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Science of Sex Differences - Session 3

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Disclosures

CURRENT FUNDING

National Institute of Mental Health

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R01 DA039062

CURRENT EMPLOYER

University of Maryland School of Medicine

Professor and Chair - Department of Pharmacology

UM MIND

Director: University of Maryland – Medicine Institute for Neuroscience Discovery

Why study sex differences in the brain?

Because BOYS are more likely to…

1	Be born prematurely
2	Suffer injury at birth
3	Have worse outcomes following injury
4	Be diagnosed with a neuropsychiatric or neurological disorder with origins in development.

WOMEN are more likely to…

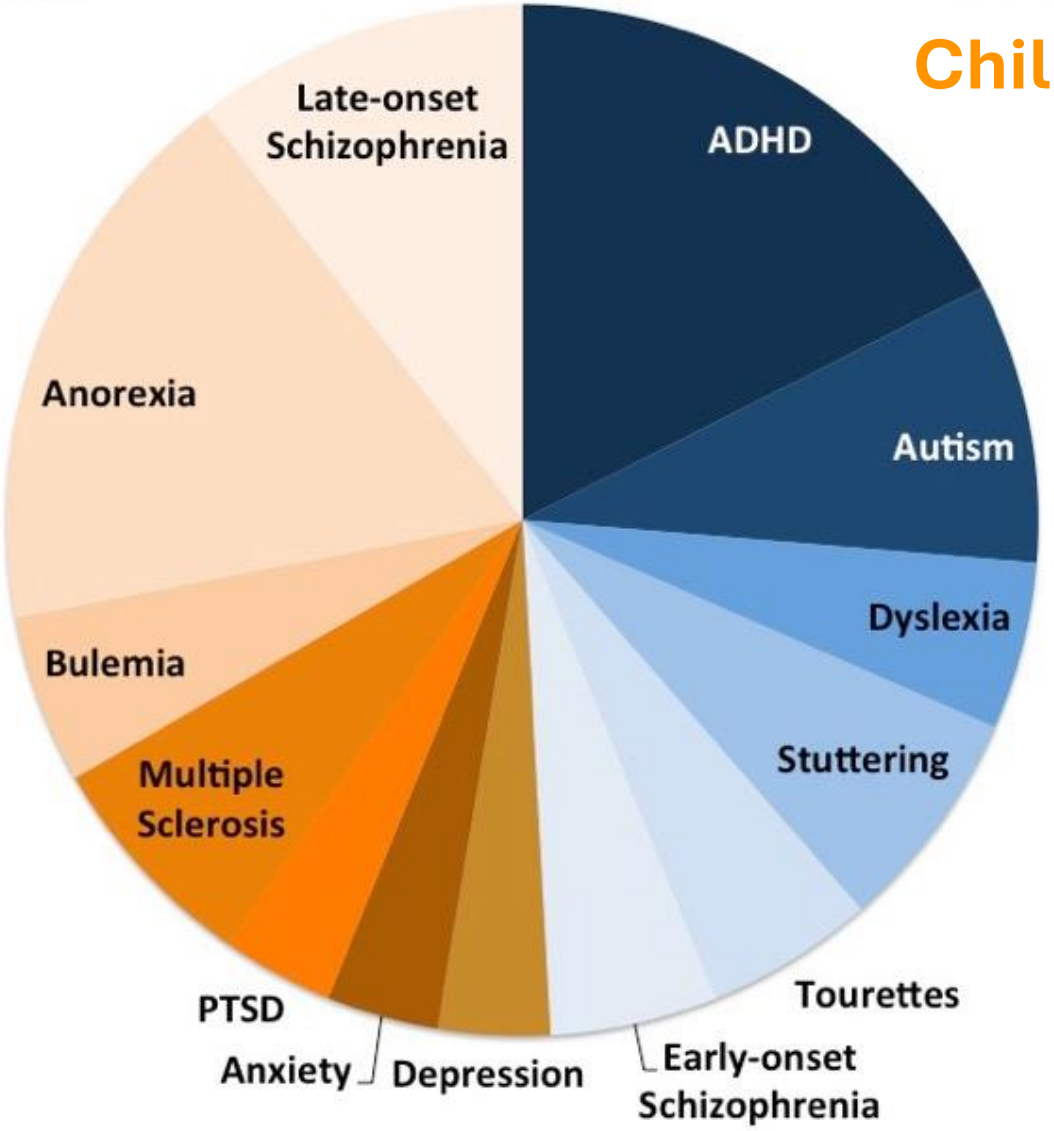
1	Experience intrapersonal or sexual violence
2	Suffer from an affective disorder
3	Endure chronic pain
4	Be diagnosed with an autoimmune or neurodegenerative disorder

Female biased

Adult Onset

Male biased

Childhood Onset



This profound gender bias compels us to understand the origins of both risk and resilience to disorders of the brain

Region-specific macro-anatomical sex differences in animal brains have been documented since the 1970's

Nottebohm and Arnold, 1976, Science

ELSEVIER

Brain Research

Volume 148, Issue 2, 16 June 1978, Pages 333-346

Evidence for a morphological sex difference within the medial preoptic area of the rat brain

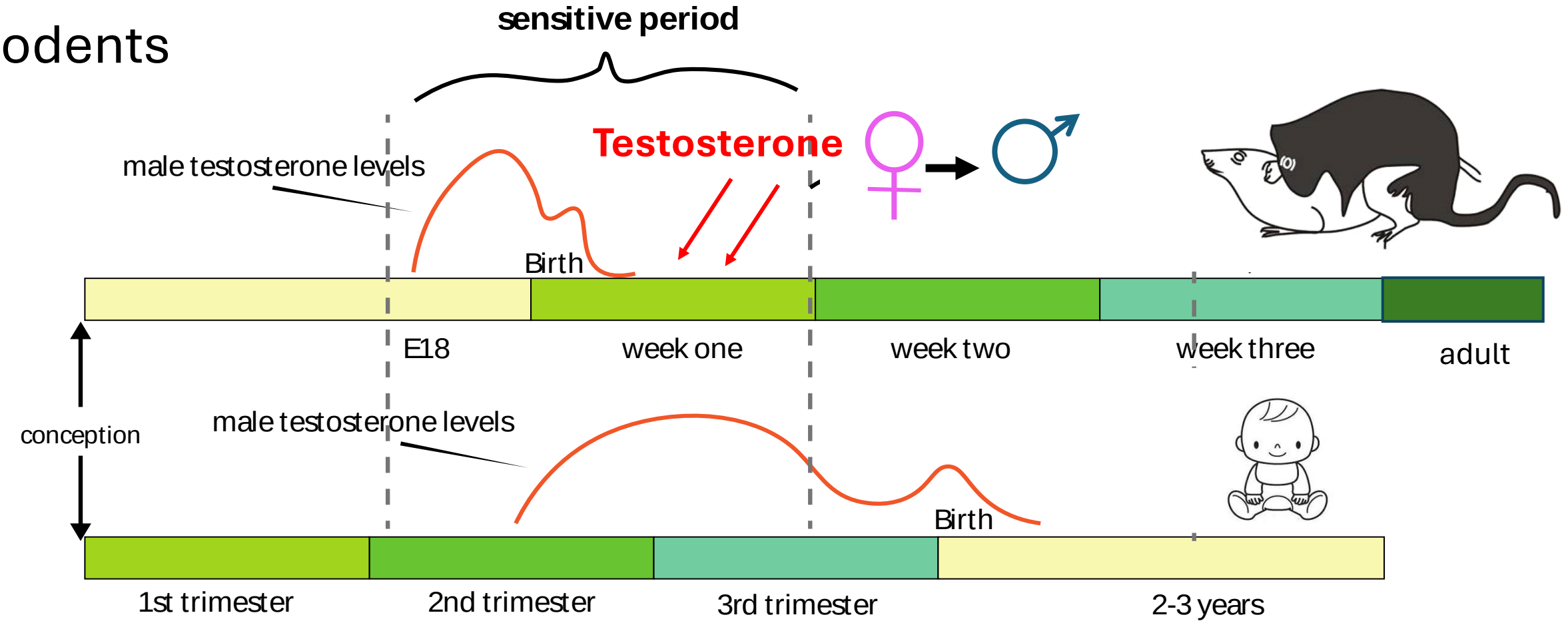
Gorski et al., 1978, Brain Research

SDN – sexually dimorphic nucleus

Is there value in studying sex differences in rodent brains?

Brain sexual differentiation occurs early in development during a sensitive period

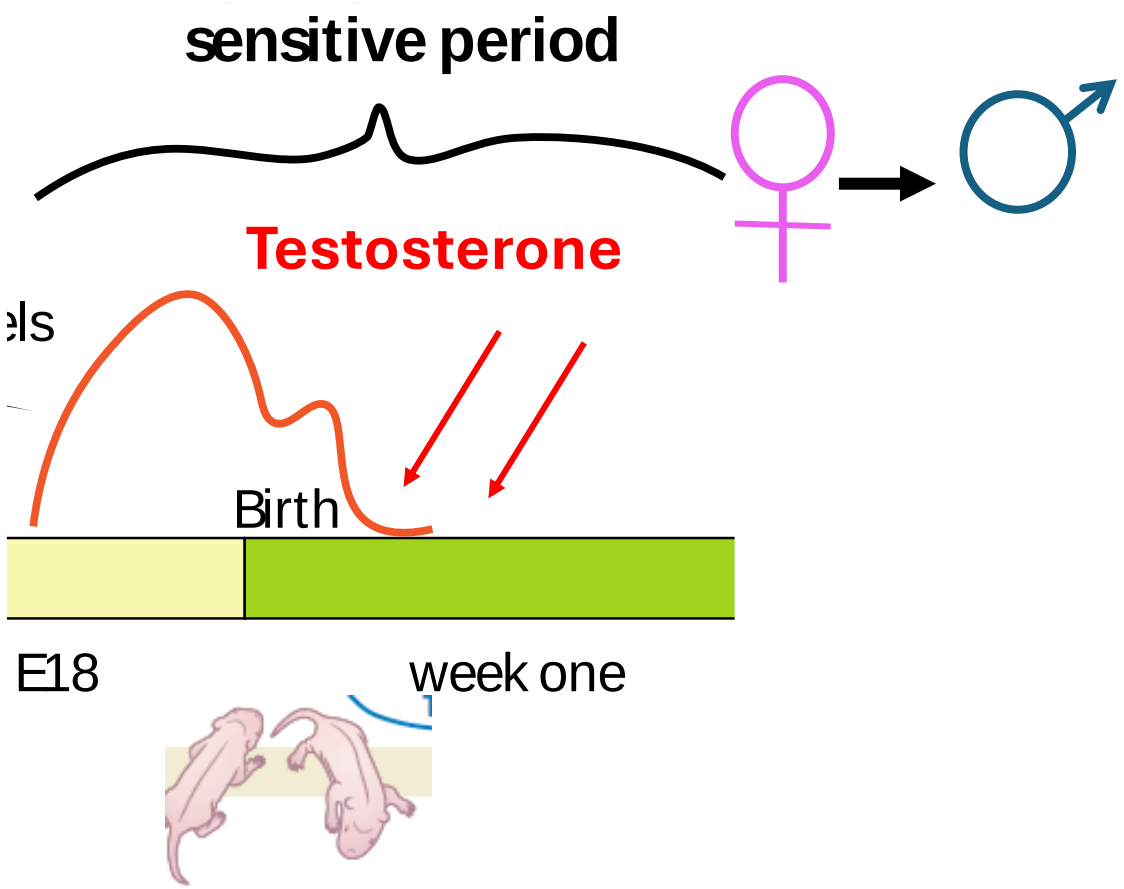
Rodents



Humans

We have known this since the 1960's

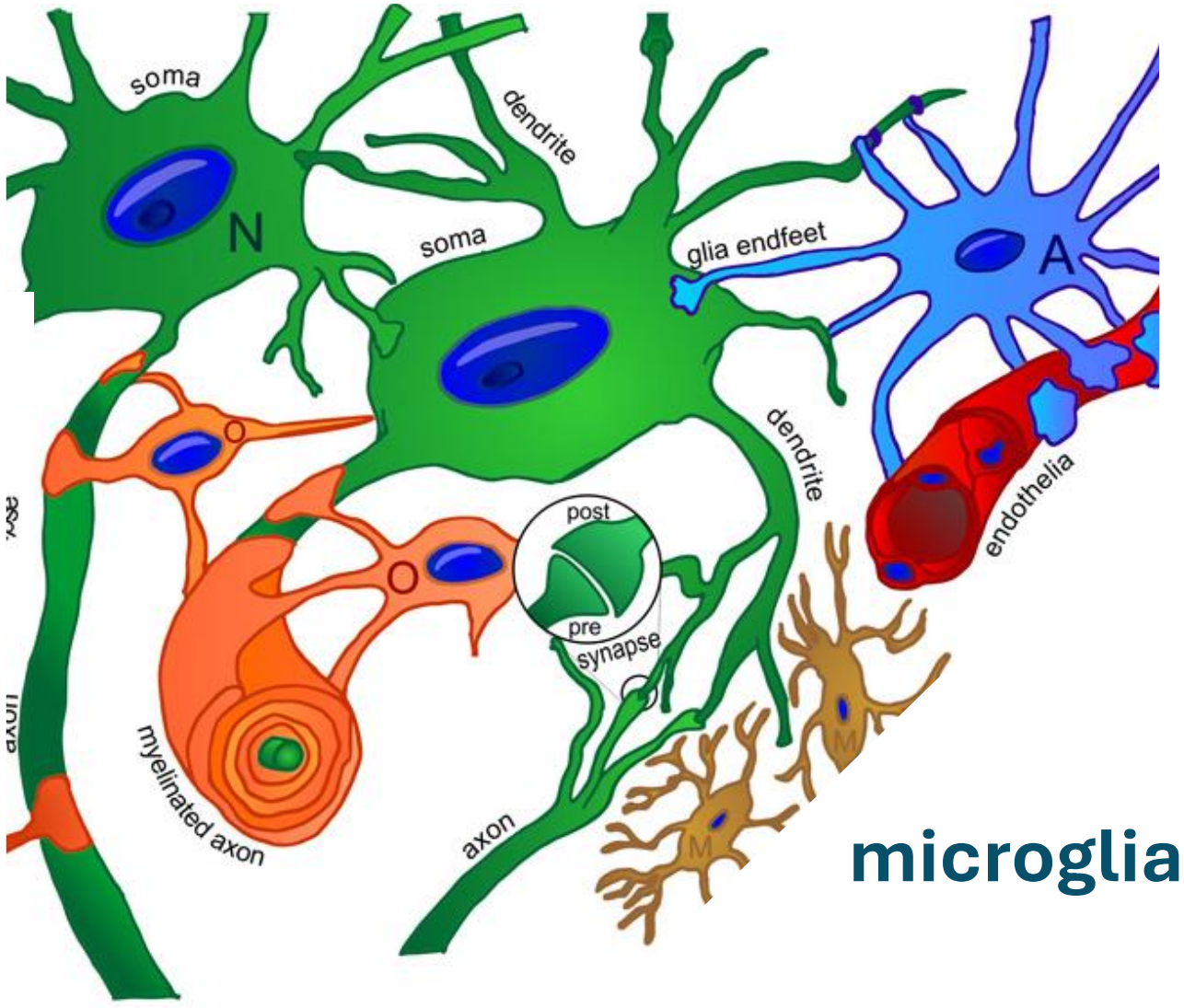
My lab focuses on the sensitive period and asks 3 questions:



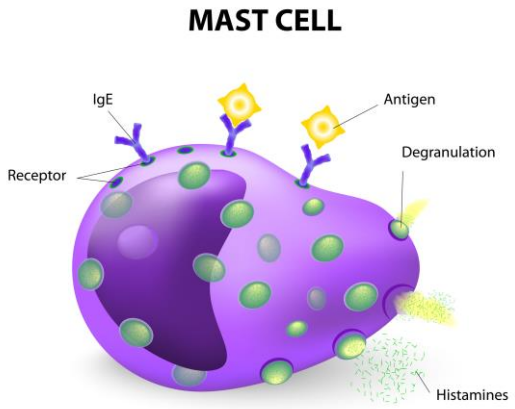
1	What are the sex differences
2	How do they happen
3	What do they mean

We also focus on non-neuronal cells, astrocytes, microglia and mast cells (innate immunity)

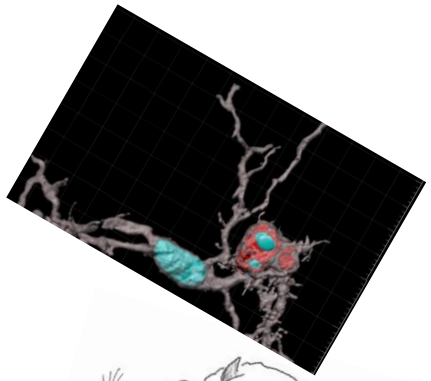
neurons

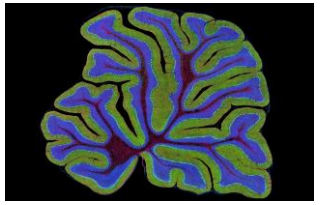


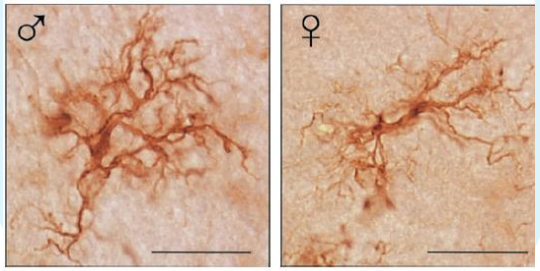
astrocytes (glia)



microglia



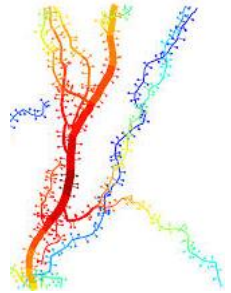


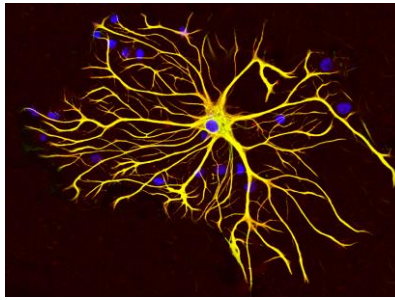


Astrocytes are more activated in males

2002

2002 Prostaglandin E2 promotes synapse formation in males

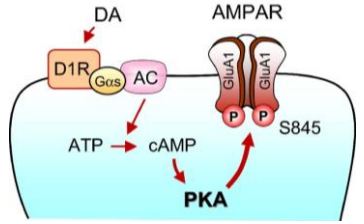




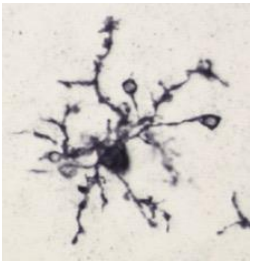
Astrocytes make PGE2

2004 PGE2 masculinizes mating behavior

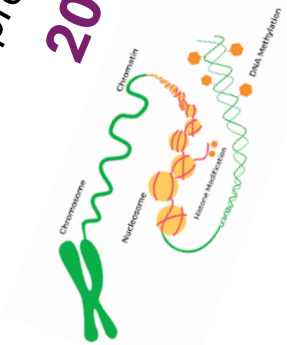
2011 PGE2 phosphorylates AMPA receptors



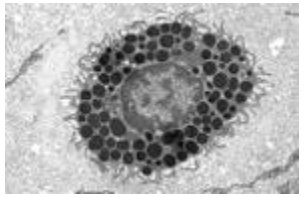
2013 Microglia are more activated in males



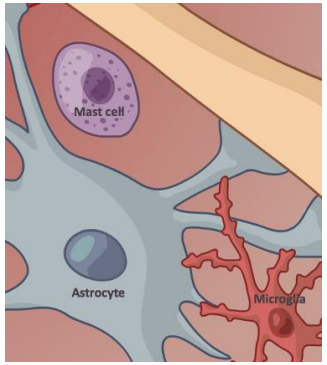
2013 Immune genes are epigenetically repressed in females



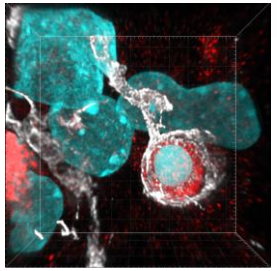
2018 There are more mast cells in male brains



2019 Mast cells direct microglia to make PGE2



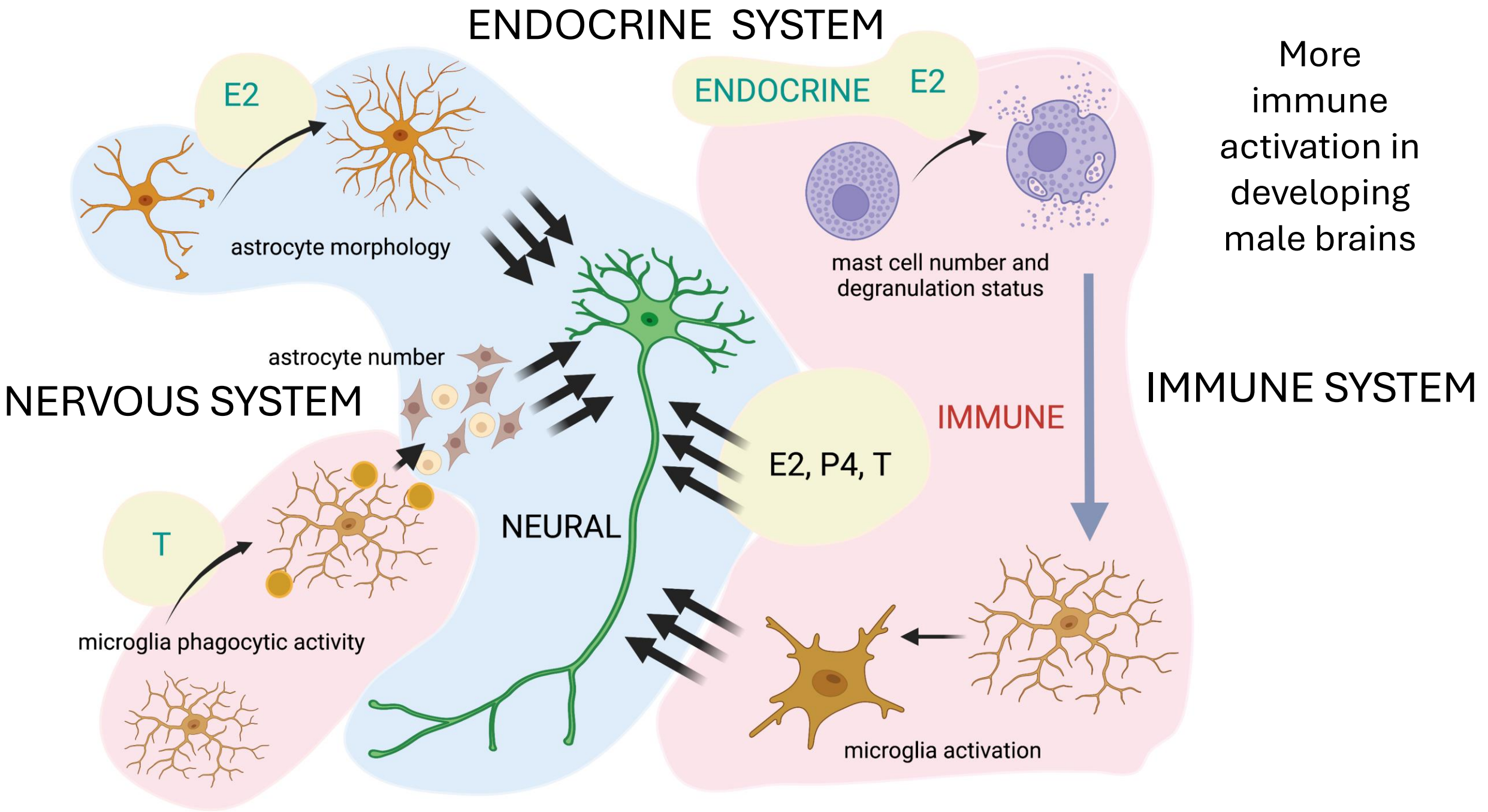
2023 Microglia are more phagocytic in males, promoting play



2024 sex differences In inflammation in human cerebellum

Microglia eat more neurons in females

What have we found?


ENDOCRINE SYSTEM
E2
astrocyte morphology
ENDOCRINE
E2
mast cell number and degranulation status
More immune activation in developing male brains
astrocyte number
NERVOUS SYSTEM
IMMUNE SYSTEM
IMMUNE
E2, P4, T
NEURAL
T
microglia phagocytic activity
microglia activation

How does inflammation influence human cerebellum development and are there sex differences?

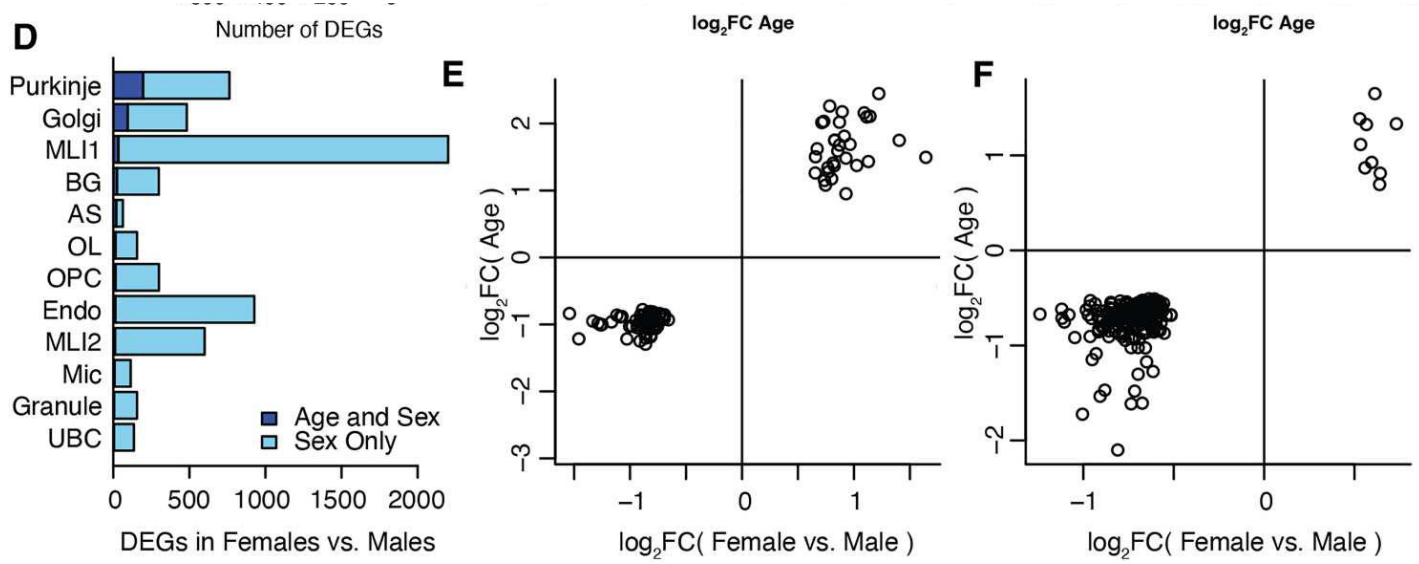
Compared the single nucleus transcriptome from children (>5 yrs old) experiencing systemic inflammation around the time of death (n = 17) versus those not experiencing inflammation (n = 25).

Science Translational Medicine | RESEARCH ARTICLE | FIRST RELEASE

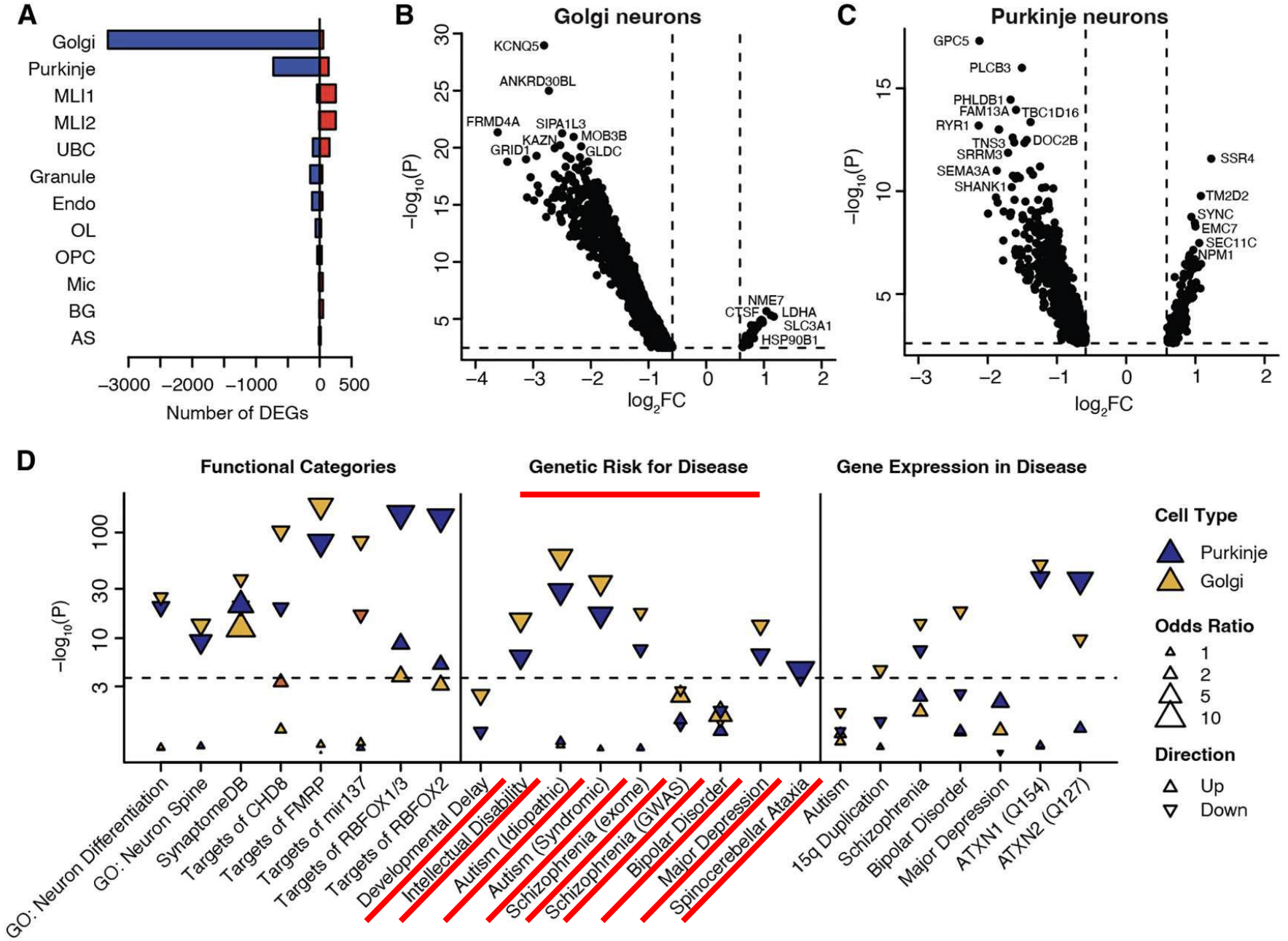
BICCN

A single-cell genomic atlas for maturation of the human cerebellum during early childhood

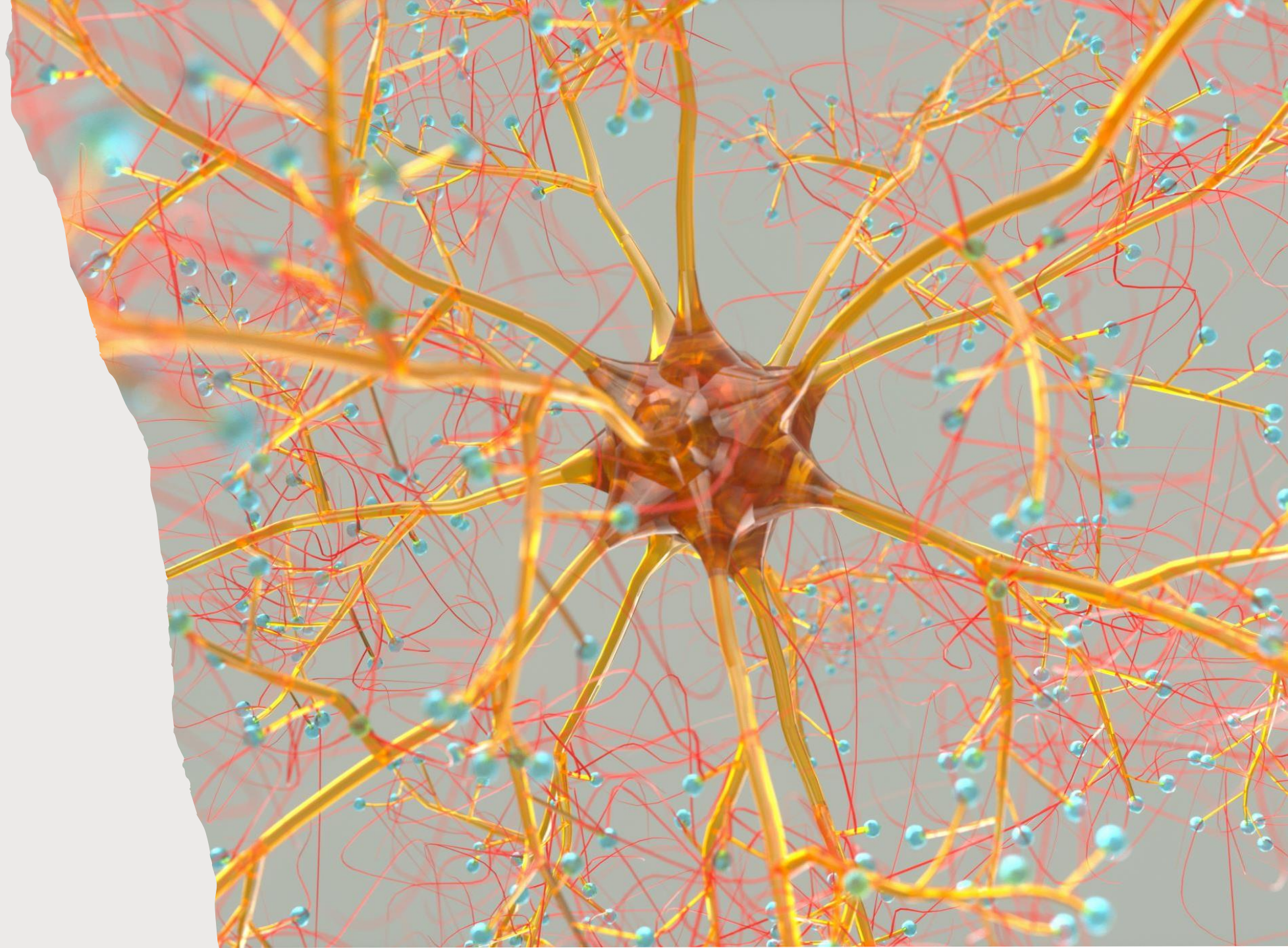
Seth A. Ament[1,2,3]*, Marcia Cortes-Gutierrez[1], Brian R. Herb[1,4], Evelina Mocci[1,5], Carlo Colantuoni[1,6], Margaret M. McCarthy[3,4]*



Main cell types affected are Golgi Cell interneurons and Purkinje Cells



Broader impacts



Being male is the leading biological predictor of relative risk for a developmental neuropsychiatric disorder

Early life inflammation is the leading environmental predictor of relative risk of a developmental neuropsychiatric disorder

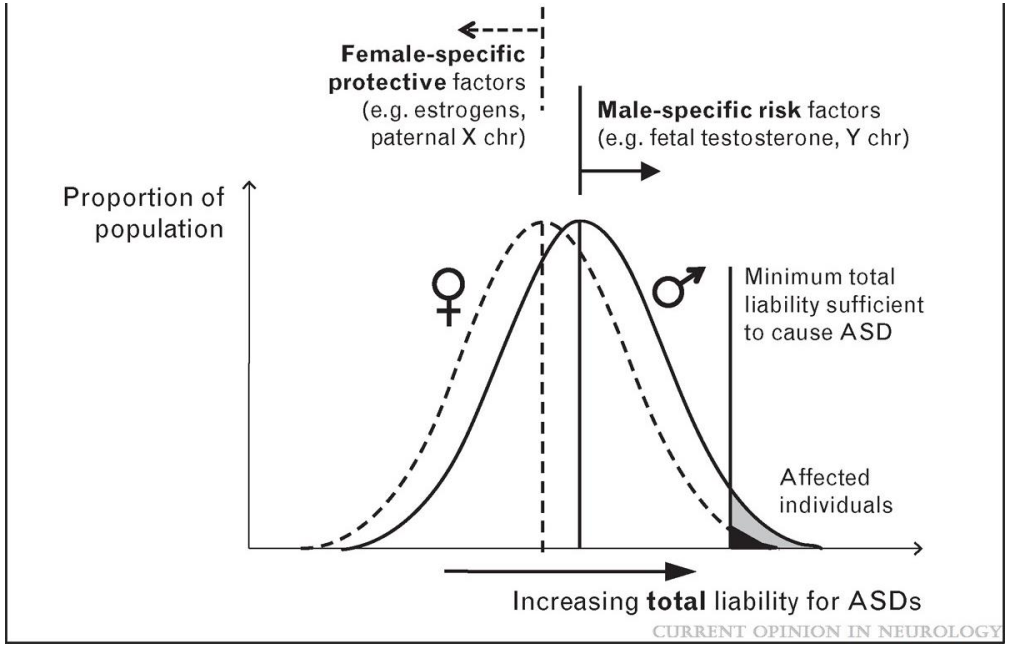
Autism Spectrum Disorder

4.5 : 1 Boys to Girls

Mast cells and Autism

- **4.5 : 1 Boys to Girls**
- Often have food allergies and skin rashes
- 10X higher incidence in children with mastocytosis
- Increased incidence if parent has mastocytosis or asthma
- (Theoharides – *Eur J Pharmacol* 2016)

Female Resilience versus Male Vulnerability



[Sex differences in autism spectrum disorders]

Werling, Donna M.; Geschwind, Daniel H.

Current Opinion in Neurology26(2):146-153, April 2013.

2 Hypotheses:

1) Autism Risk Genes are expressed higher in males
2) Genes associated with sex differentiation are dysregulated in ASD males

Wolters Kluwer

Neither!

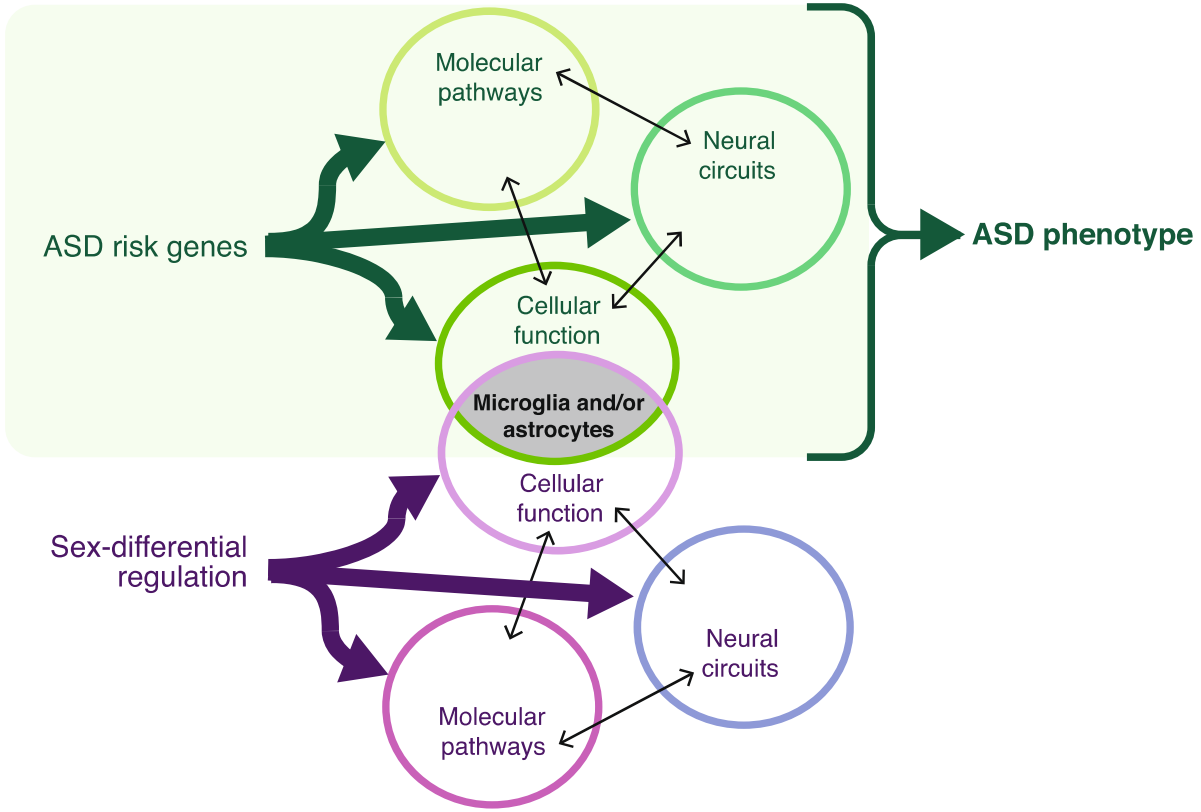
Werling *Biology of Sex Differences* (2016) 7:58
DOI 10.1186/s13293-016-0112-8

Biology of Sex Differences

REVIEW Open Access

The role of sex-differential biology in risk for autism spectrum disorder

Donna M. Werling



***"Microglia and astrocyte markers and genes** up regulated in ASD brain tend toward higher expression in prenatal male brain"*
Werling et al., 2016 Nat Comm.

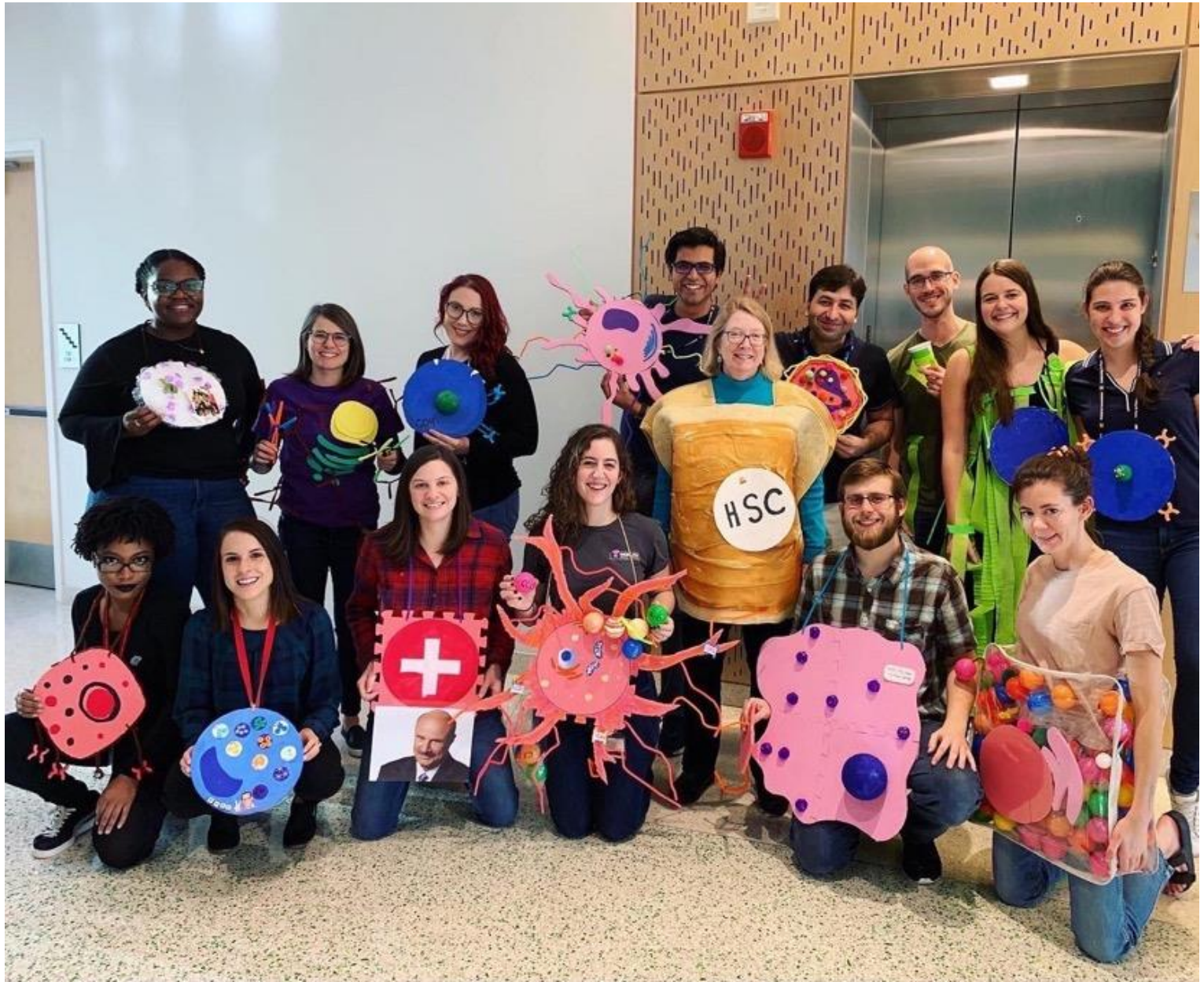
"…most important areas or approaches that need to be considered when conducting basic and translational studies aimed at generating new knowledge that could improve women's health"

- Greater understanding of steroid hormones and associated effects across the lifespan, integrated with the nervous and immune systems.
  - We are blind to the levels of steroids in the brain
  - Most neuroscientists ignore steroids (at their peril!)
- More "blue-sky" research on the biological origins of sex differences
- Women's Health needs to embrace "Girl's Health"

Are we "creating a legacy in this research space?"

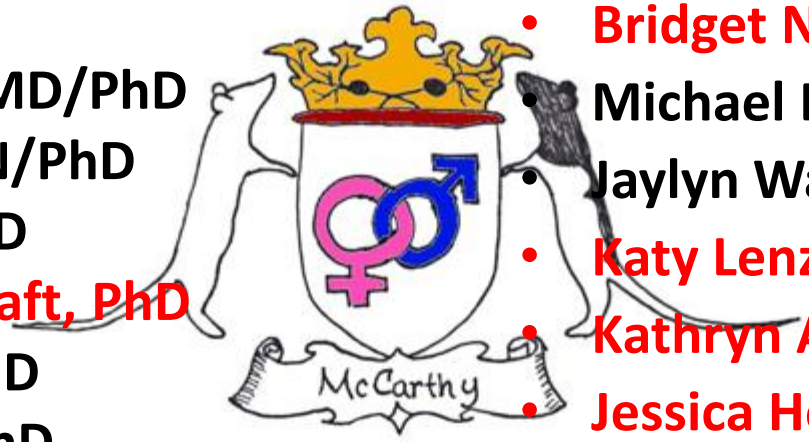
- Interest among PhD and MD/PhD students is extraordinarily high, from men and women.
- I currently have 7 students (2 MD/PhD) and one postdoc, and am actively turning students away.
- While in my laboratory, trainees have received F30 (3), F31 (2), F32 (3), K01 (2), R03 (1) and K99/R00 (1) awards.
- At least weekly inquiries from undergraduates, high school students and post-bacs.
- 18 of my trainees have held Assistant Professor positions, 12 on the tenure track.
- 6 are currently funded and active in research relevant to women's health

More support for trainees!



But most of all to many excellent students and postdocs

- Stuart Amateau, MD/PhD
- Tony Auger, PhD
- Scott Burkes, PhD
- Aline Davis, PhD
- Shannon Dean, MD/PhD
- Genell Hilton, RN/PhD
- Anne Konkle, PhD
- Desiree Krebs-Kraft, PhD
- Jessica Mong, PhD
- Joseph Nunez, PhD
- Tara Perrot-Sinal, PhD
- Lindsay Pickett
- Jonathan Van Ryzin
- Sarah Stockman
- Lidia Escudero, PhD
- Sheryl Arambula, PhD



- Jaclyn Schwarz, PhD
- Debra Speert, PhD
- Bridget Todd, PhD
- Christopher Wright, PhD
- Jian-Min Zhang, MD
- Susan Zup, PhD
- Bridget Nugent, PhD
- Michael Bowers, PhD
- Jaylyn Waddell, PhD
- Katy Lenz, PhD
- Kathryn Argue, PhD
- Jessica Hoffman, PhD
- Kathy Kight
- Miguel Perez Pouchoulen, PhD
- Pedro Peredes, PhD
- Ashley Marquadt
- Erin Reinl, PhD
- Amanda Holley, PhD