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
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. 
What about synaptic patterning in the POA?

The Preoptic Area (POA)

Adult male

Adult female
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$_2$

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Synapse formation in the POA requires prostaglandin synthesis.
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
Males have more “activated” microglia

And they produce more PGE2

Lenz et al., J. Neuroscience 2013
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.

Newborn males make twice as many new hippocampal neurons as females.

Krebs-Kraft et al., PNAS 2010

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

• 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

Krebs-Kraft et al., PNAS 2010
neurogenesis migration myelination synaptogenesis synaptic pruning Caspases; BAX apoptosis

neurulation glial genesis dendritic growth

conception gestation adulthood

birth infancy adolescence
Classic view on apoptosis
Sexually dimorphic nucleus (SDN) is a naturally occurring model of apoptosis.

David Spratt, University of Cambridge
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

TNFa/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 complement 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

**Disorders with developmental origins**
- ADHD
- Dyslexia
- Cerebral palsy
- Learning disability

**Disorders with microglia or immune involvement**
- Autism
- Schizophrenia
- Tourette’s
- Depression
- Anxiety
- PTSD

**Disorders with sex biases in prevalence or severity**
- Bipolar disorder
- Anxiety

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