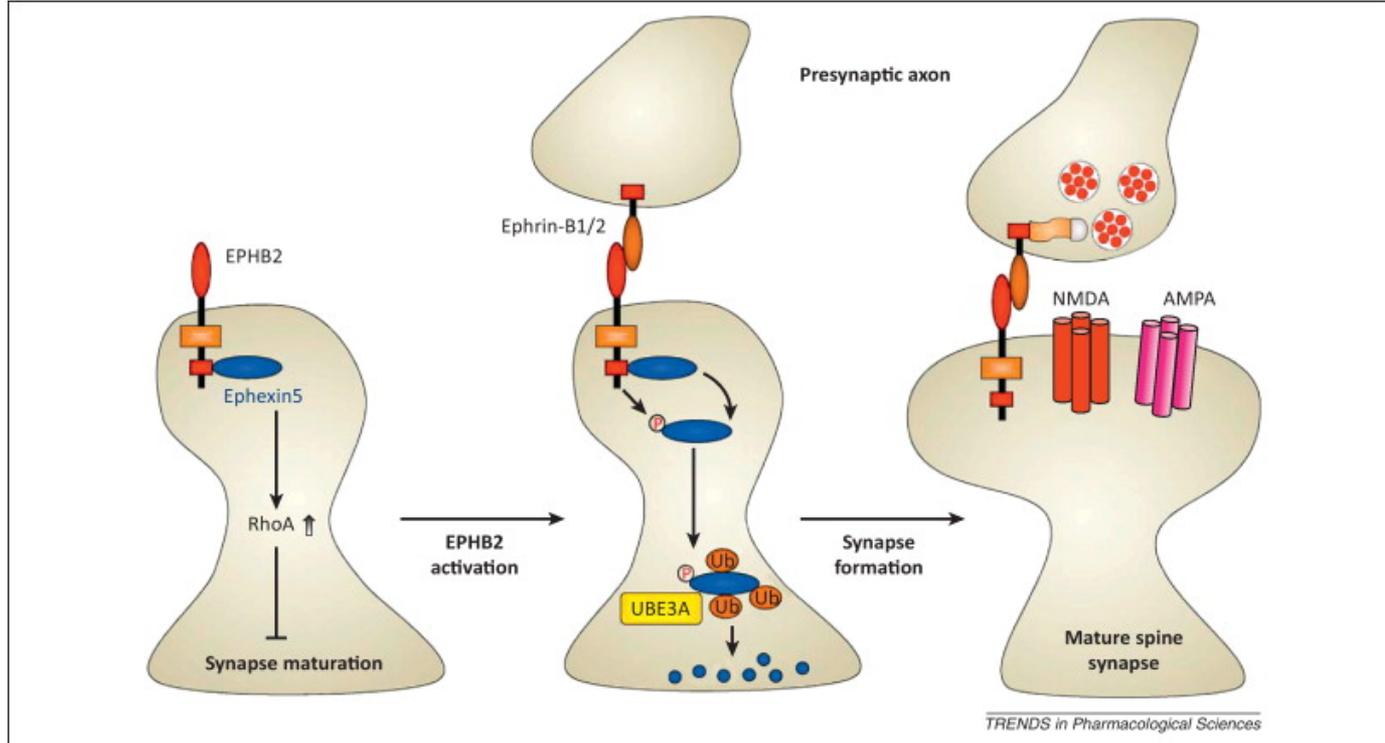


Guy N. Elston, Tomofumi Oga, and Ichiro Fujita.  
*Spinogenesis and Pruning Scales across Functional Hierarchies.* *J. Neurosci.* 29: 3271-3275

# What about synaptic patterning in the POA?

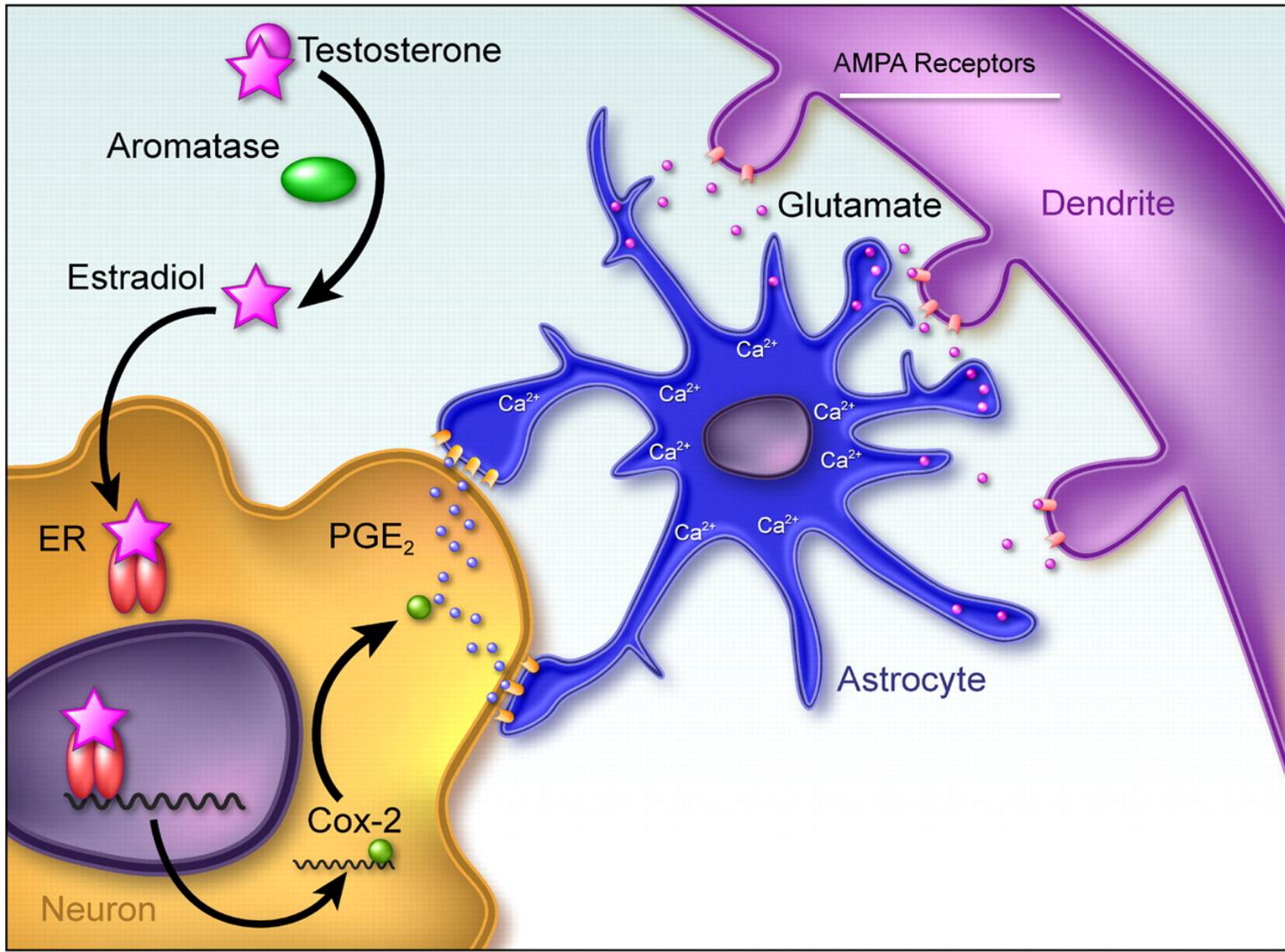


# Synaptogenesis



Prevailing view that synapses are formed by physical contact with axons and that glutamate receptors then follow – *Spooren et al., TIPS 2012*

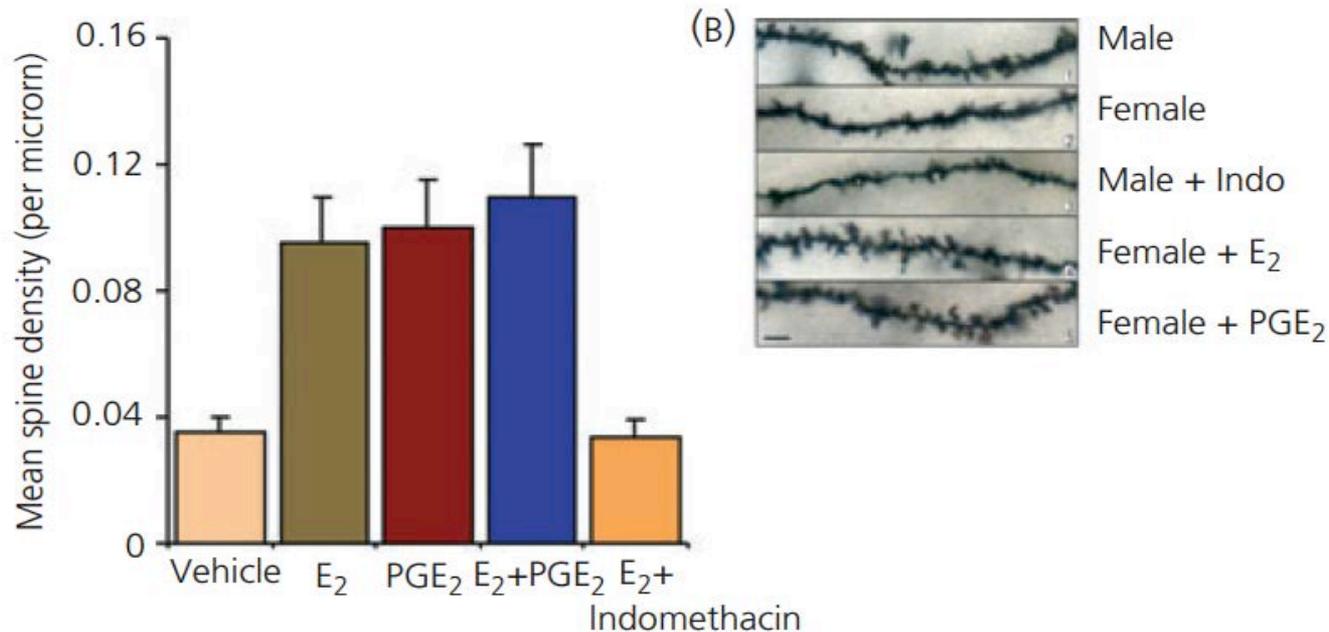
# Synapse formation in the POA *requires* AMPA receptor activation



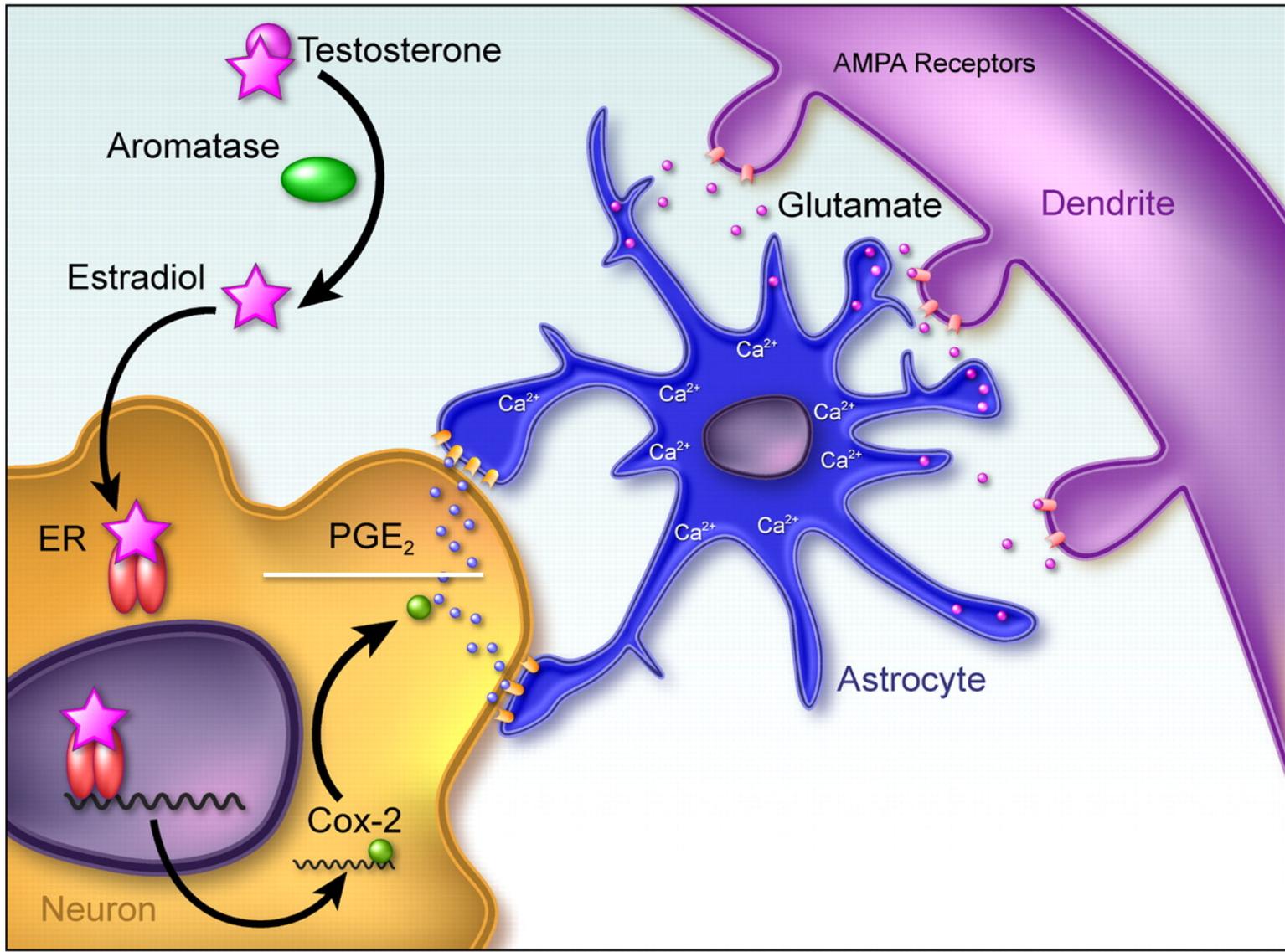
# A Novel Mechanism of Dendritic Spine Plasticity Involving Estradiol Induction of Prostaglandin- $E_2$

Stuart K. Amateau<sup>1</sup> and Margaret M. McCarthy<sup>1,2</sup>

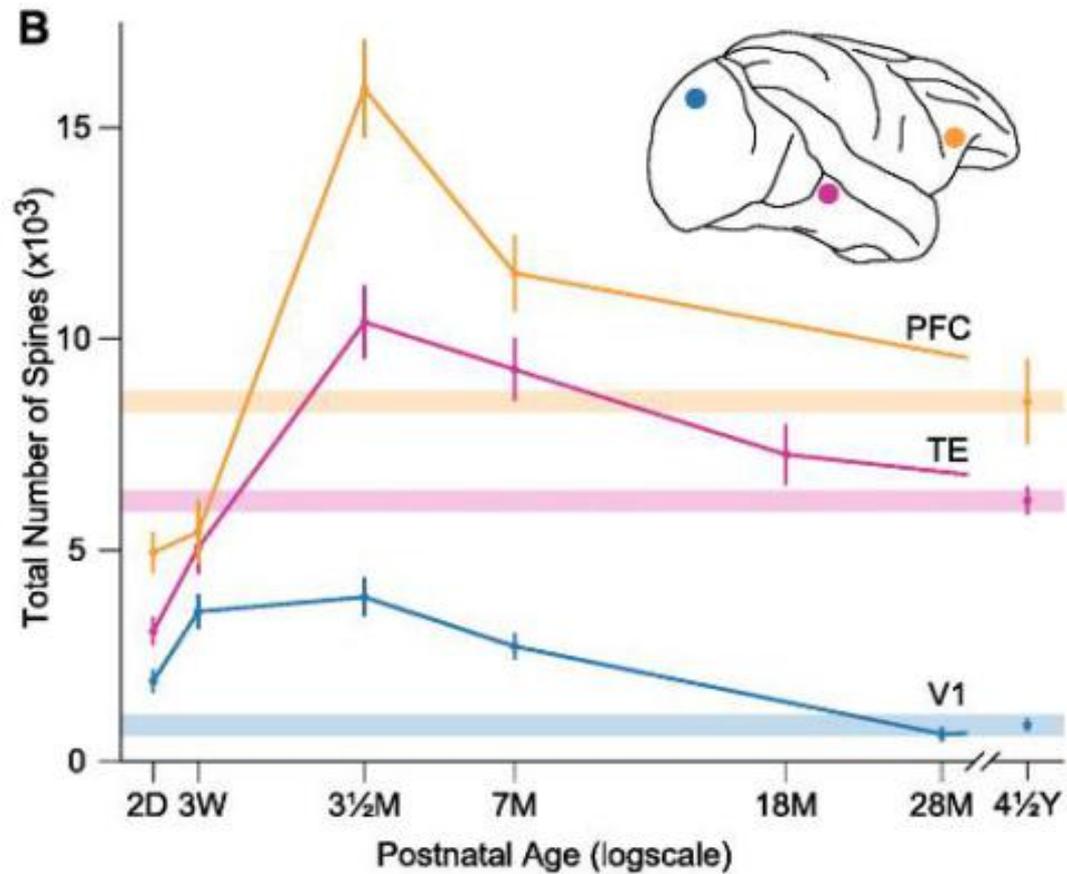
<sup>1</sup>Program in Neuroscience and <sup>2</sup>Department of Physiology, University of Maryland at Baltimore, School of Medicine, Baltimore, Maryland 21201



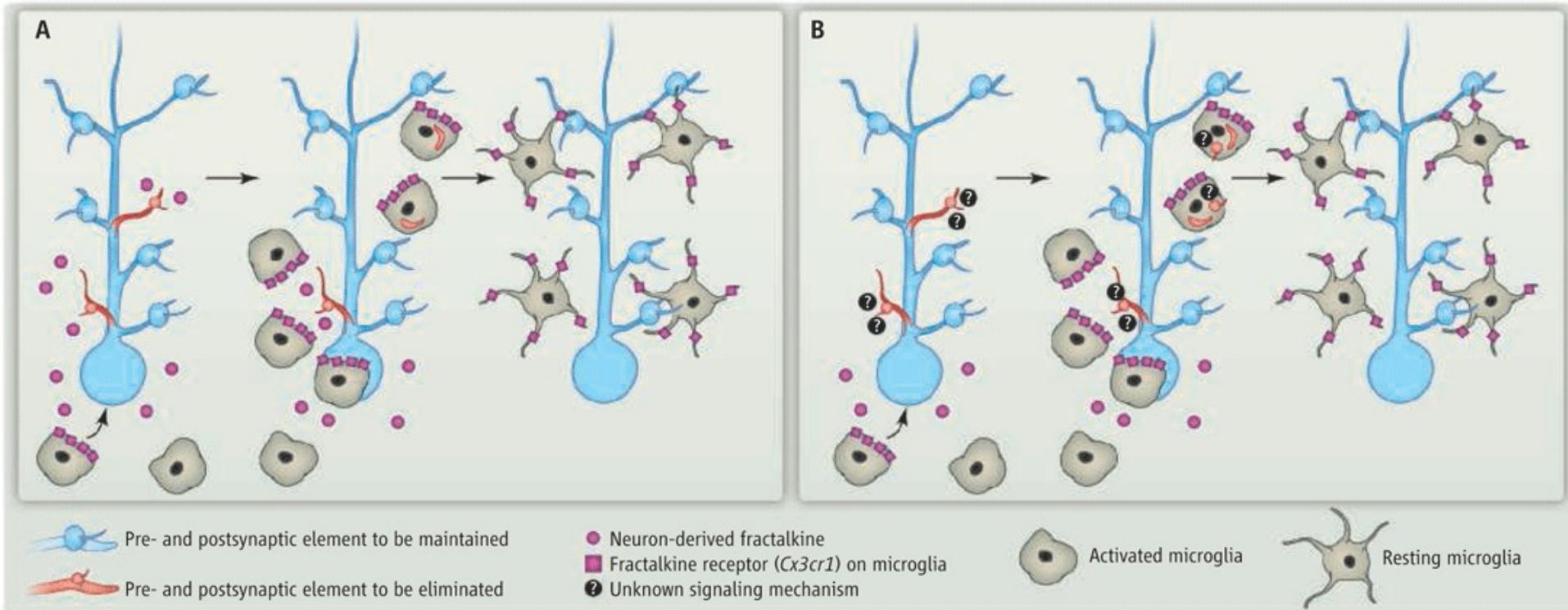
# Synapse formation in the POA *requires* prostaglandin synthesis



# Synaptic Patterning/Pruning



# Microglia mediate pruning



Schafer et al, Neuron 2012 (Beth Stevens - Harvard)  
Paolicelli et al., Science 2012 (Cornelius Gross – EMBL)

# microglia:

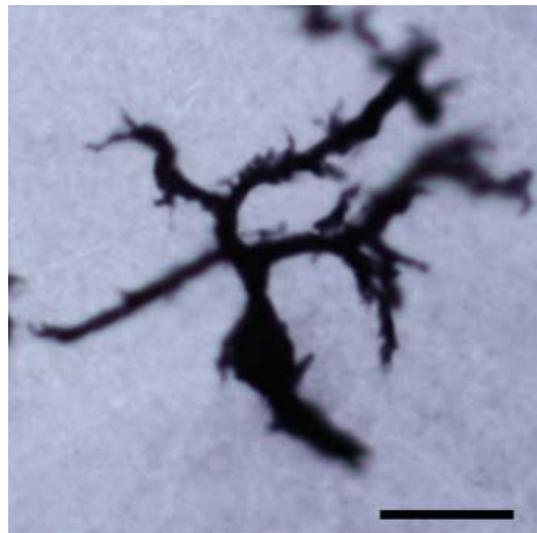
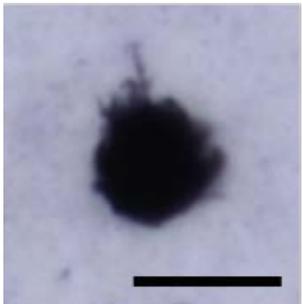
- Primary immunocompetent cells of the brain – derived from macrophages in the embryonic yolk sac
- Both respond to and produce prostaglandins

Thin

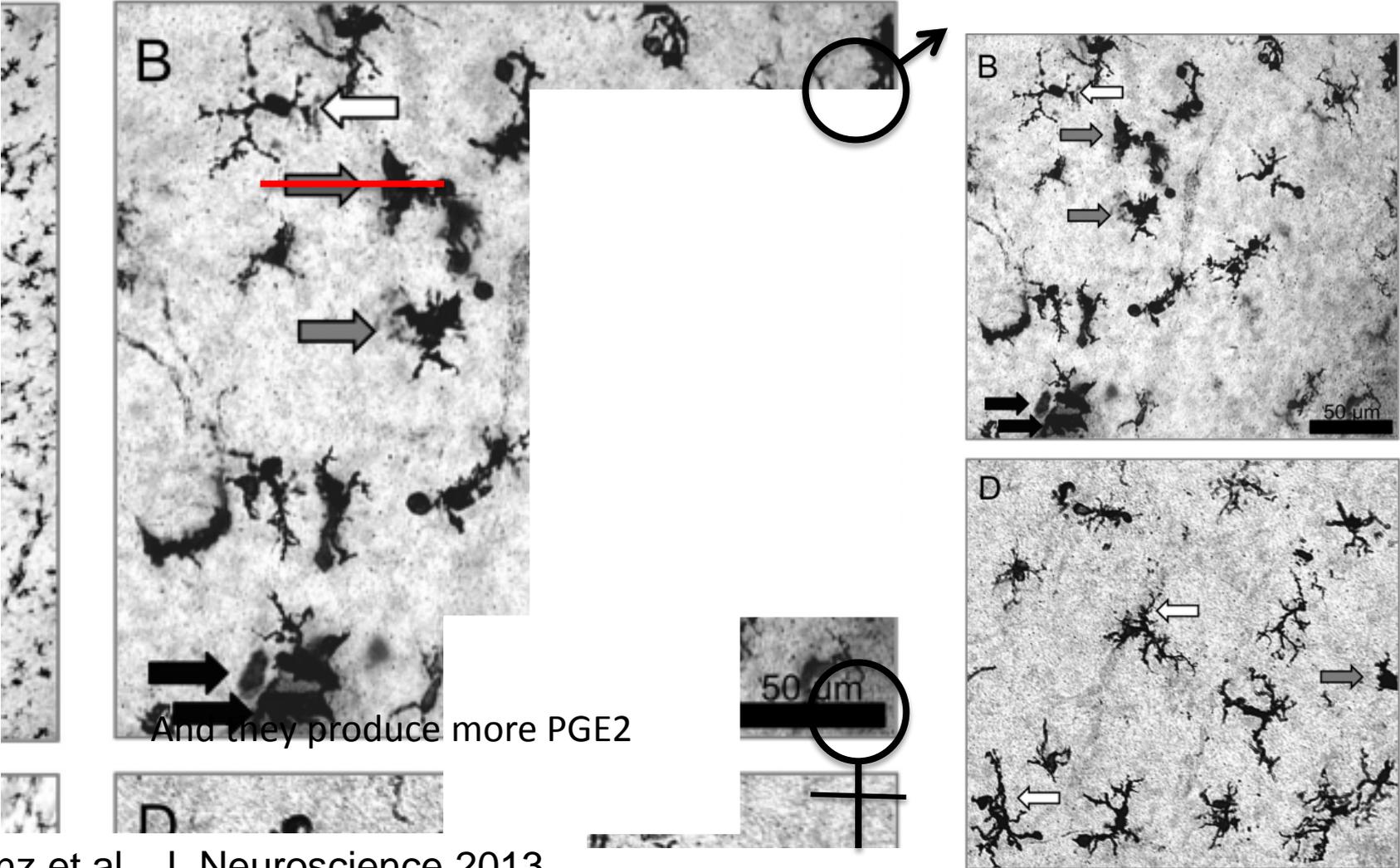
Thick

Stout

Ameboid

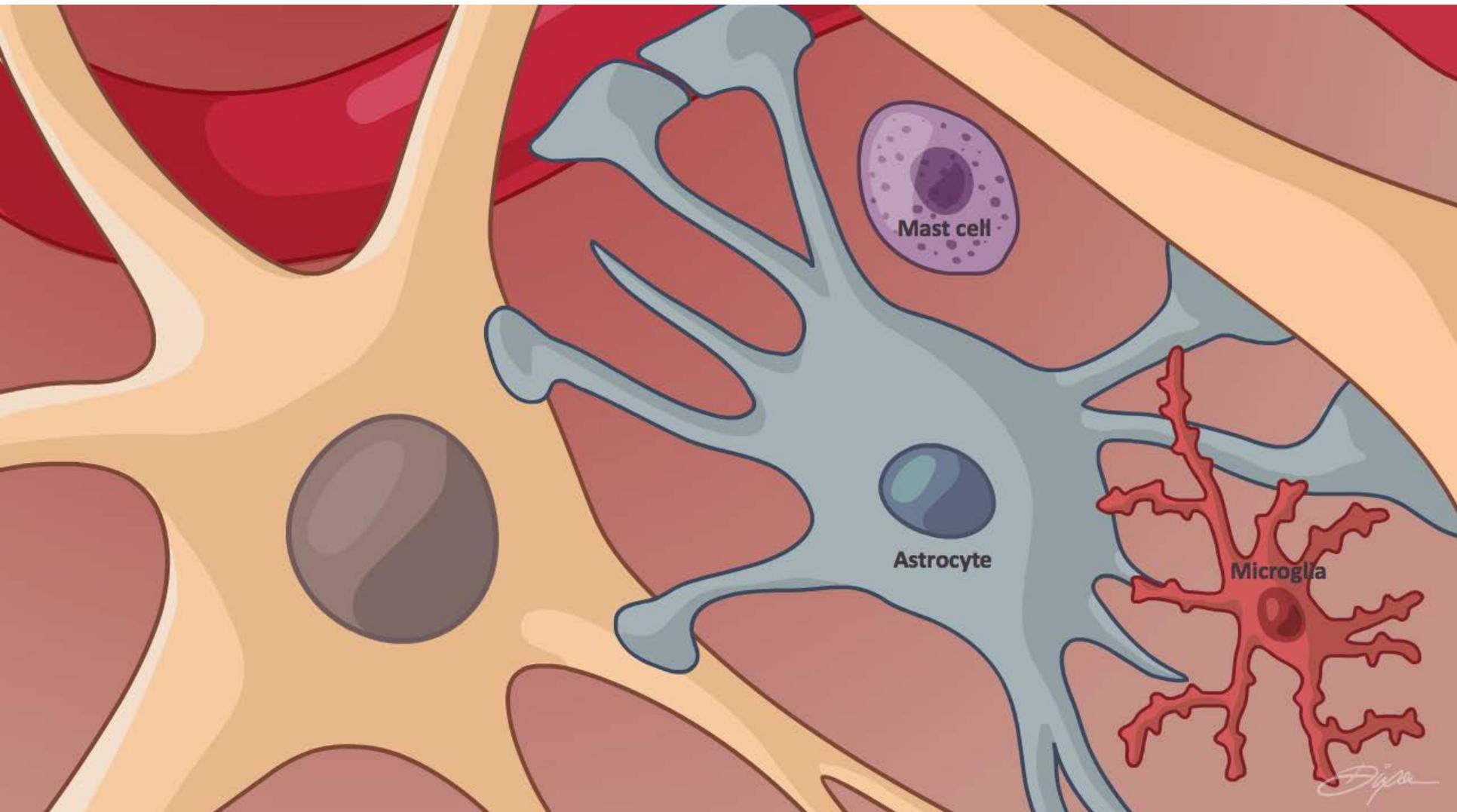


# Males have more “activated” microglia



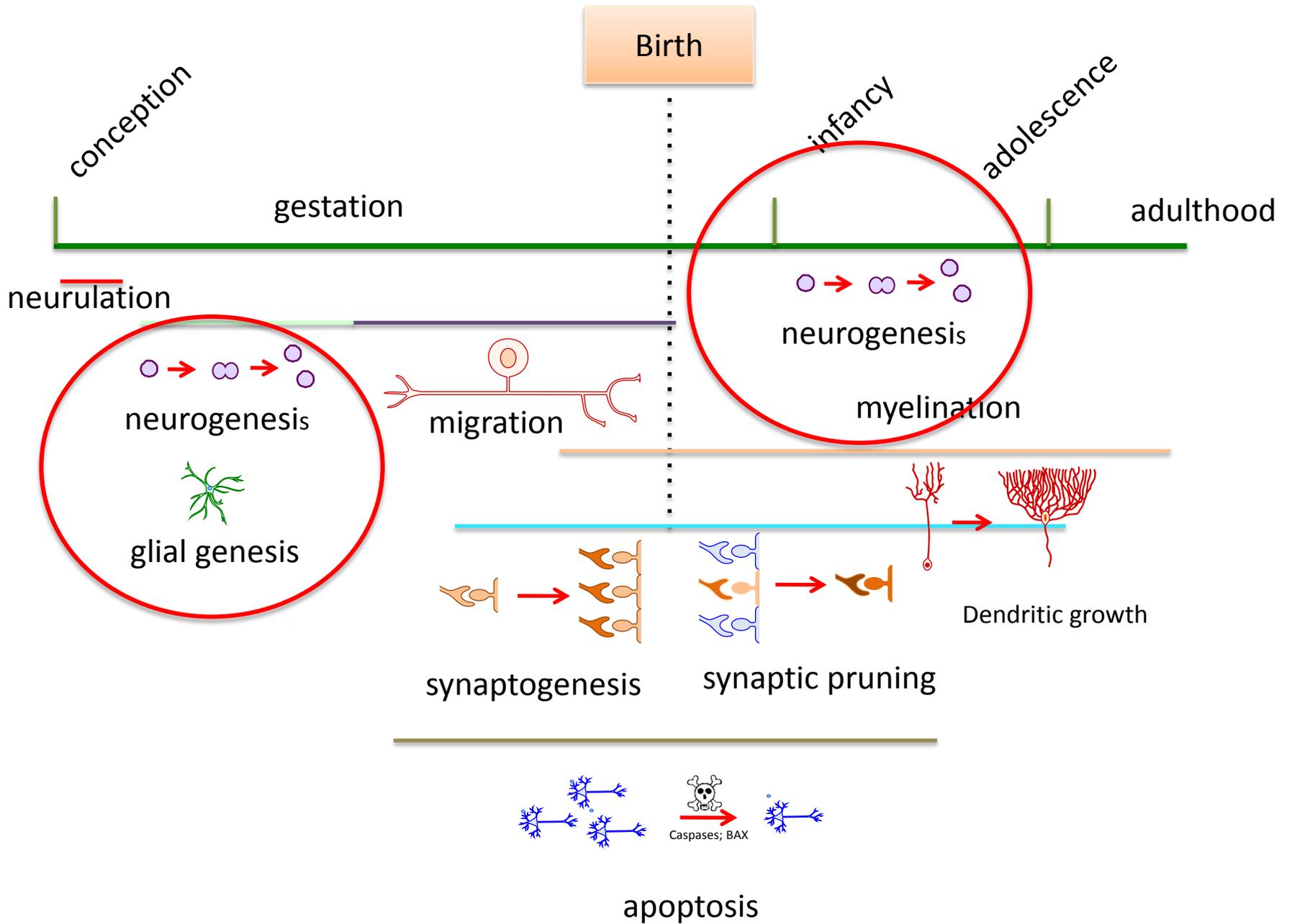
And they produce more PGE2

# Microglia are required for synaptic patterning in the POA



And they are of non-neuronal origin

So instead of microglia pruning synapses, they are essential to the formation of synapses in the POA

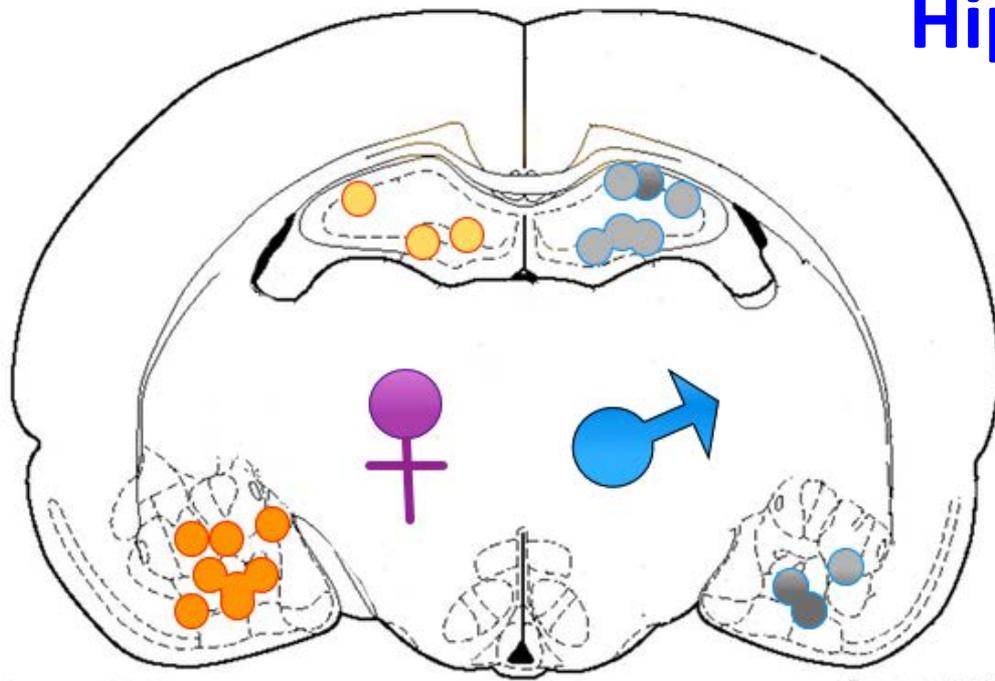


# Cell genesis is different in males and females in the telencephalon

Newborn females have more new neurons and astrocytes in the amygdala as males

## Amygdala

*Krebs-Kraft et al., PNAS 2010*



## Hippocampus

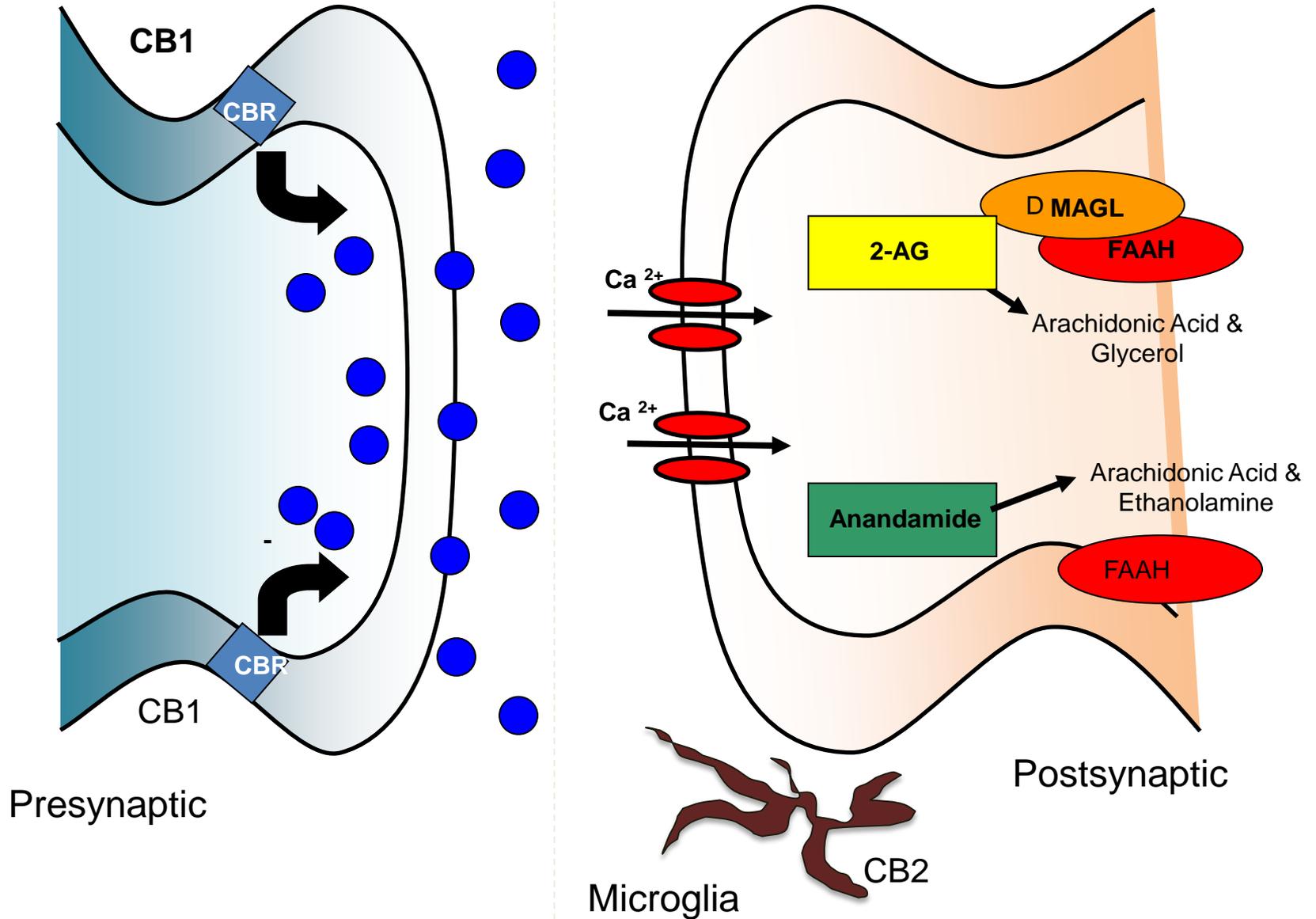
Newborn males make twice as many new hippocampal neurons as females

*Bowers et al., Biology of Sex Differences 2010*

# What mediates the sex difference in neurogenesis?

- In the adult, neurogenesis is promoted by depolarizing GABA
- But in the neonate we found something completely different

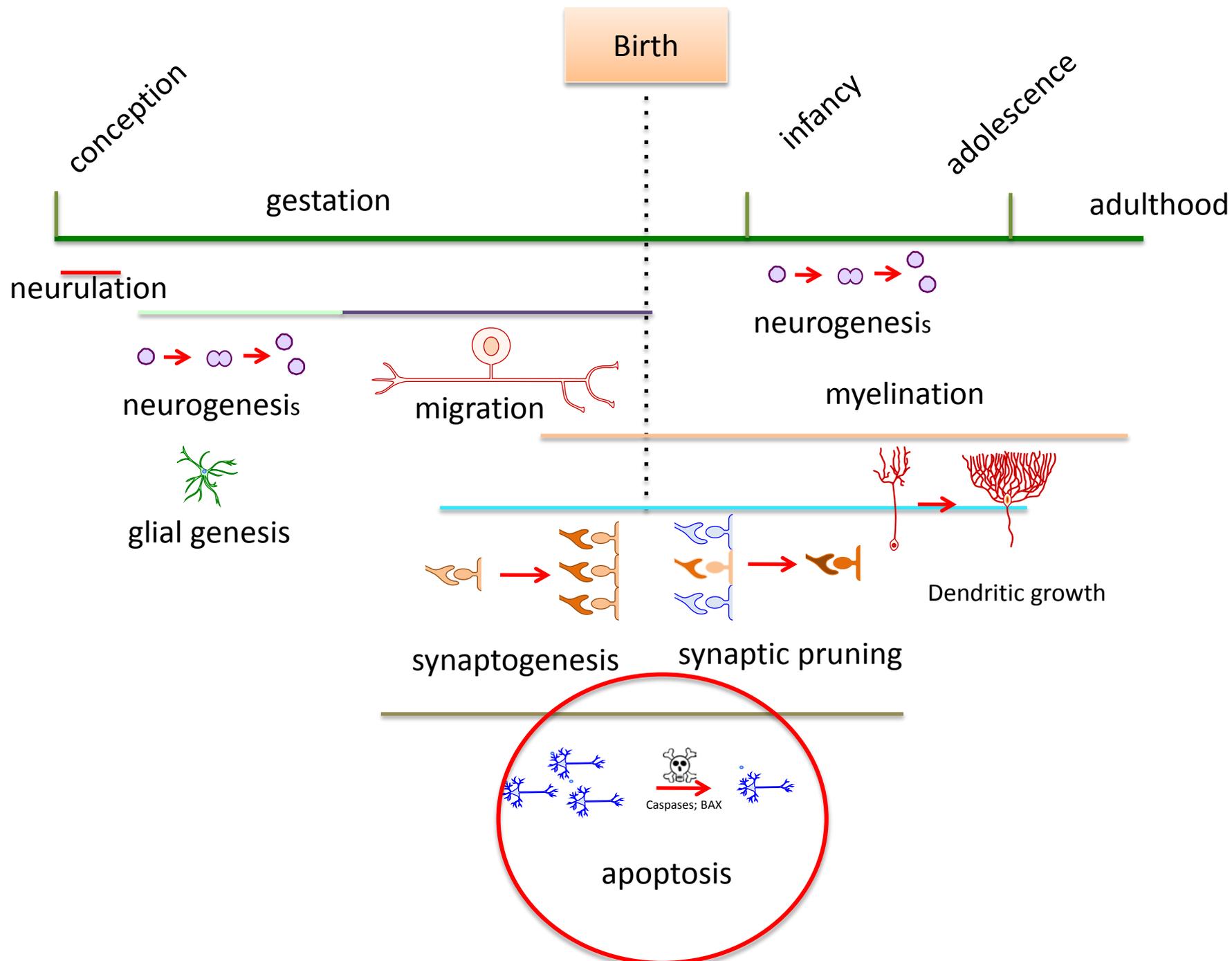
# Endocannabinoids



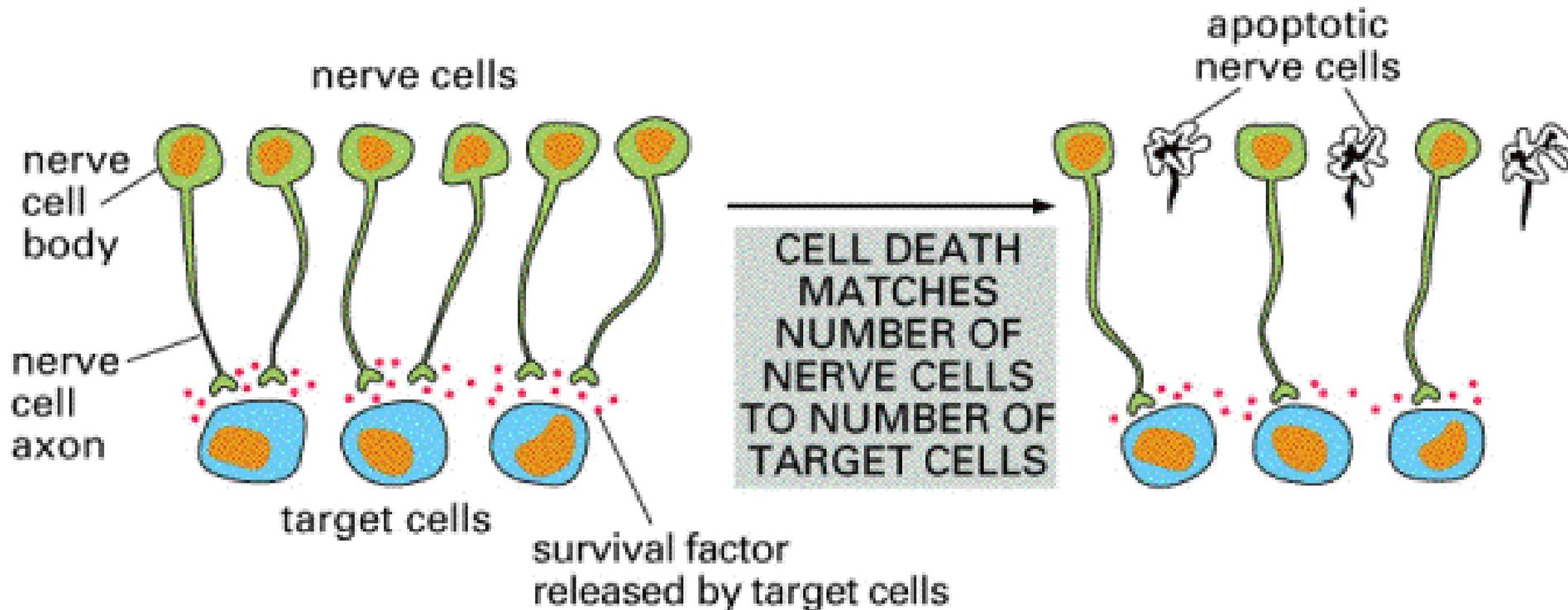
# Endocannabinoids



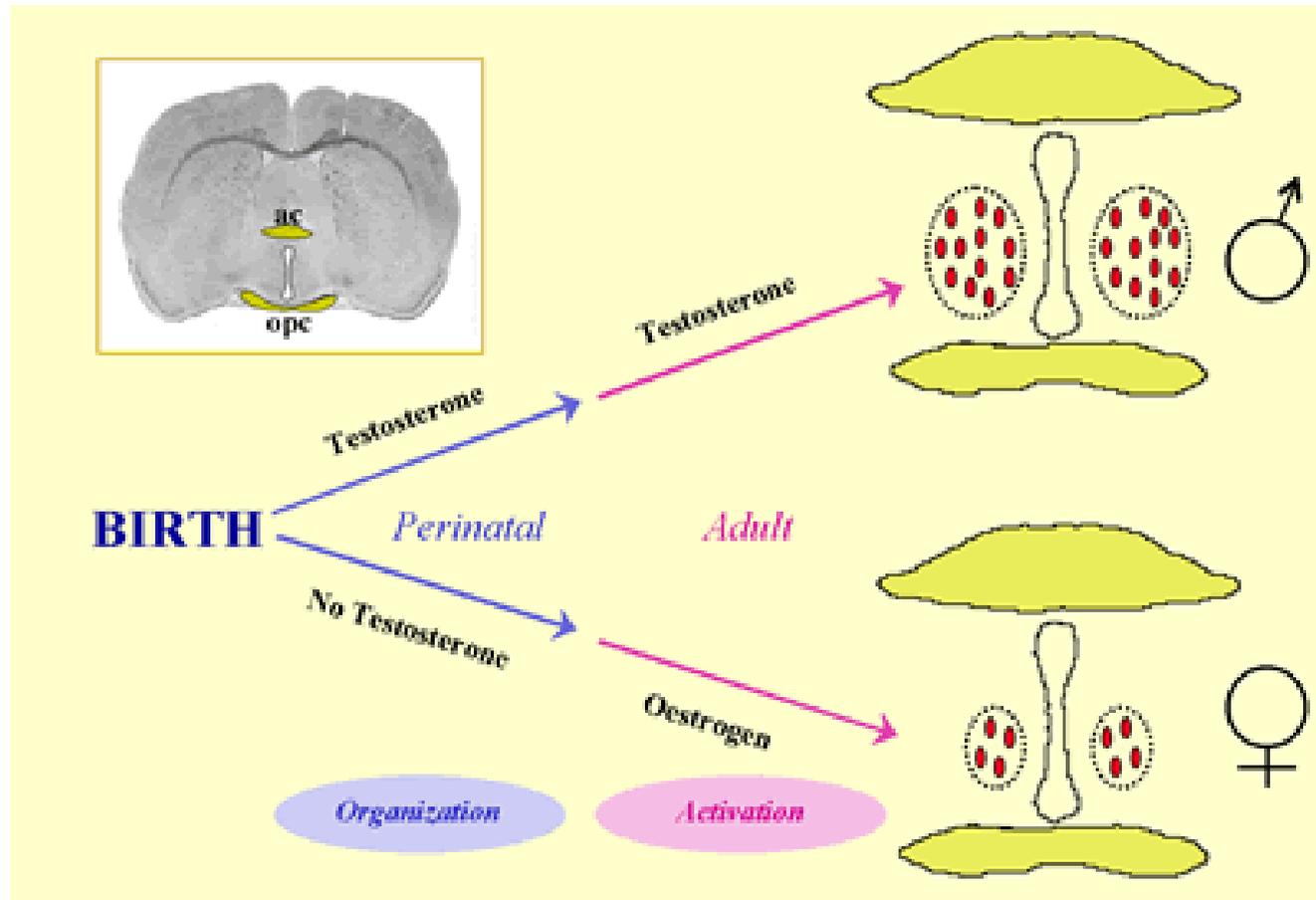
- Ubiquitous membrane derived signaling molecules implicated in neural plasticity
- **Newborn males have a higher endocannabinoid tone in the amygdala** – more Anandamide and 2-AG, less FAAH and MAGL
- Higher endocannabinoid tone represses cell genesis in males



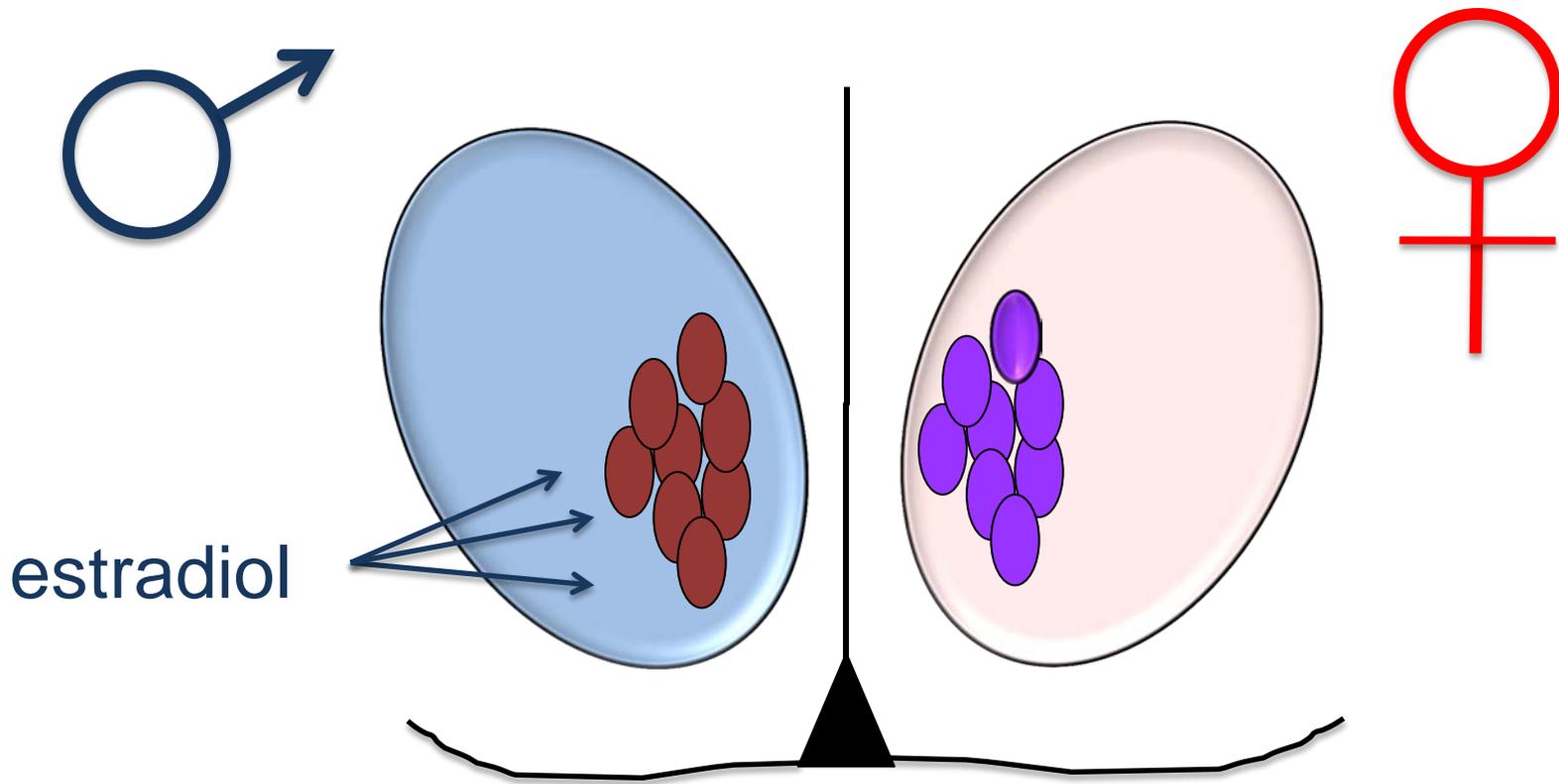
# Classic view on apoptosis



# Sexually dimorphic nucleus (SDN) is a naturally occurring model of apoptosis



# Testosterone / estradiol promotes survival of SDN neurons



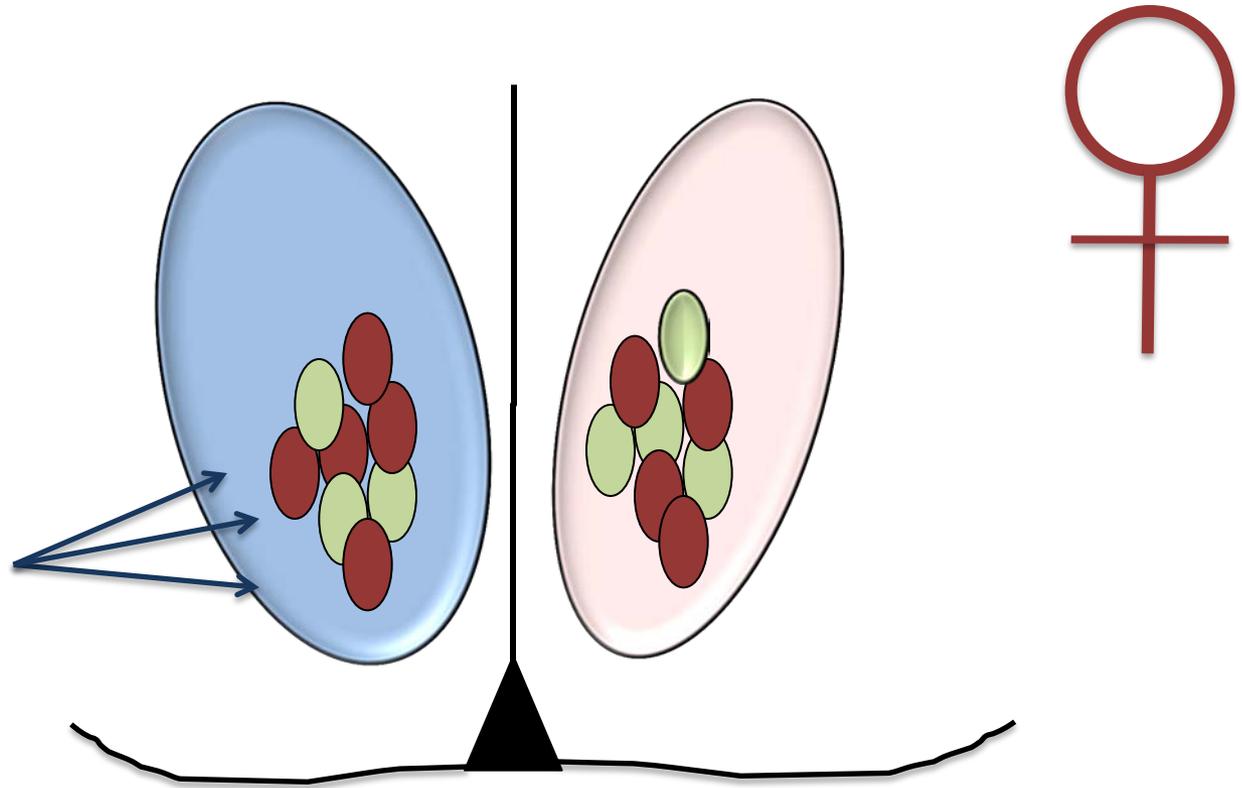
Resulting in the larger male SDN

# But in the AVPV estradiol KILLS in a selective and directed manner

Caspase 3  
death of  
**dopamine**  
**neurons** –  
*Waters and*  
*Simerly, J.*  
*Neuroscience*  
*2009*

TNF $\alpha$ /TRIP  
induced death  
of **GABA**  
**neurons** –

*Peterson et al*  
*PNAS 2010*



Resulting in the larger female AVPV

Why has the value of studying sex differences not been widely embraced?

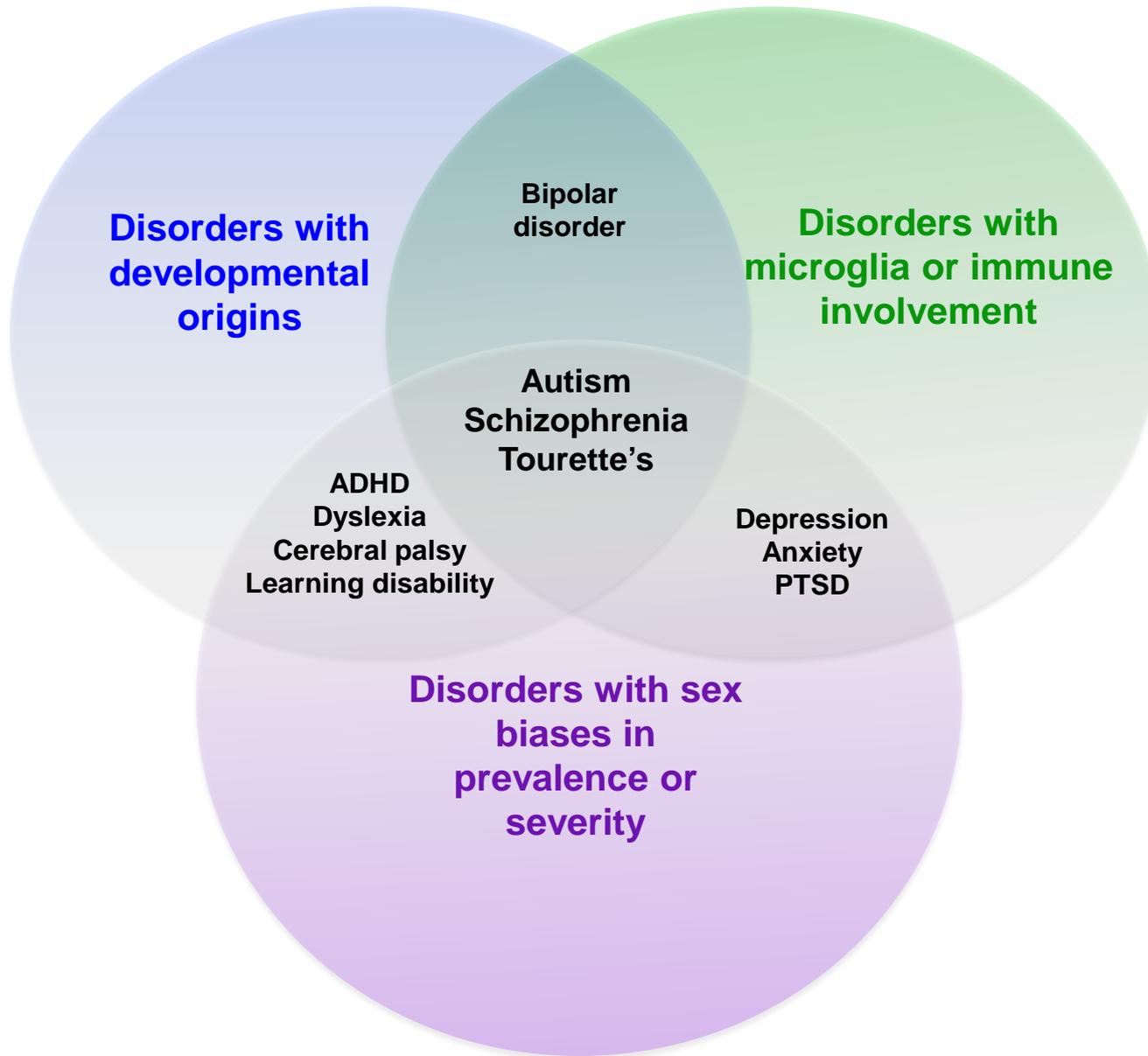
# In the past we had tunnel vision

- Discovery that gonadal hormones permanently influence the developing brain dates to 1959 (*Phoenix, Goy, Gerall & Young, Endocrinology, 1959*)
- Subsequent emphasis on reproduction associated endpoints and brain regions.
- DOGMA: Sex differences in the brain are **determined by hormones**, are only **relevant to reproduction** and are restricted to a **few brain regions**

# 3 important challenges to the dogma

- 1) Hegemony of hormones overthrown, **chromosome compliment matters** too
- 2) Sex differences in the brain are **pervasive** and multi-factorial
- 3) Sometimes a sex difference is not a sex difference.

# Understanding sex differences benefits both sexes



# Special thanks to those NIH institutes and centers that recognize and support research into sex differences



OFFICE OF RESEARCH ON WOMEN'S HEALTH

