



dstein

SEX Differences In The Brain?  
Do They Matter?

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# Why Should We Be Concerned About Sex Differences?

- Until very recently, the majority of laboratory studies were performed in male rats or mice.
- The female hormonal cycle can influence the effects of many drugs or other treatments.
- Having to study both males and females can double the time and cost of most laboratory studies.
- Subtle differences in behaviors are often missed and this oversight can affect conclusions about treatment effects.

# Lost In Translational Biology: Understanding Sex Differences To Inform Studies Of Diseases Of The Nervous System.

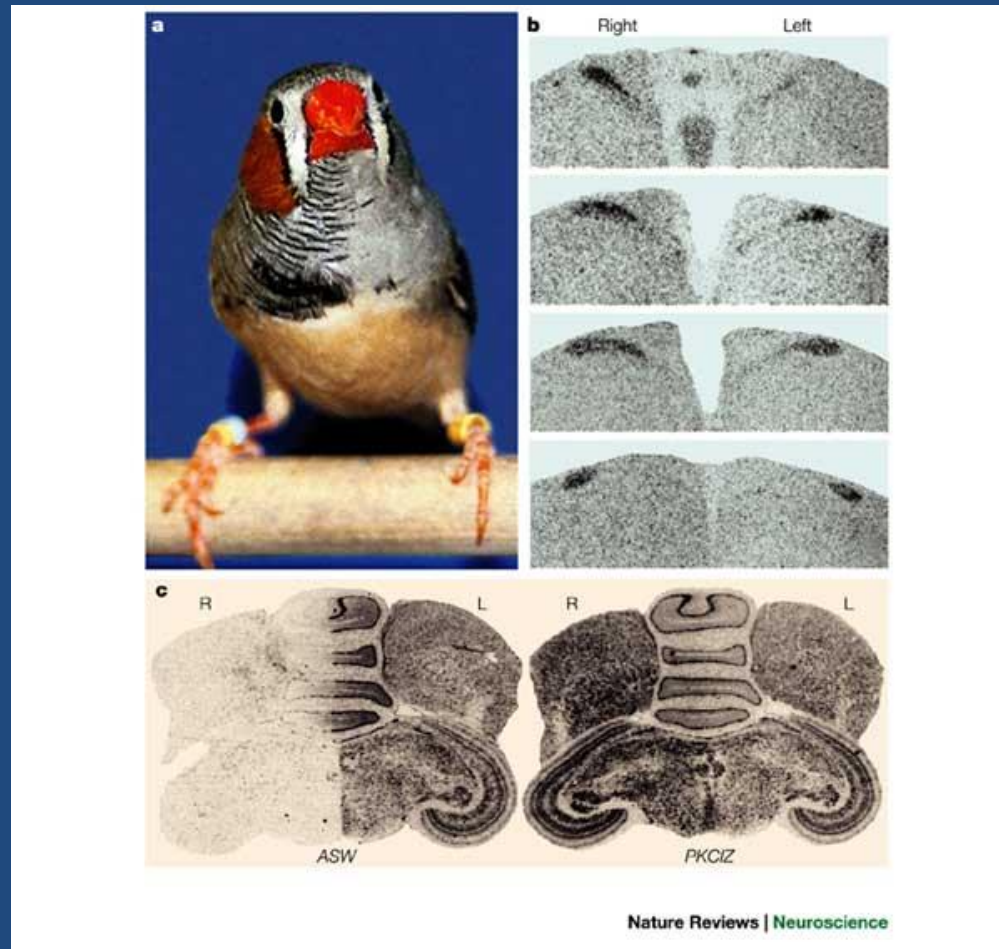
*Pearse, RV, Et Al Brain Res, 1722, 2019*

- While ethnic and geographical genomic variation plays a role in differential human biology, the greatest biological variability is between males and females.
- Virtually every neurodegenerative and neuropsychiatric disease shows some variation between males and females.
- Males and females differ in the prevalence, expression and symptoms of: Alzheimer's disease, Parkinson's, Multiple Sclerosis, Autism disorders, Pain and many others.
- There are often substantial sex differences in response to many classes of drugs.
- Male and female brains are not the same in both structure and function.

# Comparing Males and Females

- Age at time of testing or doing procedures is a critical variable because of maturational factors at both ends of the developmental spectrum.
- Sex differences seen at one age may not be apparent at another.
- Females may differ from males only on some days of the estrous cycle (e.g. in brain injury outcome).
- Women on contraceptives could have different outcomes than those not and both could be different from men.
- Drug doses can vary across estrous cycle.

# Even Birds Show Sex Differences In Brain Structure And Function

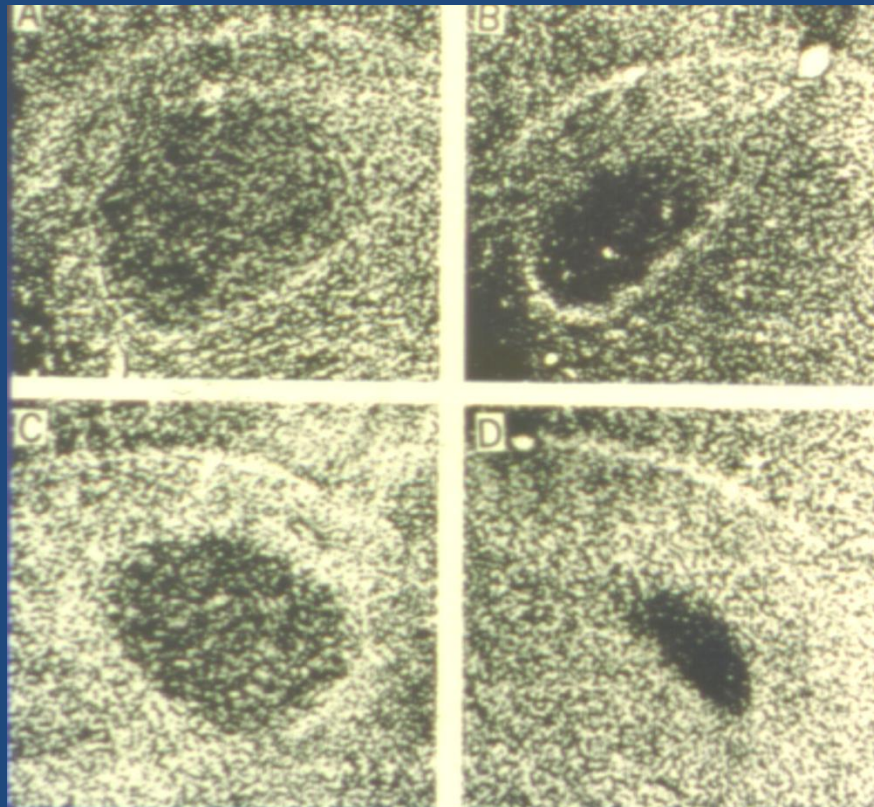


# Sexual Dimorphism in a Vocal Control Area (Robust Nuc. of the Archistriatum) of the Songbird

Male

Female

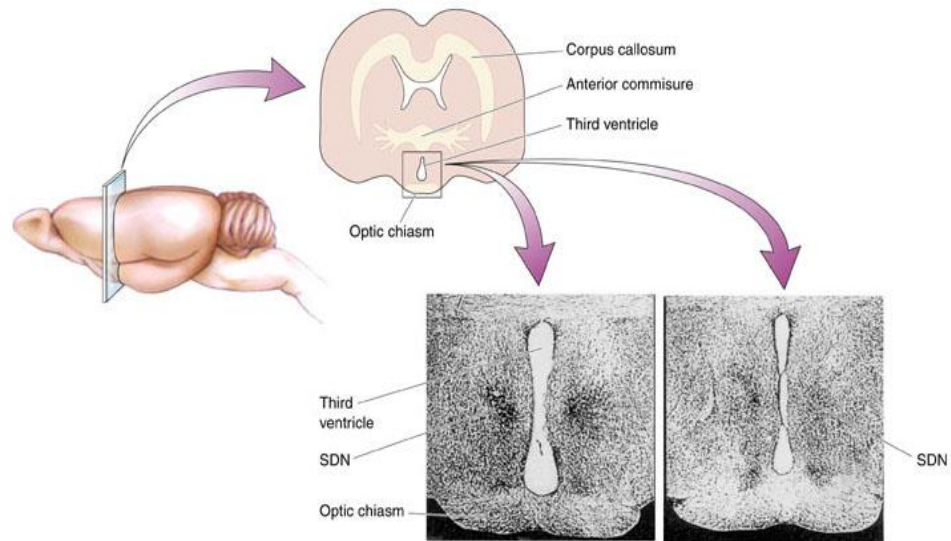
Canary



Zebra-finch

# Structural Differences in Male & Female Rodent Brains

**Figure 17.12**  
Sexual dimorphism in rats. The sexually dimorphic nucleus (SDN) in the hypothalamus of male rats (left) is much larger than the SDN in female rats (right). (Source: Adapted from Rosenzweig et al., 1999.)





# What Do Imaging Studies Reveal About Sex Differences In The Brain?

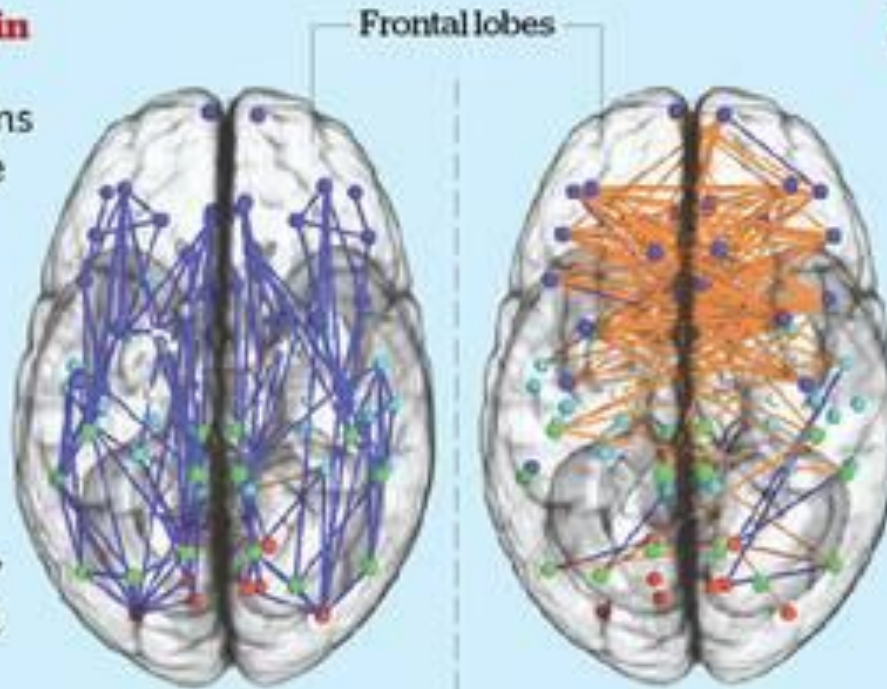
# Are Male and Female Brains 'Wired' Differently?

## The male and female brain

A new way of showing the connectivity of the brain - called "connectome" maps - reveals significant differences between men and women

### Typical male brain (top view)

Most connections run between the front and back parts of the same brain hemisphere, which could account for the better spatial skills and motor (muscle) control in men



### Typical female brain (top view)

Many more neural connections go from side to side across the left and right hemispheres of the brain. Scientists say this could account for women's better verbal skills and intuitive abilities

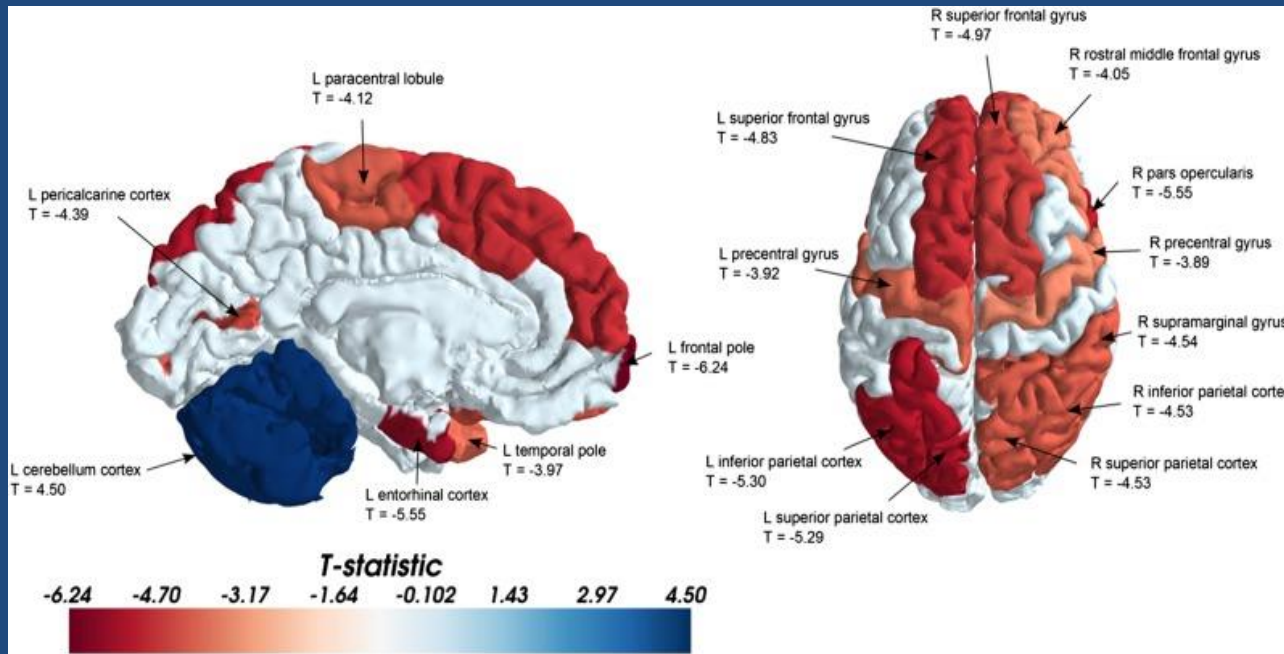
# Sex Differences In The Structure Of The Human Brain?

Ingalhalikar, M, et al, PNAS, 2014, v111

- Males have better motor and spatial abilities, but females have superior memory and social cognition skills.
- There are more connections between the 2 hemispheres of the brain in females.
- Overall, results suggest that male brains are structured to facilitate connectivity between perception and coordinated action.
- Female brains are designed to facilitate communication between analytical and intuitive processing modes.

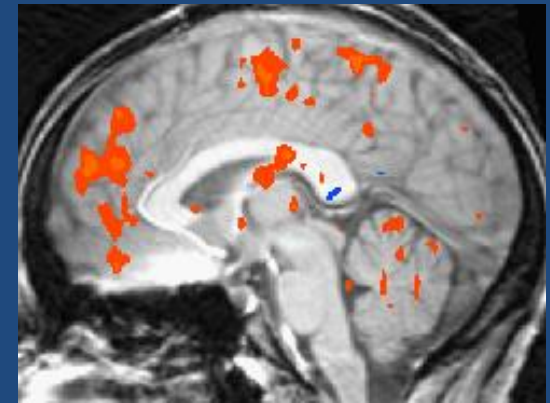
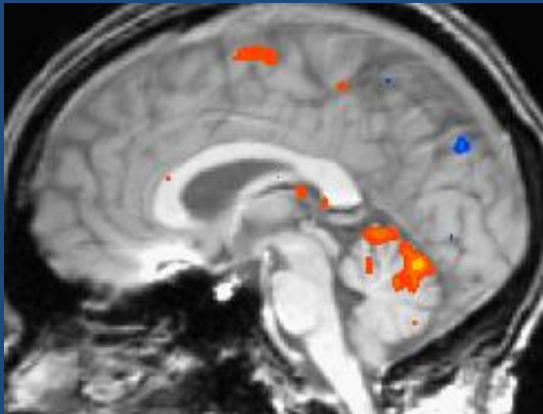
# Sex differences in the structural 'connectome' of the human brain

Ingalhalikar, M, et al, PNAS, 2014, v111



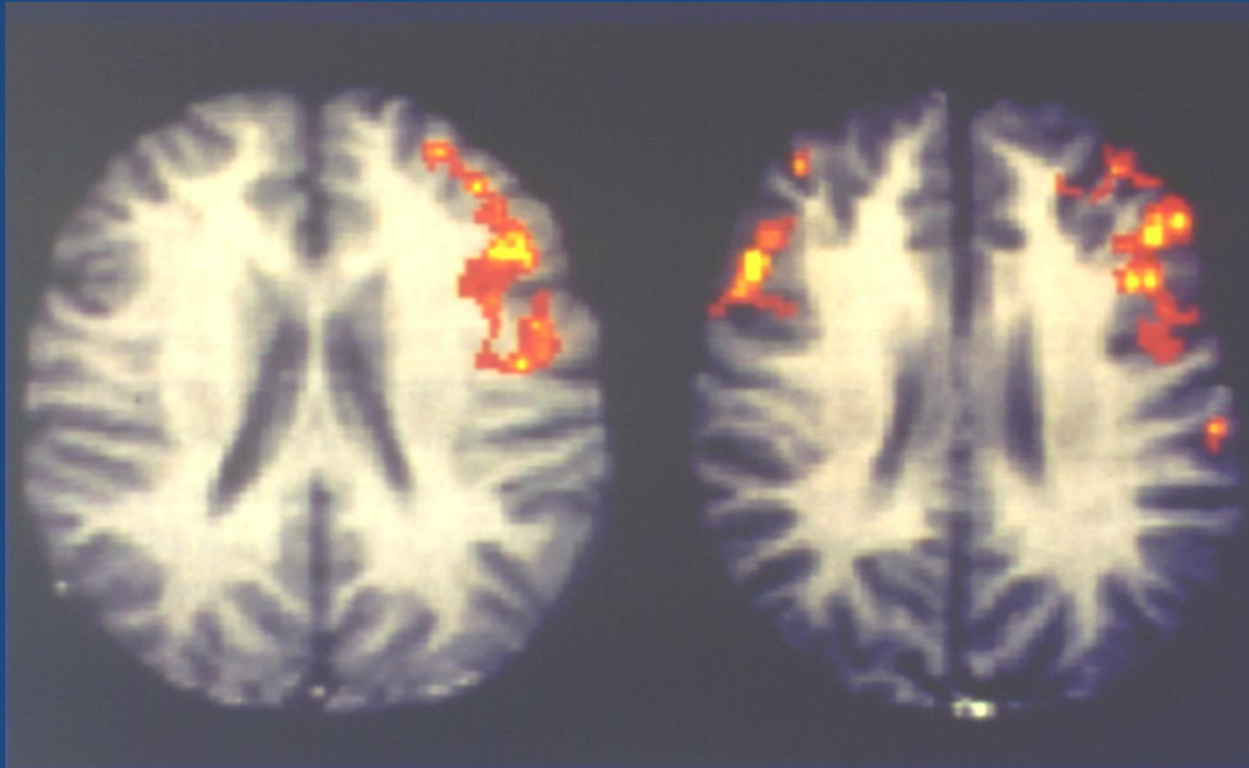
Representative regions of the brain that have a higher *PC* at a significance level of  $P < 0.001$ . Red indicates a higher *PC* in the females, and blue indicates a higher *PC* in males (mainly localized to the cerebellum). Representative regions and their corresponding *T* values are shown in the figures. These tests revealed that although multiple regions have higher *PC*s in females, the cerebellum has a higher *PC* in males. L, left; R, right.

# Uh Oh! Individual Differences In Brain Mapping. Any Implications??



- Three Individuals performing the same finger-tapping task—note variability in activation.
- Where is it localized? What are the implications?

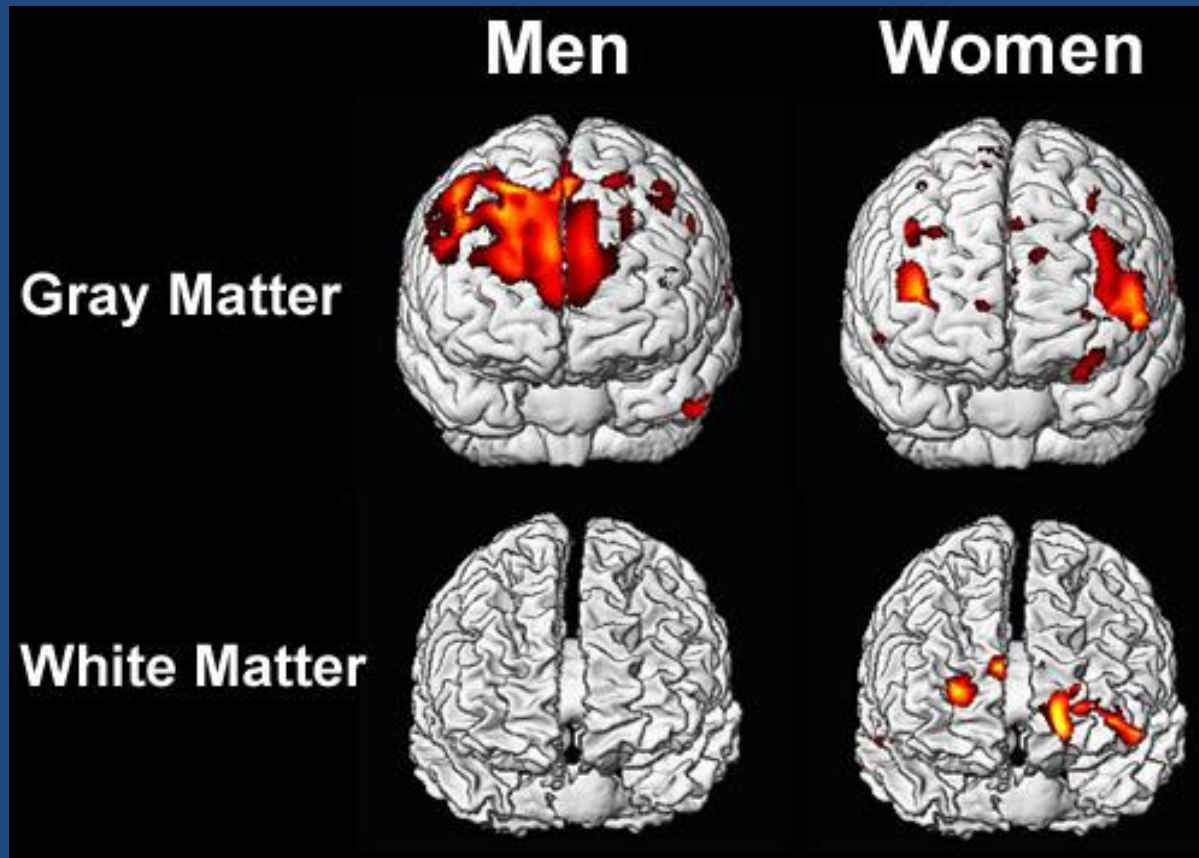
# Activation of brain regions during a rhyming task



Males

Females

# Sex Differences In Thinking About SEX



Nature Versus Nurture?



# On The Other Hand, What About Environmental Factors”? A Current Theory On Why Women Have Better Language Skills Than Men



# Misconceptions About Sex Differences And The Brain

- Sex differences are small and unreliable therefore not worth considering.
- Sex differences (in brain function) are rare and due to a few extreme cases....not at all typical.
- Differences within sex are more important than between sex.
- Differences are only due to estrogen during development.
- Neural mechanisms underlying behavior are identical for males and females.

# Some Environmental Factors Contributing To Male Female Differences

- Diet and body fat.
- Frequency and duration of Exercise.
- Types of testing to measure deficits
- ER responses to injury.
- Sensitivity to drugs before, during and after an injury.
- Hormonal status prior to, and at injury.
- Women uniquely experience distinct life stages marked by levels of circulating sex hormones, as well as by physiological changes that are nonexistent in men.

# Sex Differences In Brain Anatomy?

- Nerve cells tend to be larger in women; especially in left hemisphere, but males tend to have more cells.
- Women are more frequently right handed but have better language skills than males.
- Women survive brain injuries better than males.

## Sex Differences In Metabolic Dys)function: Implications For Treatments

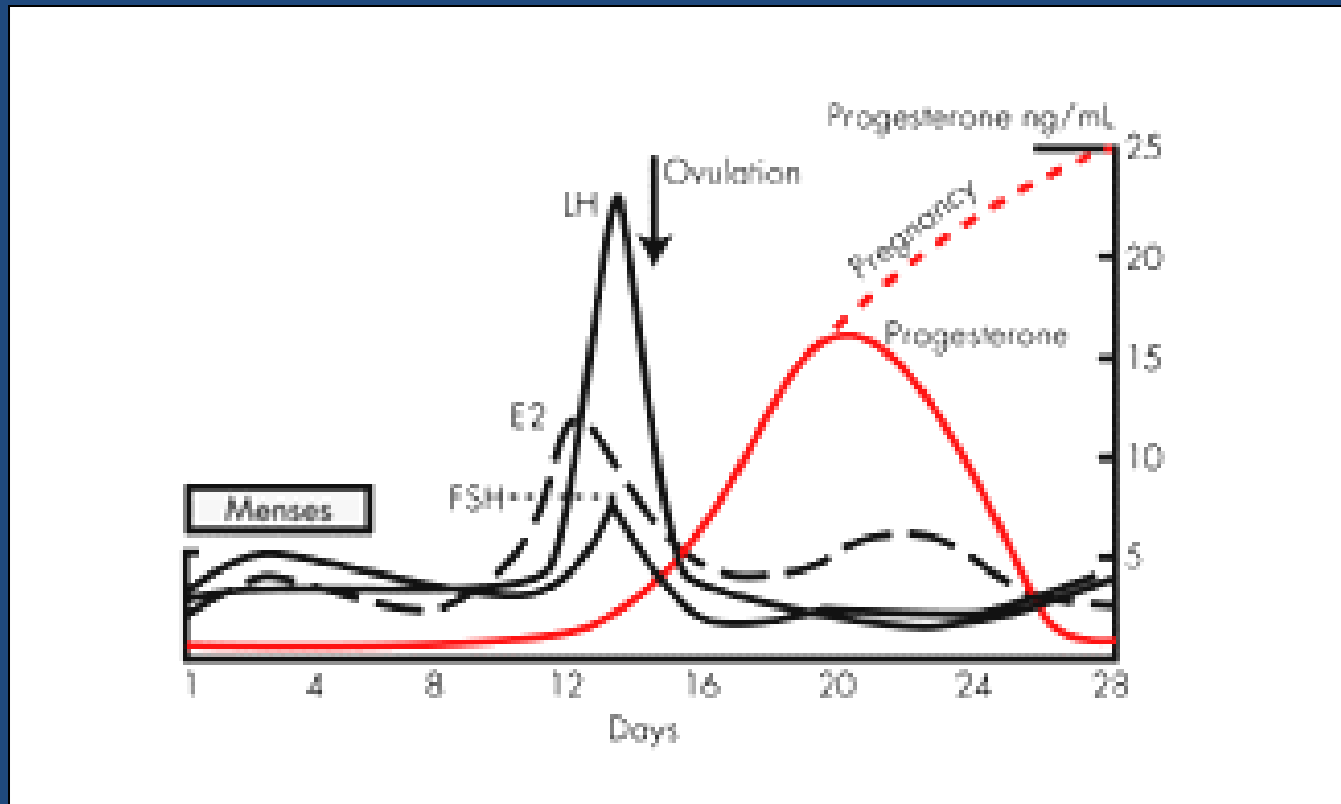
- Mitochondrial metabolic dysfunction is a common feature of CNS injury.
- Mitochondrial metabolism and cell death signaling are different in males and females. That is, biomarkers used to assess damage may not be the same in males and females.
- Evidence suggests males predominantly use proteins while females predominantly use lipids as a fuel source within mitochondria.
- These differences may significantly affect how the brain recovers following injury. .

## **Its complicated, And Its Not Just About Neurons: Sex Differences In Glia Reactivity After Cortical Brain Injury.**

- Males have a higher density of immune cells in the wound area than females.
- Males also have a higher density of healthier neurons in the lesion edge than females.
- These findings indicate that male and female mice have different inflammatory responses after a cortical injury, and suggest that sex differences in reactive gliosis can contribute to the differences seen in neuroinflammatory diseases and brain injury.

Sex Differences In The Outcome of Brain  
Injury May Can Be Mediated By Sex  
Hormones

# HORMONAL CYCLING





# Sex differences In Patients With Moderate to Severe Head Injuries

Berry, C et al J. Trauma, 67, 2009

- A total of 72,294 patients with moderate to severe TBI were studied.
- Women compared to males:
  - Had significantly less complications.
  - Shorter hospital length of stay.
  - Shorter ICU stay.
  - Substantially reduced mortality in women
  - Similar results reported in two other studies involving about 250K patients.

# What About Stroke And Stroke Incidence?

# STROKE IMPACT

- 1.8 million new strokes per year in industrialized countries
- Third leading cause of death  
(1st: heart disease, 2nd: all cancers)
  - Death rate 54.3 for 2003
  - Every 45 seconds someone has a stroke.
- Over 2.4 million stroke survivors
- Leading cause of adult disability
- Less than 5% of patients receive any treatment other than rehab

# MALES AND FEMALES DIFFER IN STROKE INCIDENCE AND SURVIVAL

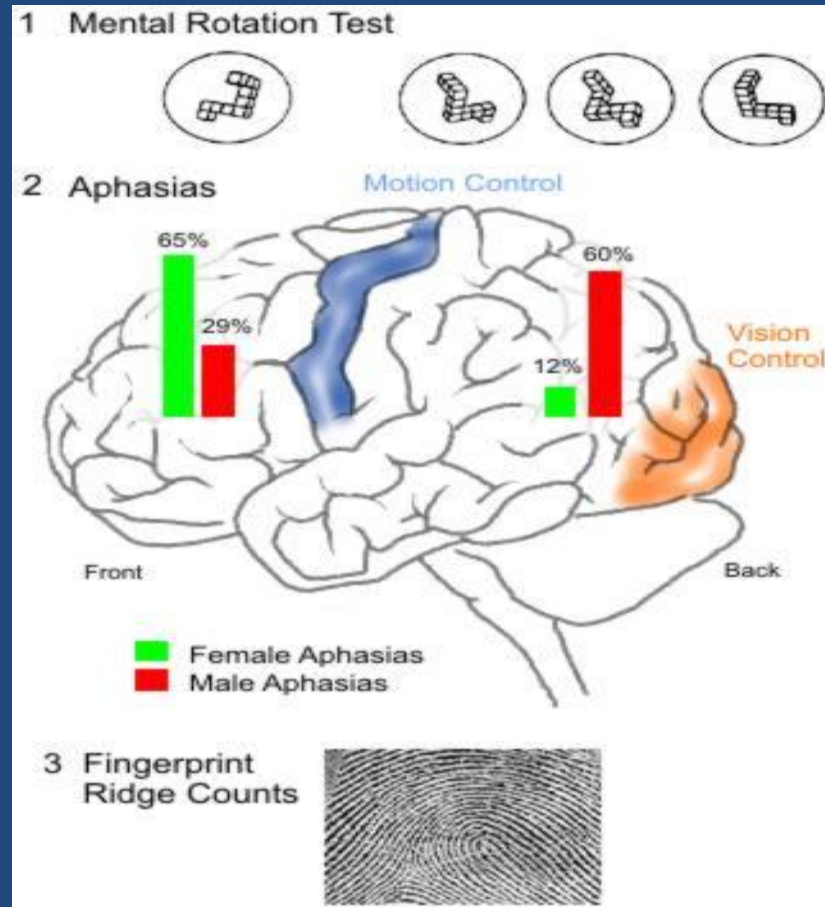
*Hurn, Vanucci, Hagburg, Stroke, 2005 v36*

- Overall incidence of stroke is lower in women across cultural and ethnic backgrounds.
- This effect extends beyond menopause.
- At cellular level female cells live longer than male cells and are less subject to cytotoxicity.
- Male mice more subject to ischemia and concussive injuries than females.

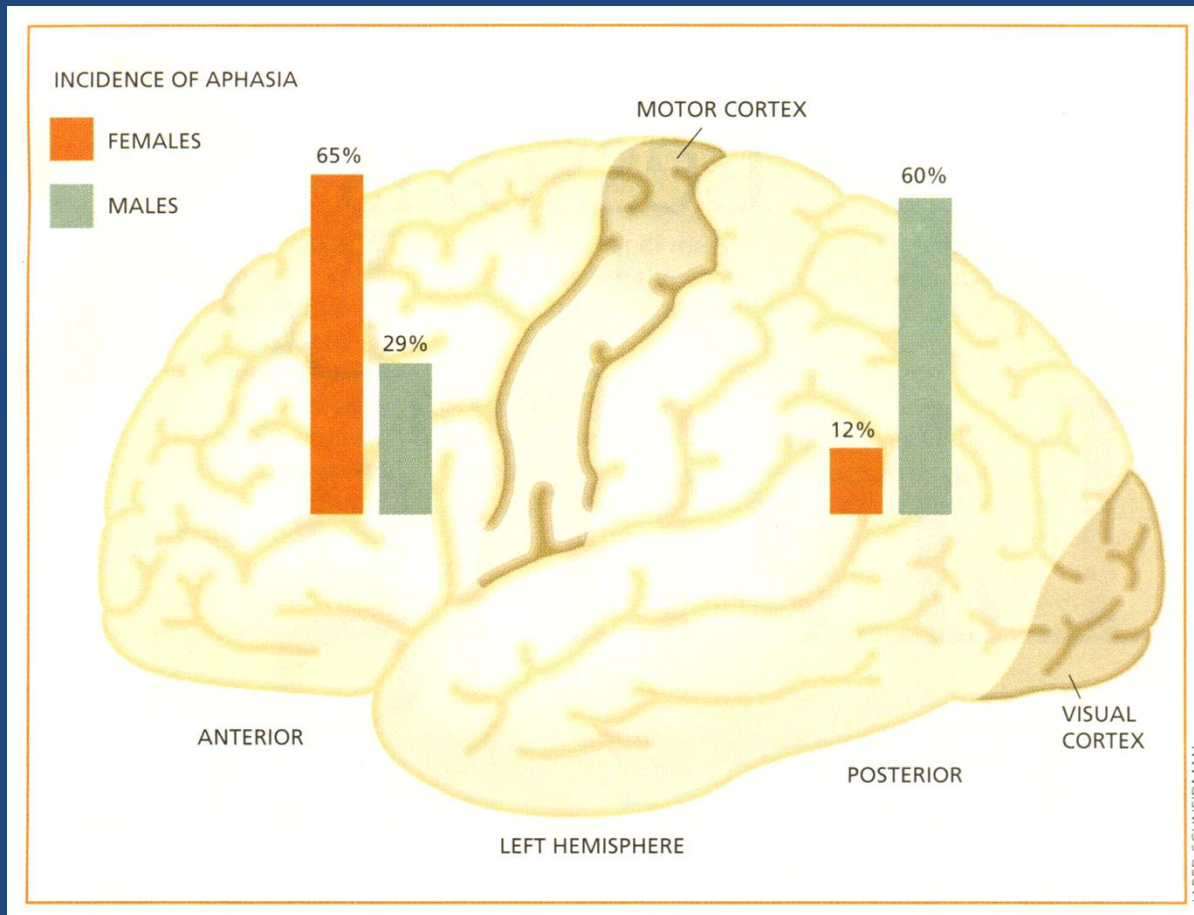
# SOME SEX DIFFERENCES IN STROKE OUTCOMES

- Ischemic events are more frequent in men.
- Women are less likely to have a stroke in early and mid-adulthood than men.
- Stroke rates do not equalize until women are over 75.
- Women respond better to tPA treatment.
- Incidence of speech disorders after stroke is higher in women if injury is to the left frontal cortex, while the opposite is true for males.
- After arriving in ER women experience greater time delay in stroke treatment than men & are more likely to receive anti-anxiety meds than blood pressure meds or aspirin.

# Are There Functional Sex Differences In Response To Stroke?



# Potential Sex Differences In Aphasia Outcome

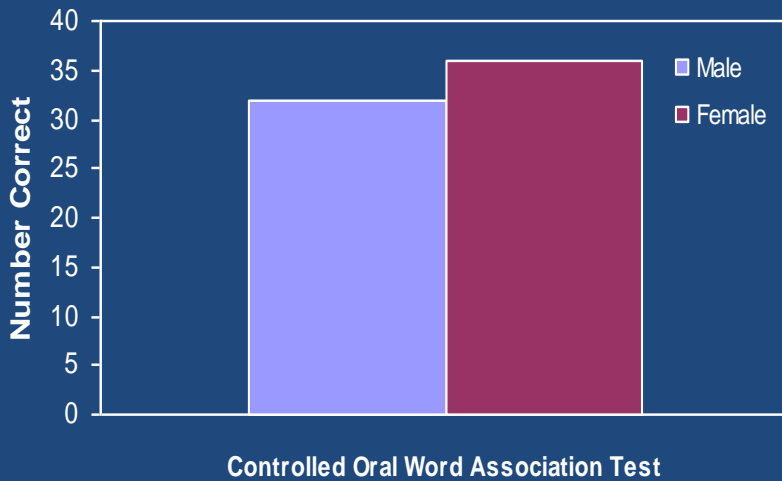


# Sex Differences In Brain Injury

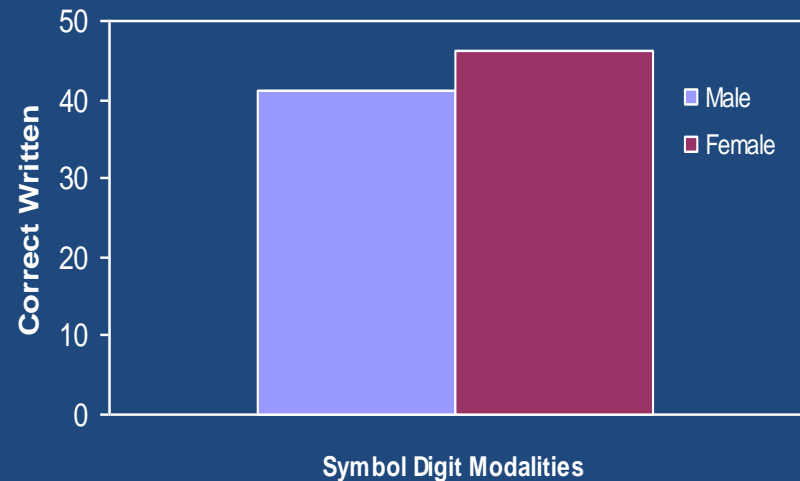
- Males and females do not differ in spatial learning tasks but following entorhinal cortex injury, females do much better than males on retention of spatial learning tasks (Roof et al 1993).
- In low birth weight children @ 2 years of age, females do much better than males “in all areas of social and developmental testing (Hindmarsh, et al 2000)
- In children with intracranial hemorrhage, girls significantly outperform boys on all tests (Raz, et al 1995).
- Girls with blunt TBI do significantly better on all verbal testing compared to boys (Donders and Hoffman 2002).



# Sex Differences in Recovery 1 Year After Traumatic Brain Injury



Women's language skills are better than males one year after traumatic brain injury.



Women have) greater attentionskills and working memory than males one year after traumatic brain injury.



# Conclusion



- Male & Female brains show anatomical, functional and biochemical differences in all stages of life.
- Sex differences need to be considered in studying brain structure and function.
- Helps in in early diagnosis, precise treatment and management for neurological & psychiatric diseases.
- Understanding development of normal brain and differences between the sexes is important for the interpretation of clinical imaging studies.

# Suggested Readings

- *Lost in translational biology: Understanding sex differences to inform studies of diseases of the nervous system. Pearse, RV and Young-Pearse TL, Brain Res. 2019,v.1722*
- *Sex differences in the brain: implications for behavioral and biomedical research. Choleris E, et al 2018, Neuroscie Biobehavioral Rev, v85,126-145*
- *Sex differences in traumatic brain injury: what we know and what we should know. Gupte, R et al, 2019, J. Neurotrauma, v36, 3063-3091*
- *Traumatic brain injury in women across lifespan. Neurobiol Dis*
- *2022. M Blaya, A Raval, HM Bramlett*

END

# Sex Differences In Brain Inflammatory Responses To Ischemic Injury

- Clinically, male infants are more vulnerable to ischemic insults and suffer more long-term deficits than females.
- Male and female mice were given 60-min of hypoxia at post-natal day 10 (P10). Stroke outcomes were measured 1, 3, 7, and 30 days after stroke. Inflammatory responses were measured.
- RESULTS: On day 1 of HIE, no difference in infarct volumes or seizure scores was seen between male and female neonates.
- However, female neonates showed *smaller infarct size and fewer seizures compared to males 3 days after HIE*. Females also had less brain tissue loss and behavioral deficits compared to males in the later stage of injury.
- Male mice had higher levels immune cell activation and the inflammatory response was higher compared to females at day 3.

- J Neuroinflammation. 2015