



stein

Understanding Sex Differences in Traumatic Brain Injury



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EEemory

Publications On Sex Differences: Some 'Rough' Statistics From Pubmed

“Sex differences in brain”

1970	29
1980	121
1990	337
2000	528
2010	1115
2017	1292
2024-5	2562

“Sex differences in stroke”

1970	20
1980	37
1990	91
2000	225
2010	432
2017	393
2024-5	723

“Sex differences in TBI”

1970	20
1980	37
1990	91
2000	225
2010	432
2017	393
20204-5	355

Some Environmental Factors Contributing To Male Female Differences In Functional Outcomes

- 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.

Why should we be concerned about sex differences? Some excuses for not including females in lab studies.

- In neuroscience labs 5X more studies performed in male rats or mice. Why?
- Female estrous cycle can influence the effects of many drugs or experimental manipulations. So does menopause.
- Having to study both males and females can double the time and cost of most laboratory studies.
- Subtle differences in behaviors can be missed and thus confound experimental results.
- Money: NIH is now requiring at least a good excuse for not including females.
- But, what happens when budget cuts in grants are made after the award is given?

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.

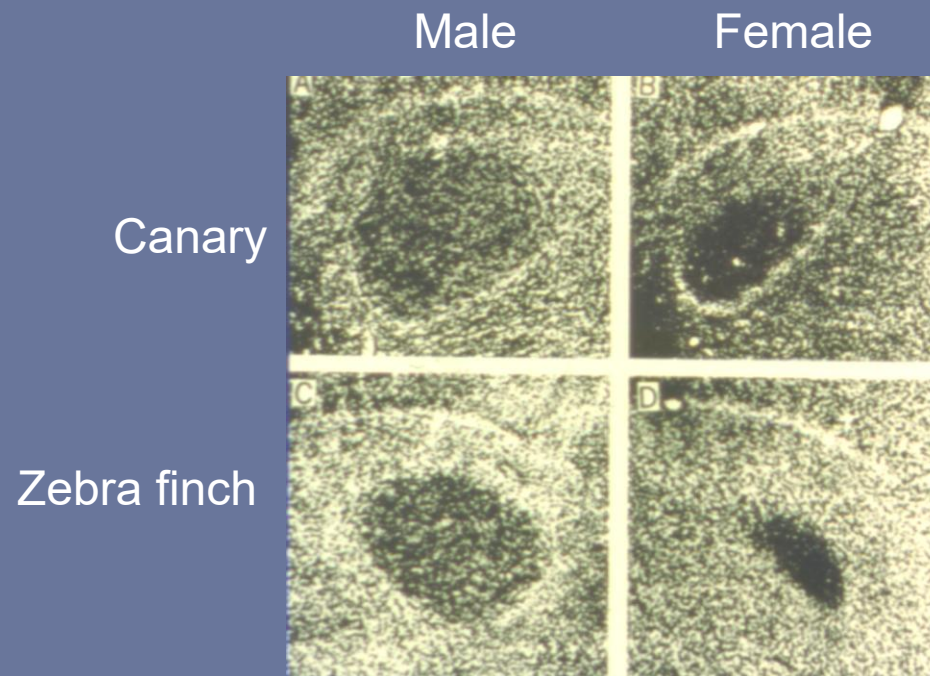
Why sex differences matter even to birds



Female canaries don't sing but ...
how could you change that?



Sexual dimorphism in a vocal control area
(Robust Nuc. of the Archistriatum) of the songbird



F. Nottebohm & A. Arnold (1976) Science, 194, 211

Practical Use Of Sex Differences In The Brain:

The Annual Canary Market In Les Halles,
Paris

Physiological differences in females that can affect drug kinetics and efficacy

- Higher percentage of body fat
- Higher cerebral blood flow
- Slower gastric emptying time
- Lower overall body weight
- Less blood volume
- Lower plasma protein binding
- Lower hepatic biotransformation of drugs
- Slower renal clearance

Sex differences in gross and cellular brain anatomy (1)

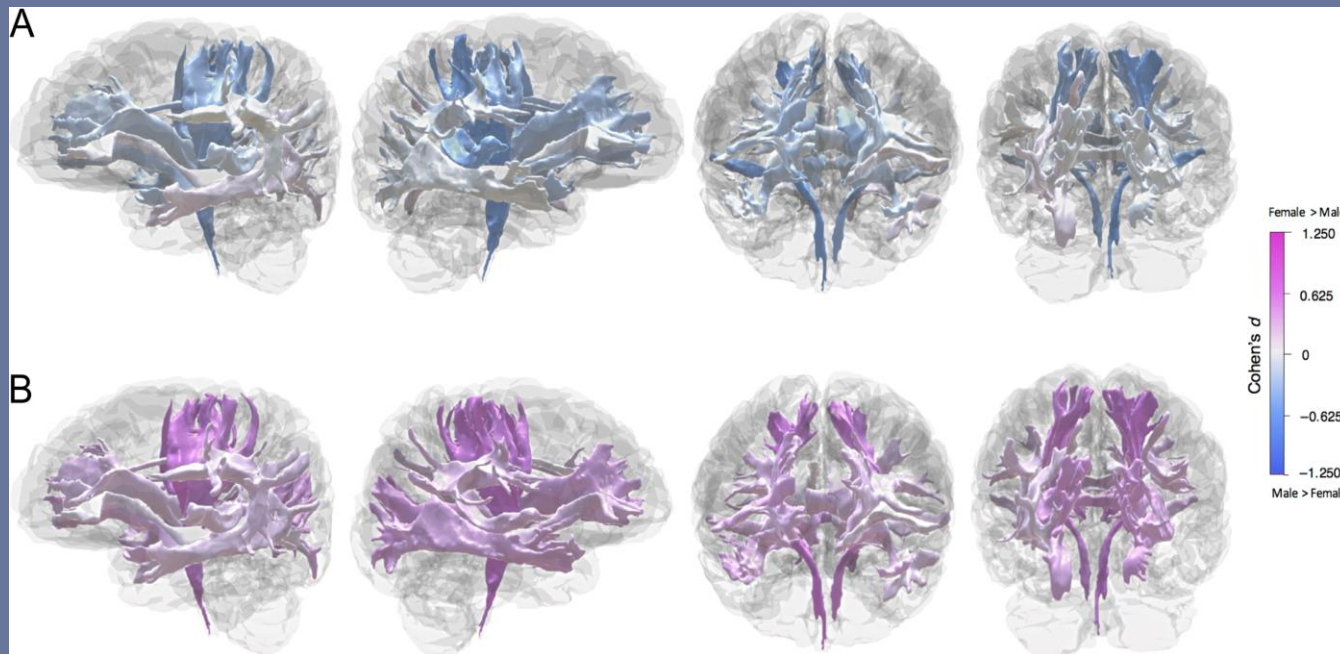
- Fewer cerebral asymmetries in imaging when normal healthy women were high in progesterone than when they were high in estrogen.
- Females have more neuropil than males but males have higher synaptic densities.
- Nerve cells tend to be larger in females, especially in the left hemisphere, but males tend to have more cells.
- Females are more frequently right handed but have better language skills than males.
- Females survive brain injuries better than males.

Sex differences in gross and cellular brain anatomy (2)

- Women have larger cortical volume than men, but frontal medial cortex, amygdala and hypothalamus are larger in men.
- Female rats show less age-related drop-off of spine density and branching in frontal and motor cortex compared to males.
- Males show greater LTP in the HC but females are more sensitive to hormone-related seizures.
- Estrous cycle can play a critical role in motor-evoked potentials (higher in follicular stage than in luteal).
- Females have better response to hypoxic pre-conditioning than males but this varies with estrous cycle.

There are important differences in brain structure.

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



From: Sex Differences in the Adult Human Brain: Evidence from 5216 UK Biobank Participants, *Cereb Cortex*. 2018;28(8):2959-2975.
doi:10.1093/cercor/bhy109

Mean sex differences in white matter microstructural measures (22 white matter tracts. For both measures, numerically the largest effect was found in the right cortico-spinal tract.

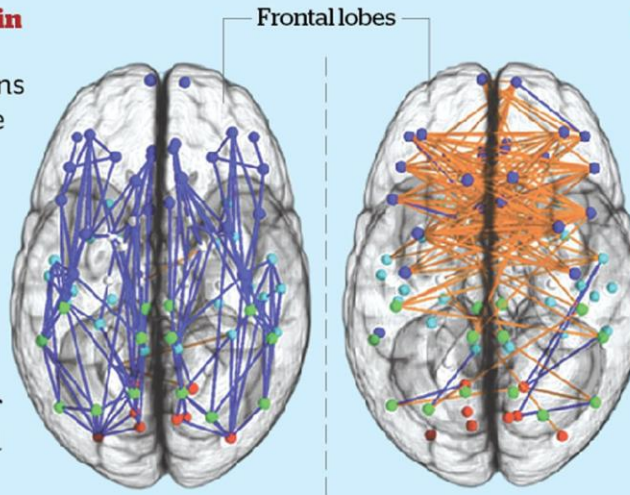
Are male and female brains wired differently?

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)

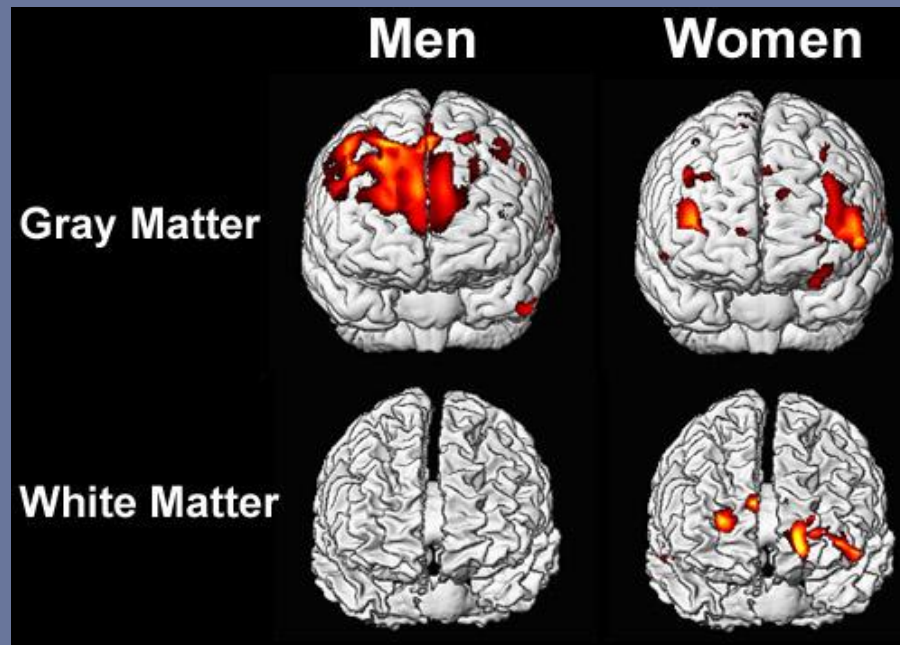
Many more neural connections go from side to side across the left and right hemispheres of the brain. Scientists say this could account for women's better verbal skills and intuitive abilities

Sex Differences In The Structure And Function Of The Human Brain?

Ingallhalikar, M, et al, PNAS, 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 thinking about complex issues



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?

Are cerebral “asymmetries” real??

- Men have approximately 6.5 times the amount of **gray matter** related to general intelligence than women, and women have nearly 10 times the amount of **white matter** related to intelligence than men.
- 84% of gray-matter regions and 86% of white-matter regions involved with intellectual performance in women were found in the brain's frontal lobes, compared to 45% and zero % for males, respectively.
- The gray matter driving male intellectual performance is distributed throughout more of the brain.
- These two very different neurological pathways and activity centers, **however, underlie performance on broad measures of cognitive ability, such as those found on intelligence tests.**
- **No single neuroanatomical structure determines general intelligence and that different types of brain designs are capable of producing equivalent intellectual performance.**

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 and what treatments might be most effective..

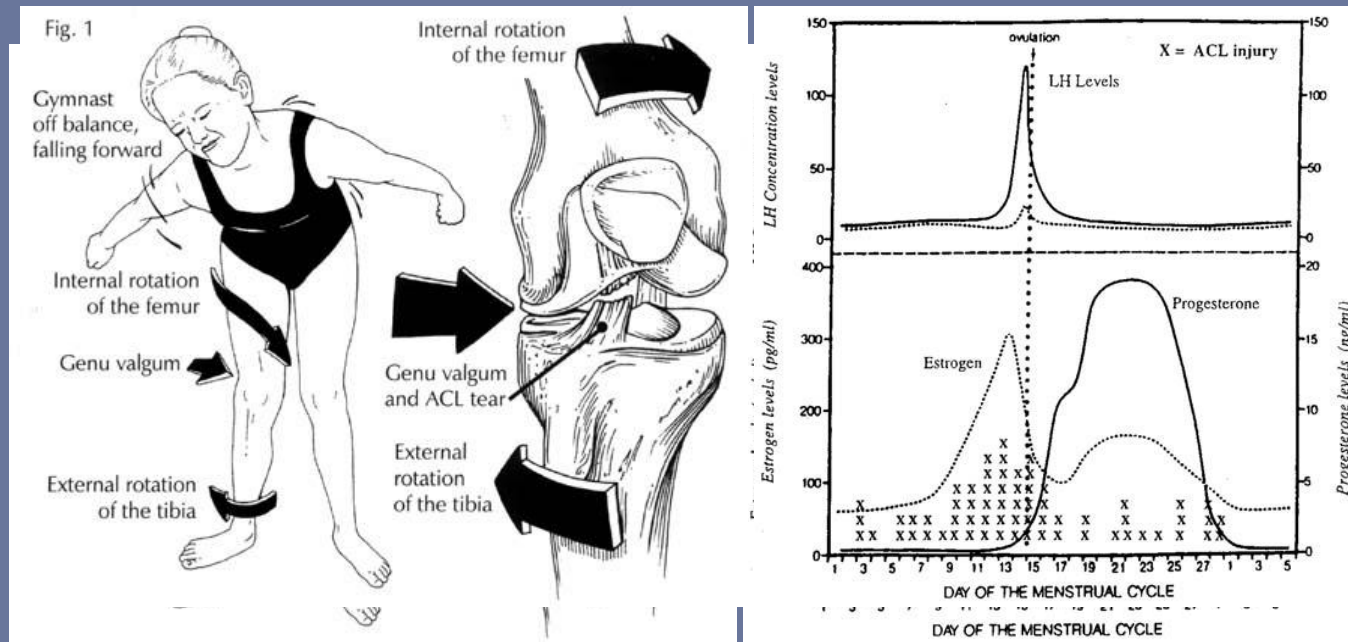
Important Sex Differences For Translational Drug Research

- Age at time of testing 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).
- Drug doses and duration of treatment can vary across estrous cycle.
- Women on contraceptives could have different outcomes from those who are not. Both could be different from men.

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It's Not Just Brain: Circulating Progesterone Levels Can Affect Injury Outcomes

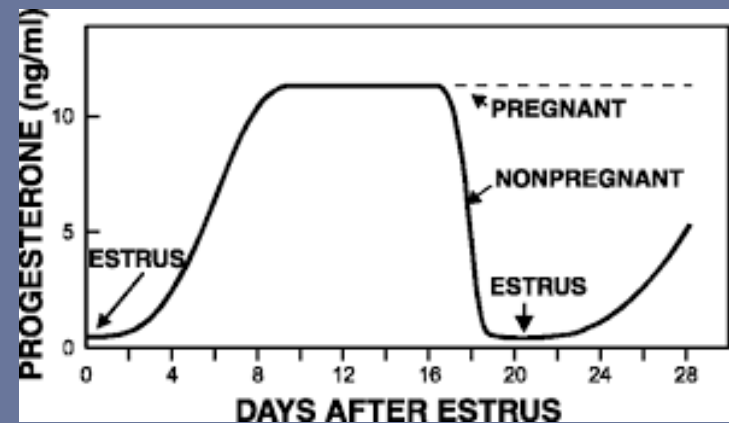


Graphic representation of the distribution of ACL injuries in relation to menstrual day. Am J Sports Med 2007, 35(4) 659-668

Sex Differences and Brain Injury

Early Observations in Traumatic Brain Injury

- In females, timing of brain injury relative to stages of the estrous cycle determined morphological and behavioral outcomes.
- Females high in progesterone at time of injury had much better outcome than females high in estrogen.
- Post-injury treatment in both males and females had beneficial effects.



Sex differences In Patients With Moderate to Severe Head Injuries

Berry, C et al J. Trauma,

- 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 new drug development(s)?

Life, 2023 Aug

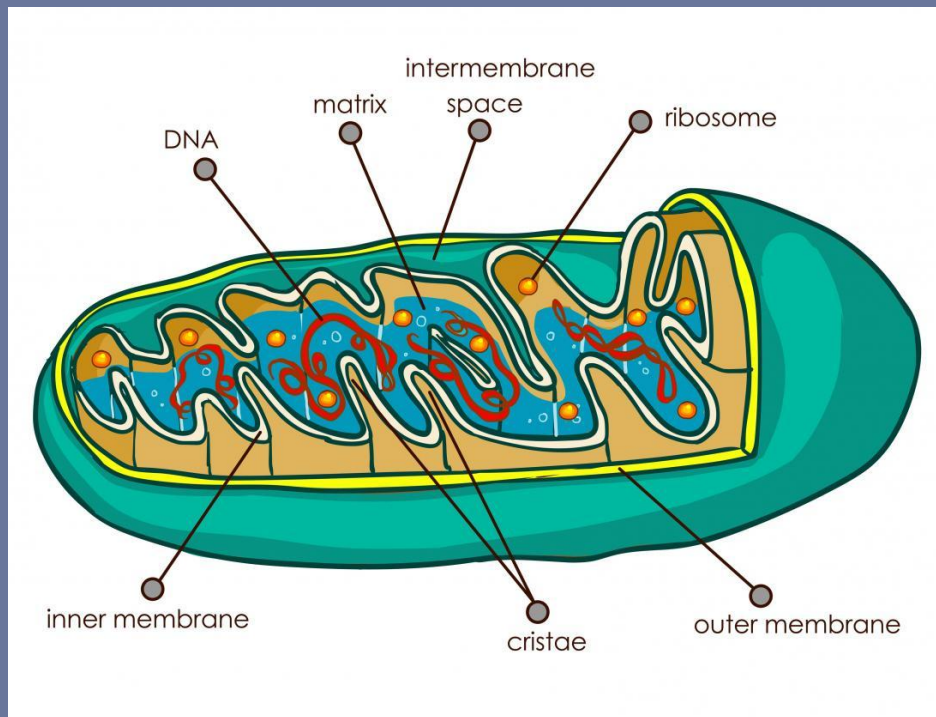
- Though women make up half the world's population, they are severely underrepresented in both pre-clinical and clinical research.
- In 10 drugs withdrawn from the market, 8 posed higher risks of bad outcomes in female patients.

Sex differences in outcomes of trauma studies with severe TBI

J.Clin Med. 2023

- A total of 1566 patients with severe TBI in a multi-center study hospital.
- Females under 45 y.o. :
- Had lower ICU rates.
- Less mechanical ventilation
- Shorter hospital stays
- Older females do better after severe TBI Than males

MITOCHONDRIA



Sex matters: sex differences in mitochondrial function after brain injury should not be underestimated

- [Sex dependent alterations in mitochondrial electron transport chain proteins following neonatal rat cerebral hypoxic-ischemia.](#) Demarest TG, Schuh RA, Waite EL, et al. J Bioenerg Biomembr. 2016;48(6):591-598. PMID: 27683241
- [Sex-dependent mitophagy and neuronal death following rat neonatal hypoxia-ischemia.](#) Demarest TG, Waite EL, Kristian T, et al. Neuroscience. 2016;335:103-13. doi: 10.1016/j.neuroscience.2016.08.026. PMID: 27555552
- [Sex differences in the mitochondrial bioenergetics of astrocytes but not microglia at a physiologically relevant brain oxygen tension.](#) Jaber SM, Bordt EA, Bhatt NM, Lewis DM, Gerecht S, Fiskum G, Polster BM. Neurochem Int. 2017 pii: S0197-0186(17)30212-7. doi: 10.1016/j.neuint.2017.09.003. PMID: 28888963
- [Brain region- and sex-specific alterations in mitochondrial function and NF-κB signaling in the TgCRND8 mouse model of Alzheimer's disease.](#) Djordjevic J, Thomson E, Chowdhury SR, et al. Neuroscience. 2017;361:81-92. doi: 10.1016/j.neuroscience.2017.08.006. PMID: 28802916
- [Sex differences in brain mitochondrial metabolism: influence of endogenous steroids and stroke.](#) Gaignard P, Fréchou M, Liere P, T et al. J Neuroendocrinol. 2017, doi: 10.1111/jne.12497. [Epub ahead of print]
- [Dynamics of enhanced mitochondrial respiration in female compared with male rat cerebral arteries.](#) Rutkai I, Dutta S, Katakam PV, et al. Am J Physiol Heart Circ Physiol. 2015;309(9):H1490-500. doi: 10.1152/ajpheart.00231.2015. PMID: 26276815
- [Tissue and sex specificities in Ca²⁺ handling by isolated mitochondria in conditions avoiding the permeability transition.](#) Chweih H, Castilho RF, Figueira TR. Exp Physiol. 2015;100(9):1073-92. doi: 10.1113/EP085248. PMID: 26096641
- [Effect of Sex Differences on Brain Mitochondrial Function and Its Suppression by Ovariectomy and in Aged Mice.](#) Gaignard P, Savouroux S, Liere P, et al. Endocrinology. 2015 ;56(8):2893-904. doi: 10.1210/en.2014-1913. PMID: 26039154

For Only \$99.00 You Can Save Your Mitochondria



Sex Differences In Glia Reactivity After Cortical Brain Injury

- Males have a higher density of immune cells in the wound area than females.
- Microglia/macrophages in that region expressed markers of activated microglia,, in a greater proportion in males than in females.
- The percentage of astrocytes involved in recruitment of immune cells and gliosis regulation was higher in males.
- Males presented a significantly higher density of neurons in the lesion edge than females.
- Male and female mice have different neuro-inflammatory responses after a cortical injury and that sex differences in reactive gliosis may contribute to sex differences in neuroinflammatory diseases.

What About Stroke
And Stroke Incidence?

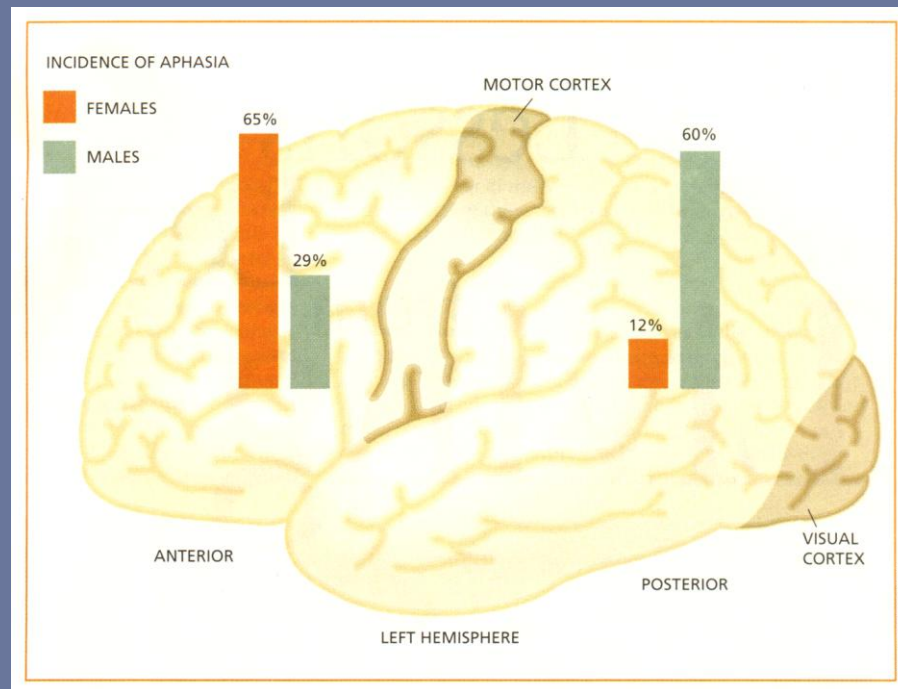
MALES AND FEMALES DIFFER IN STROKE INCIDENCE AND SURVIVAL

- 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.

Potential Sex Differences In Aphasia Outcome



Animal studies need to pay more attention to sex differences in co-morbidities



THE END

NEXT LECTURE:

What's the point of all the basic research
if we can't get it from the lab bench
to patients in need?

WE MUST HAVE CLINICAL TRIALS TO FIND NEW
TREATMENTS. SO WHY DON'T MOST OF THEM WORK?



End