

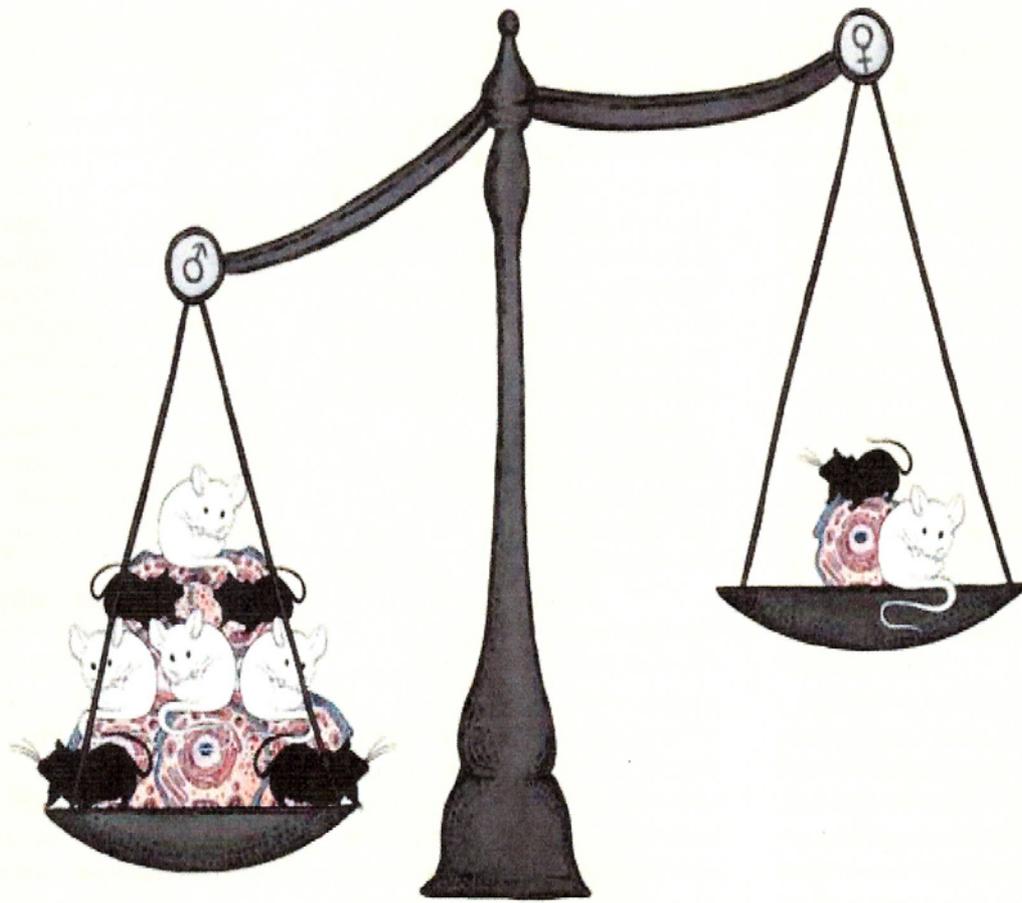
# Sex Influences on Body and Brain: *An idea whose time has come*



Larry Cahill, Ph.D.  
University of California, Irvine  
Supported by NIMH RO1 57508



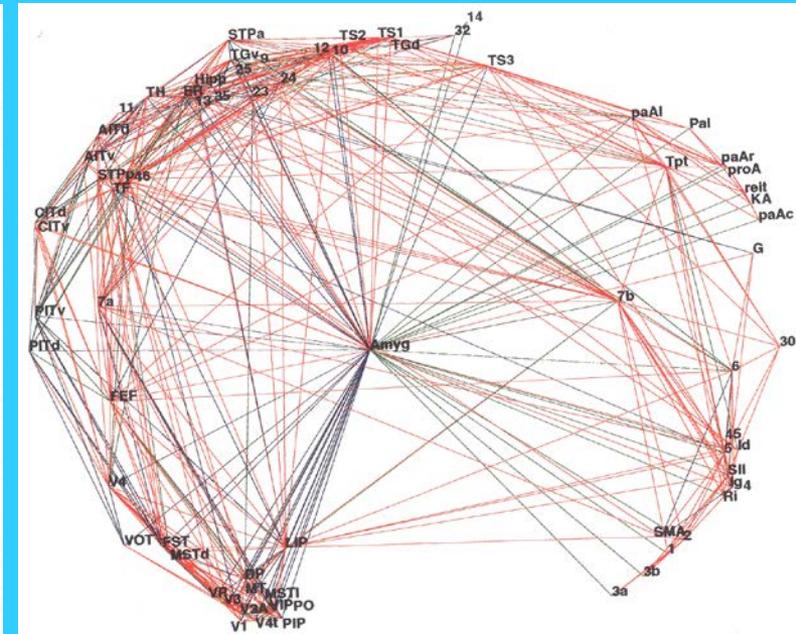
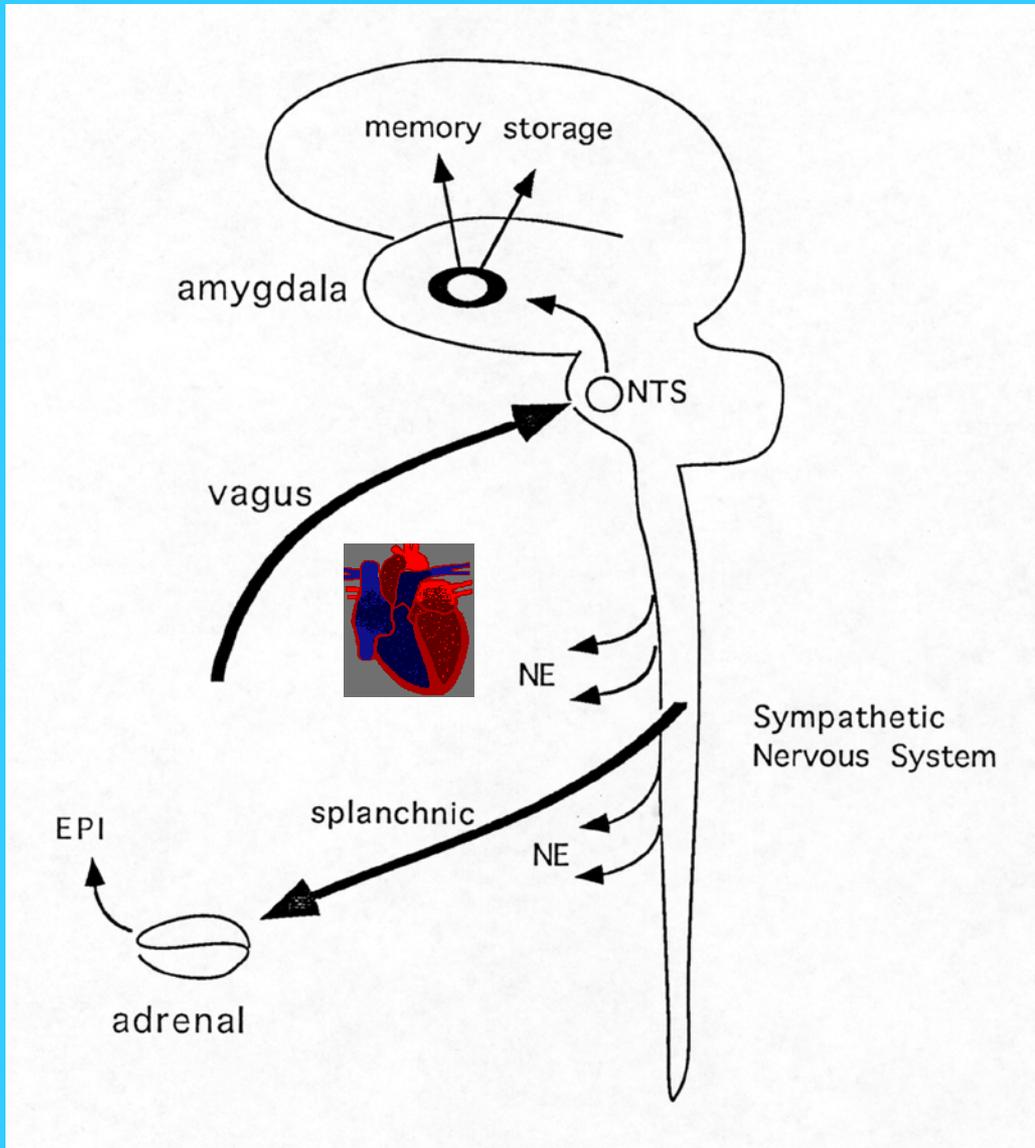
*Nature*,  
2014



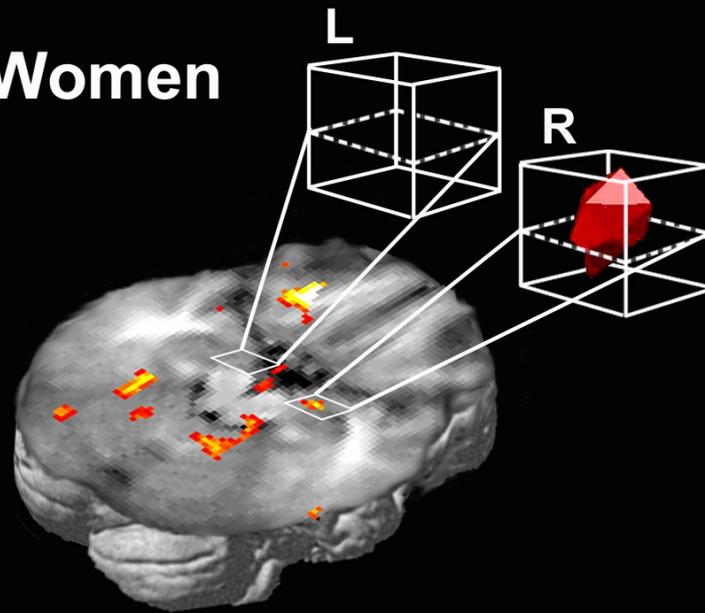
# NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

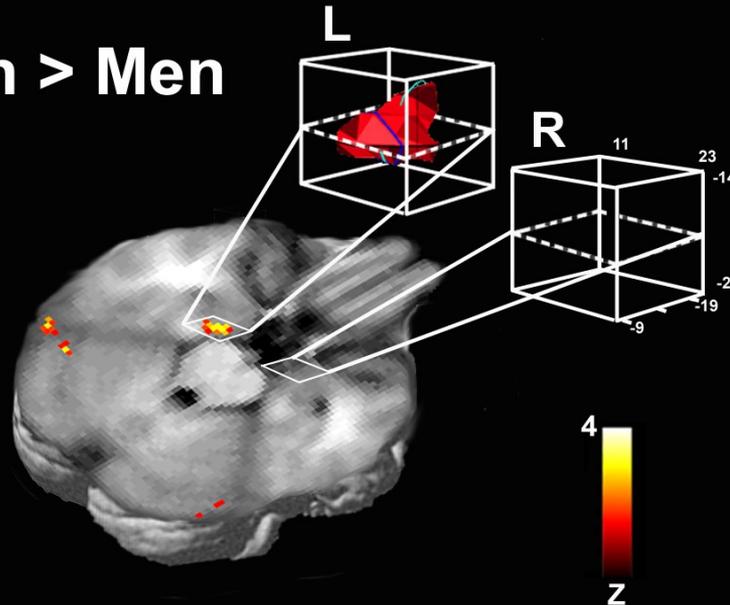
# Neural Mechanism of Emotional Memory



**Men > Women**



**Women > Men**



**Cahill et al., 2001, 2004**

# 5 QUESTIONS

- 1) Is the degree of sex bias in animal/cell research really all that bad?
- 2) Why the resistance to studying sex influences?
- 3) Where are these sex influences?
- 4) Does all this really matter for the clinic?
- 5) So what should we do about it?

# 5 QUESTIONS

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# 5 QUESTIONS

- 1) Is the degree of sex bias in animal/cell research really all that bad? **YES**
- 2) Why the resistance to studying sex influences? **Several Key Reasons**
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4) Does all this really matter for the clinic? **YES**

5) So what should we do about it? **Some Suggestions**

# 5 QUESTIONS

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Contents lists available at ScienceDirect

# Neuroscience and Biobehavioral Reviews

journal homepage: [www.elsevier.com/locate/neubiorev](http://www.elsevier.com/locate/neubiorev)



Review

## Sex bias in neuroscience and biomedical research

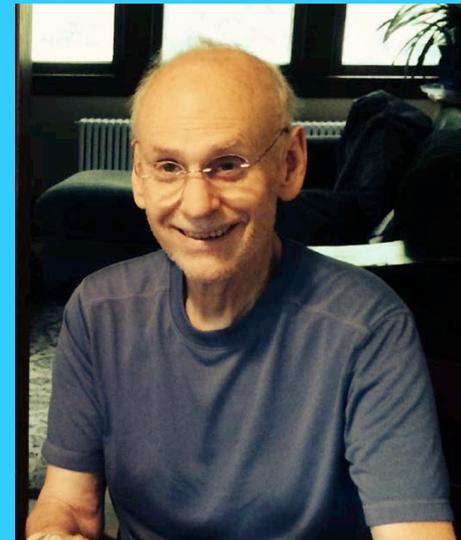
Annaliese K. Beery<sup>a</sup>, Irving Zucker<sup>b,c,+</sup>

<sup>a</sup> Robert Wood Johnson Health & Society Scholar at University of California, San Francisco and University of California, Berkeley, CA, USA

<sup>b</sup> Department of Psychology, and Helen Wills Neuroscience Institute, University of California, 3210 Tolman Hall, 1650 Berkeley, 94720 CA, USA

<sup>c</sup> Department of Integrative Biology, and Helen Wills Neuroscience Institute, University of California, 3210 Tolman Hall, 1650 Berkeley, 94720 CA, USA

Male: Female  
5.5 : 1



# Bias in Surgical Research- Kibbe



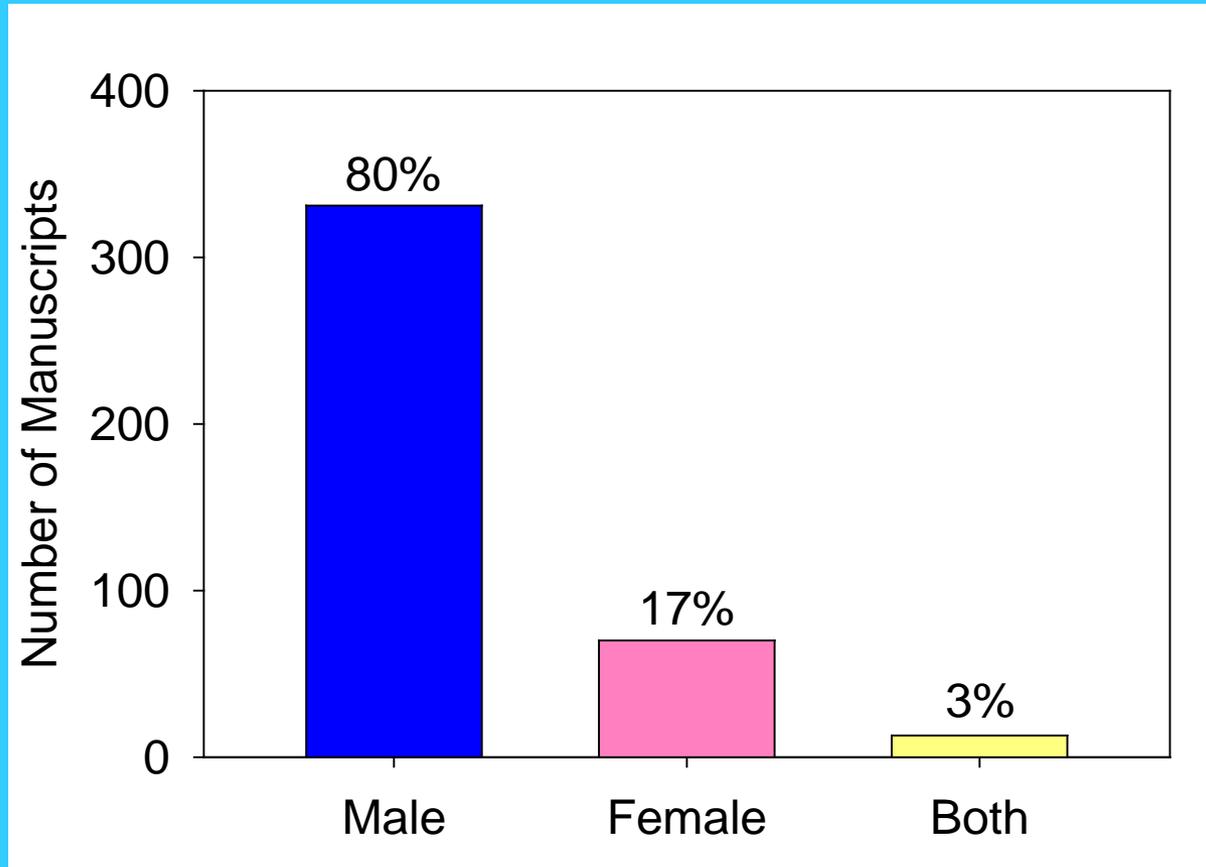
- Evaluated ALL publications in 2011-2012 in:

- Annals of Surgery
- American Journal of Surgery
- JAMA Surgery
- Journal of Surgical Research
- Surgery

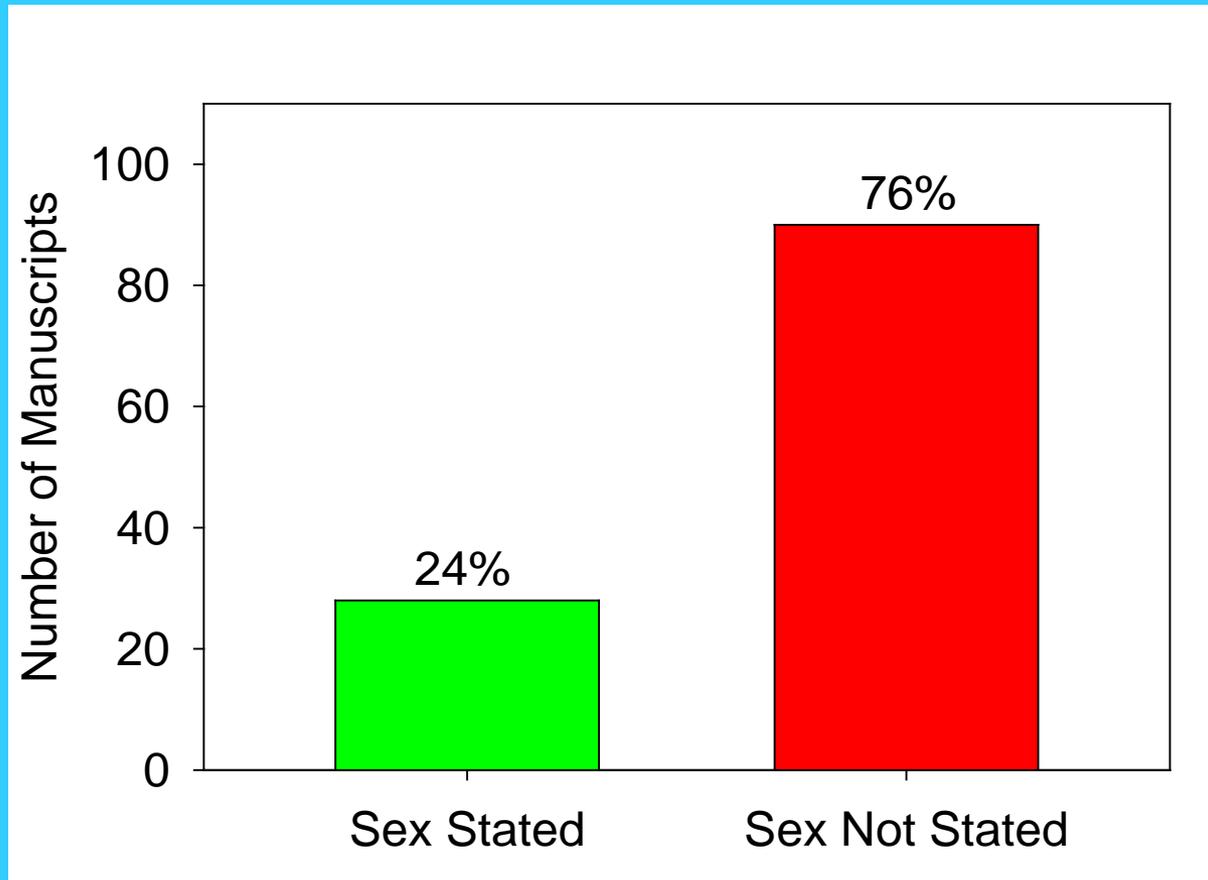
618 articles with animals and cells



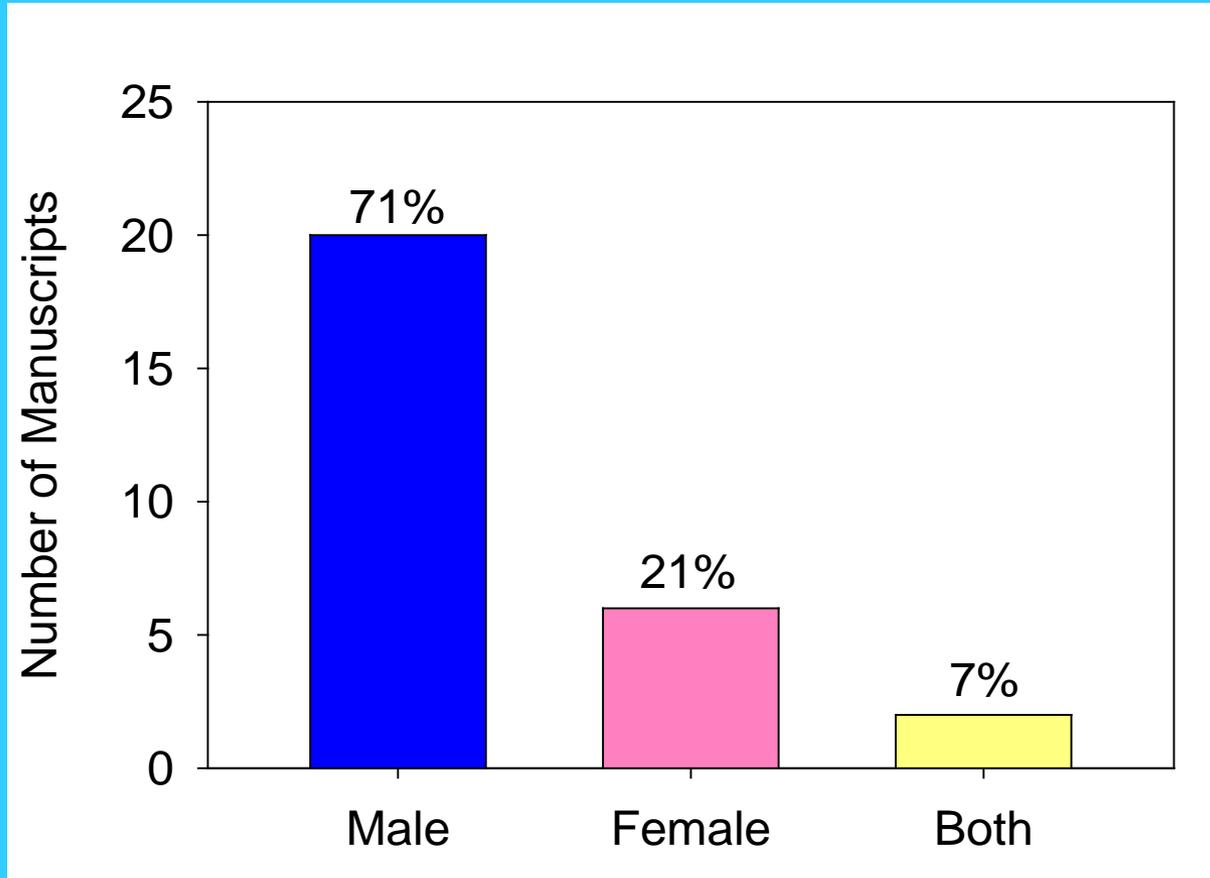
# Sex Bias Exists with *Animal* Research



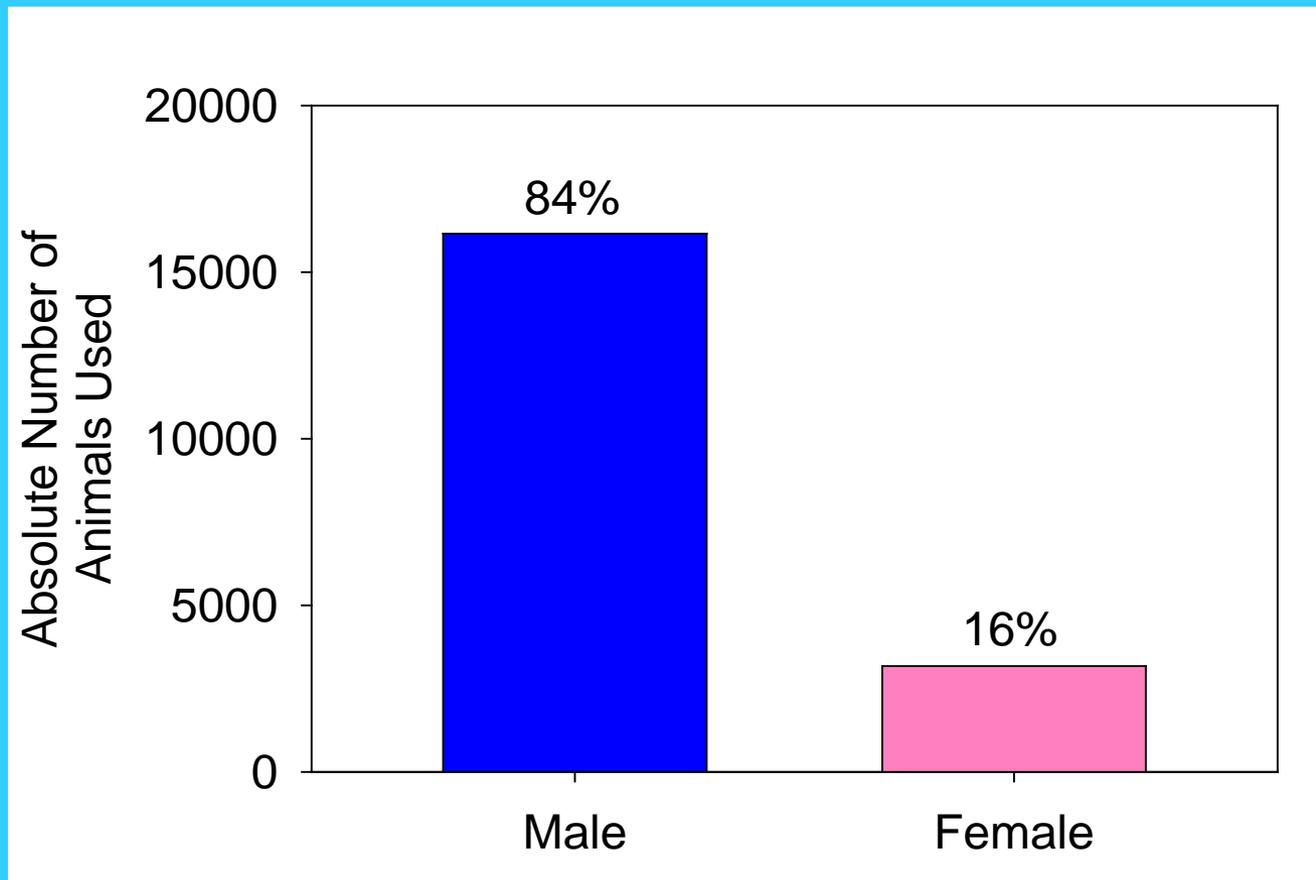
# Sex Bias Exists with *Cell* Research



# Sex Bias Exists with *Cell* Research



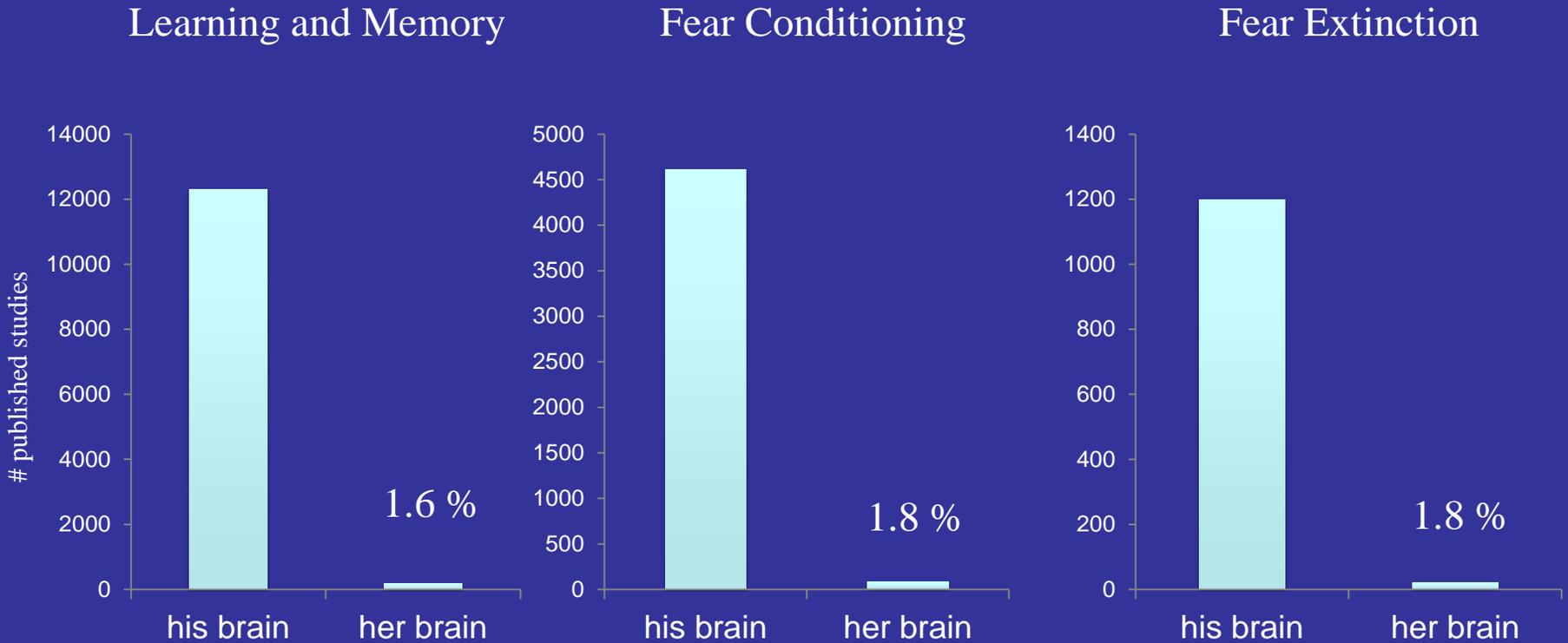
# More Male Animals Are Studied





For female-prevalent diseases, of those reports that stated the sex, only **12%** studied female animals

# Neurobiology of Learning and Memory



Lebrón-Milad and Milad,

Biology of Mood and Anxiety Disorders, 2012

# 5 QUESTIONS

- 1) Is the degree of sex bias in animal/cell research really all that bad?
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“Females are too variable and complex, and one has to deal with the estrous cycle”



Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

# Neuroscience and Biobehavioral Reviews

journal homepage: [www.elsevier.com/locate/neubiorev](http://www.elsevier.com/locate/neubiorev)



## Review

# Female mice liberated for inclusion in neuroscience and biomedical research

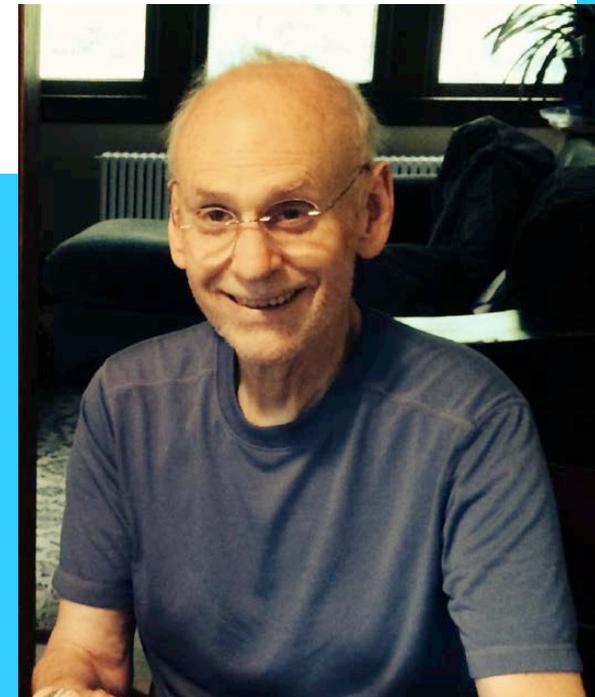
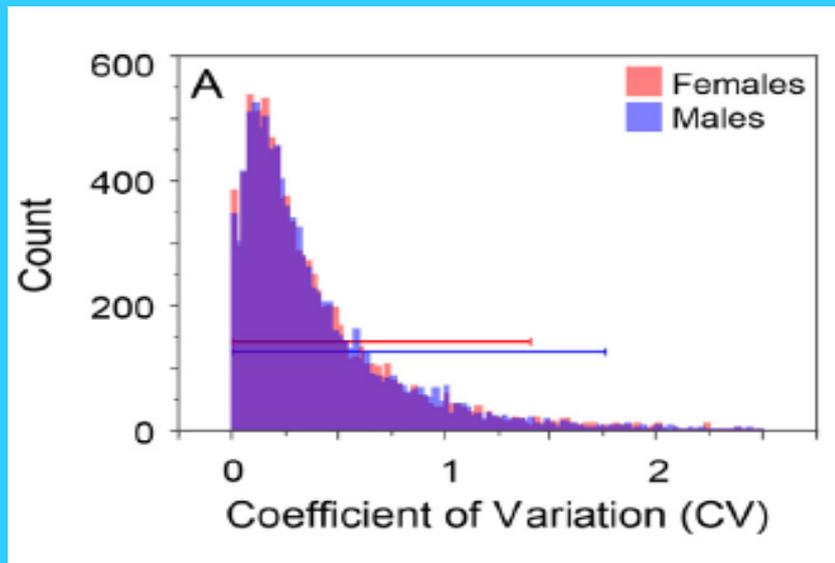


Brian J. Prendergast<sup>a</sup>, Kenneth G. Onishi<sup>a</sup>, Irving Zucker<sup>b,c,\*</sup>

<sup>a</sup> Department of Psychology and Institute for Mind and Biology, University of Chicago, United States

<sup>b</sup> Department of Psychology, University of California, Berkeley, United States

<sup>c</sup> Department of Integrative Biology, University of California, Berkeley, United States



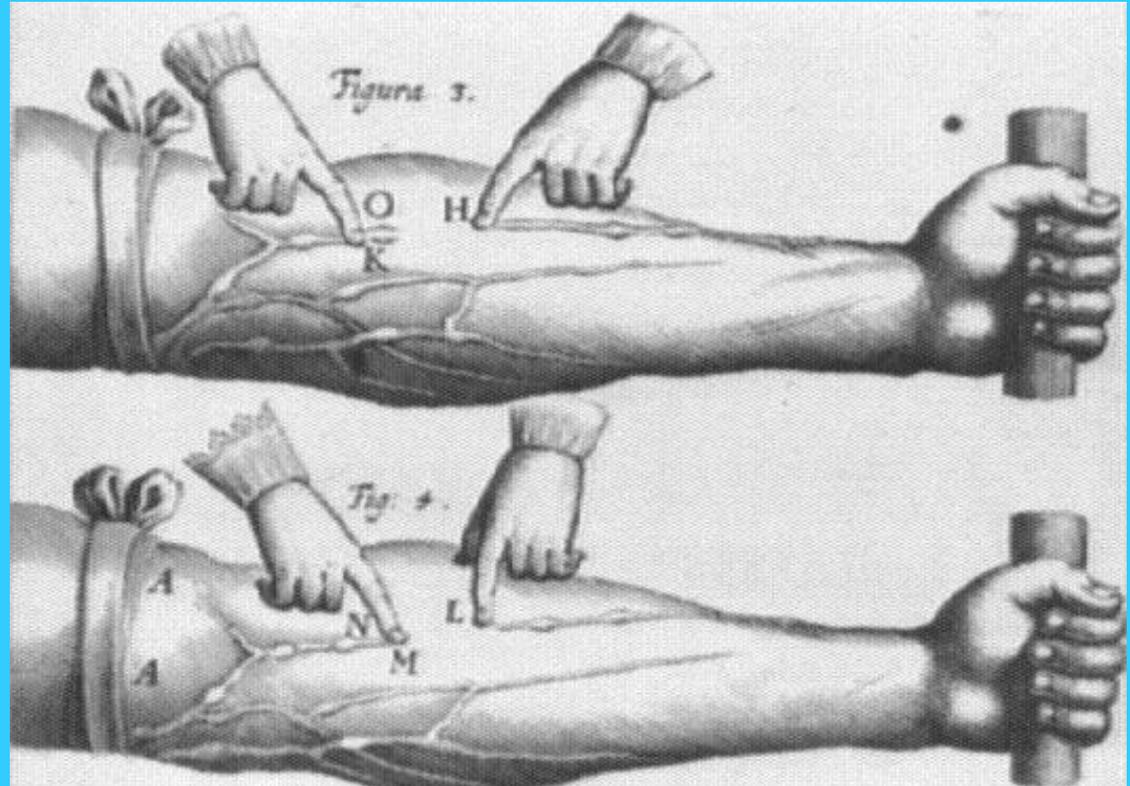
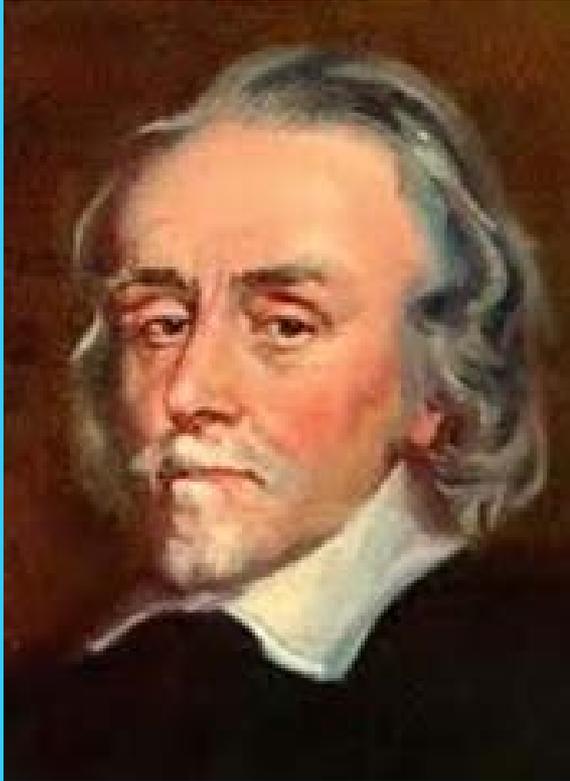
“It’s not that I am not interested in sex differences, it’s just that I want to understand the fundamental mechanisms first”

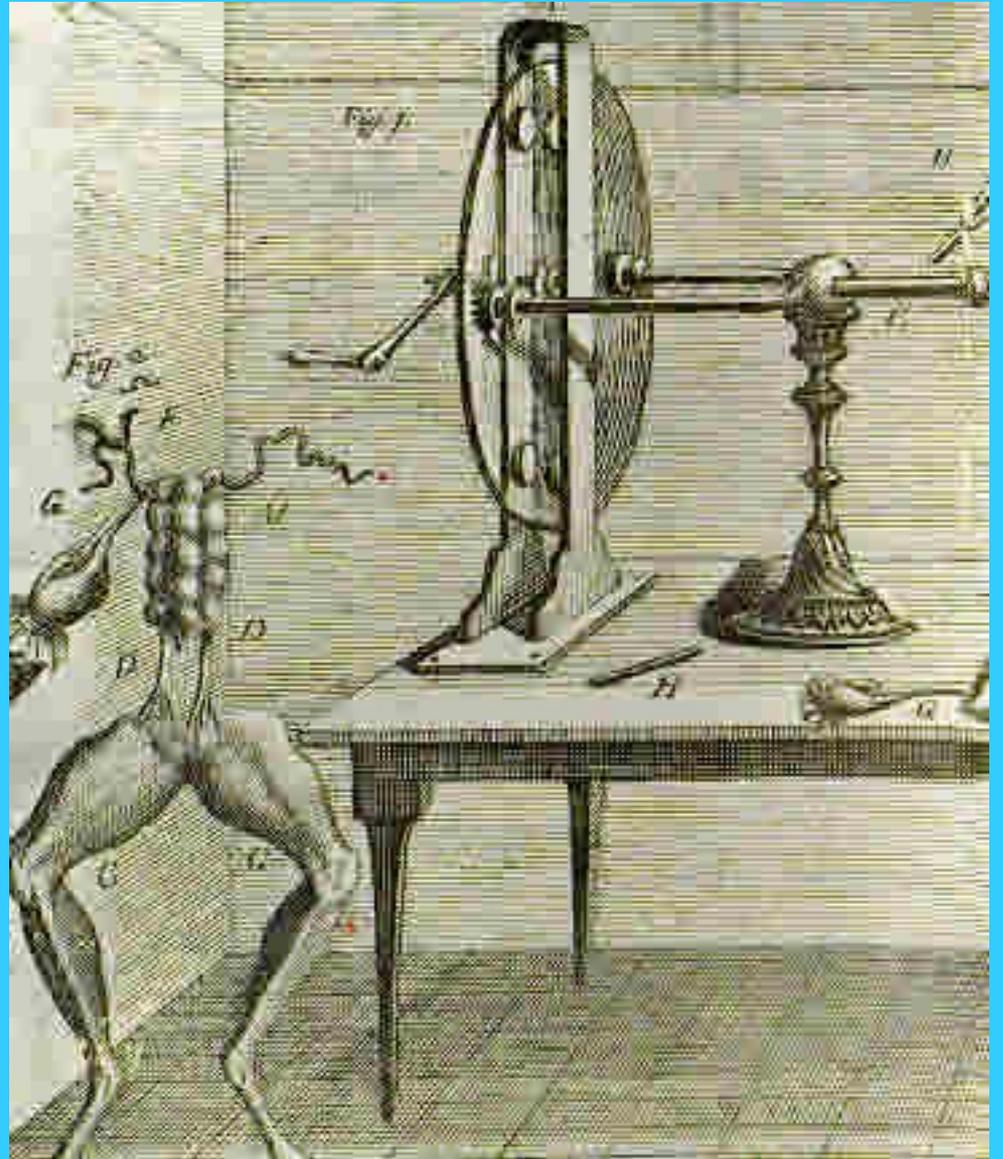
UC Irvine Professor

“It’s not that I am not interested in sex differences, it’s just that I want to understand the fundamental mechanisms first”

“Fundamental = Common/Shared”

# William Harvey





# Cajal



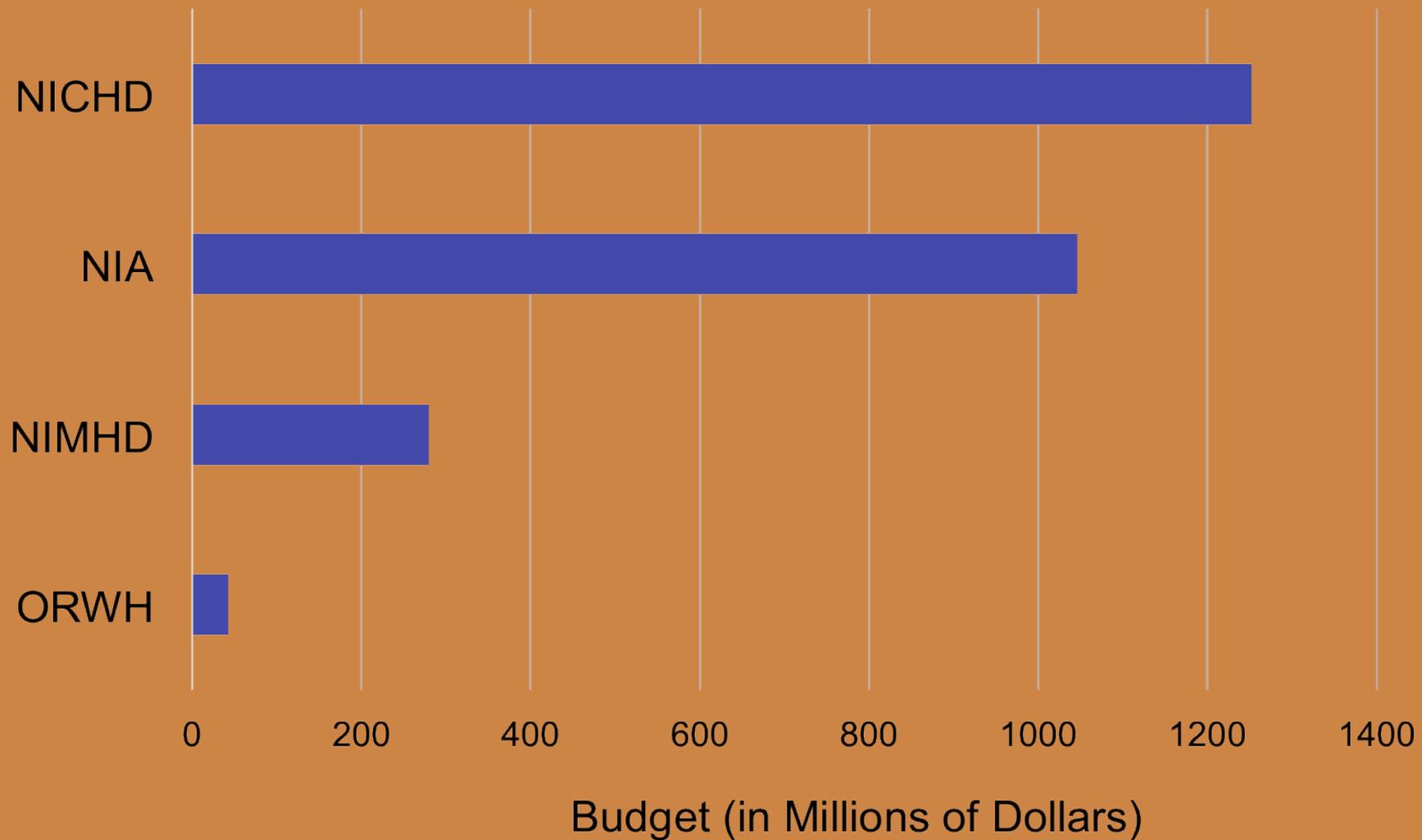


Males and Females are fundamentally similar, AND fundamentally different

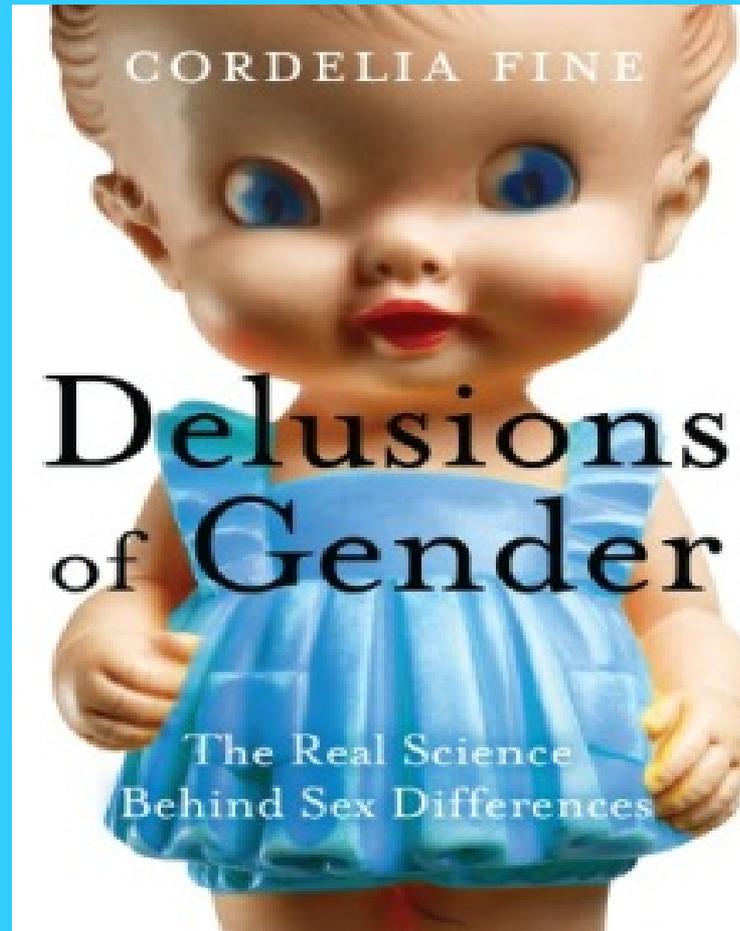


“Sex is just another of many variables that can influence outcomes”

# NIH 2013 “Individual Difference” Budget



# Neurosexists!



“its really a remnant of anti-American, crazy thinking to *do* this kind of research”

Gloria Steinem, quoted on Sex Differences Research

<http://townhall.com/columnists/johnstossel/2014/03/12/war-on-women-n1807016>

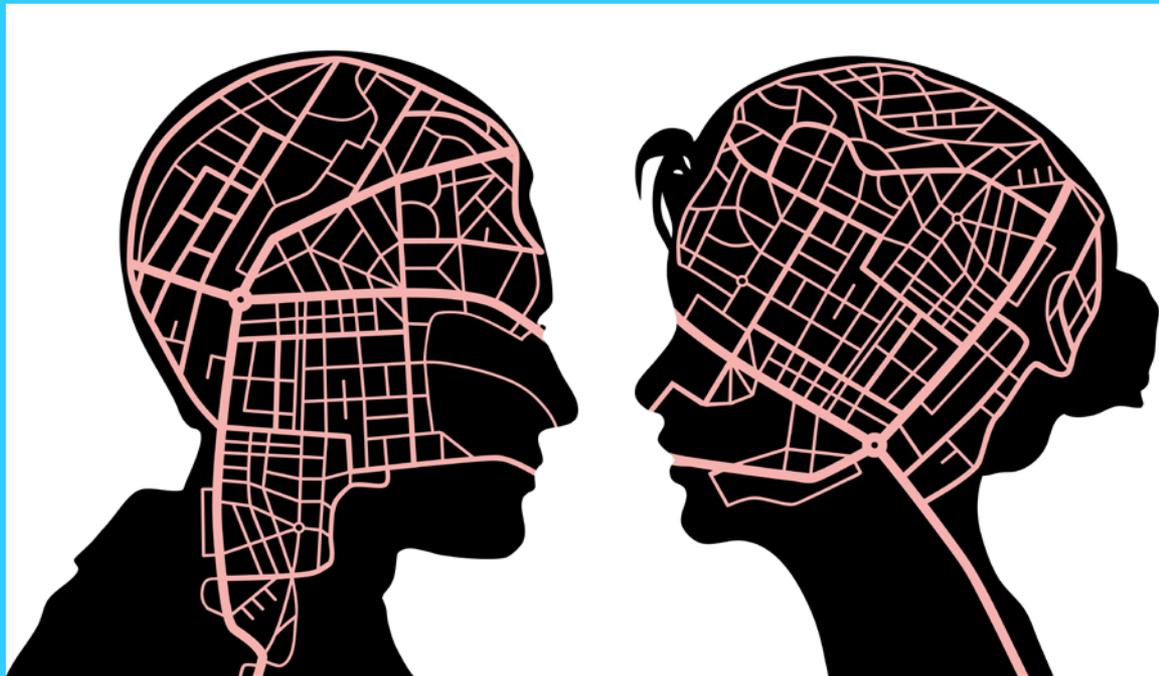


“Equal” = “The Same”

# “Equal” ≠ “The Same”

$$2 + 3 = 10 - 5$$

“Cerebrum”  
Dana Foundation  
April 2014



# 5 QUESTIONS

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# SEX DIFFERENCES IN THE BRAIN

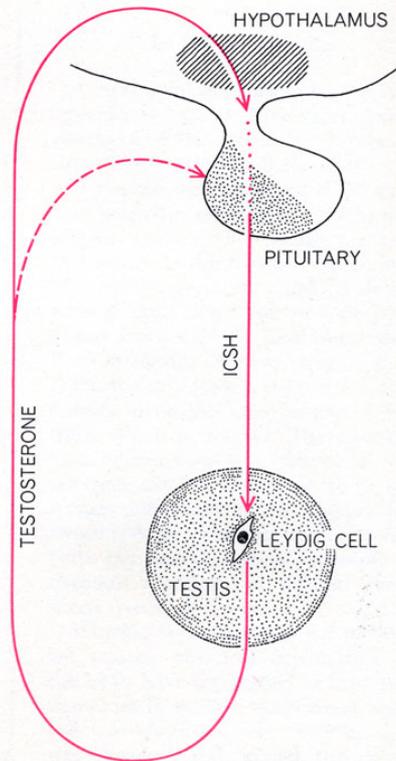
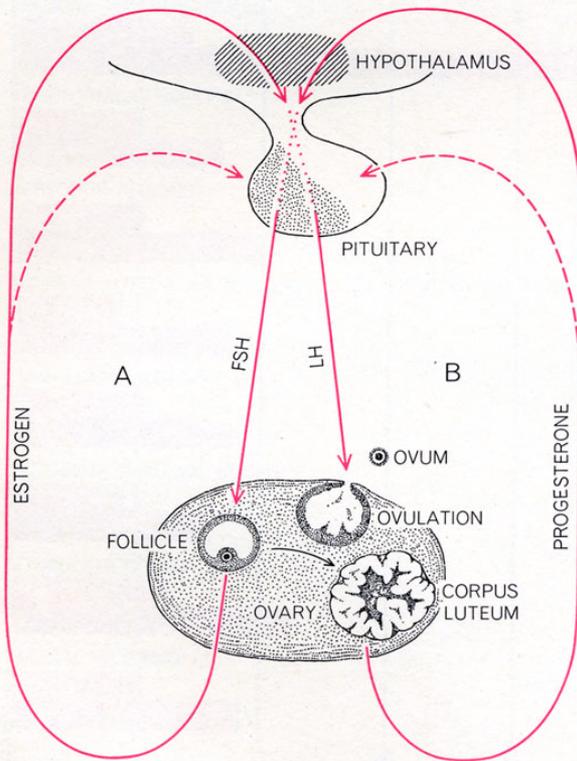
SEYMOUR LEVINE

April 1966

What makes a male mammal male and a female mammal female? We might sum up the answer in the word heredity, but this would evade the question. How is the genetic information translated into the differentiation of the sexes, as expressed in

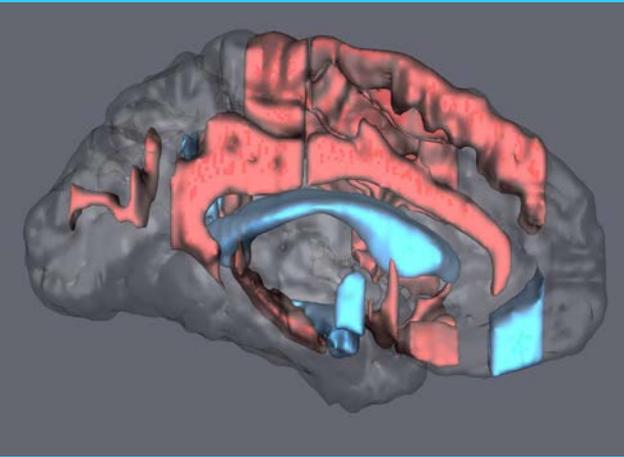
their physiology and behavior? Again we might summarize the answer in a single word: hormones. Recent investigations have revealed, however, that sexual differentiation in mammals cannot be explained solely in terms of hormones. There is now considerable

evidence that the brain is also involved. According to this evidence there are distinct differences between the male brain and the female brain in a mammal, differences that determine not only sexual activity but also certain other forms of behavior.

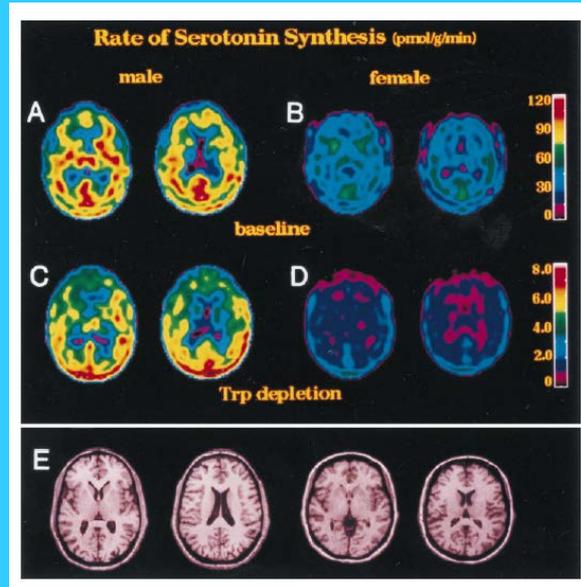


# SEX DIFFERENCES AT ALL LEVELS OF NEUROSCIENCE

## Human Anatomy



## Human Neurochemistry



## Primate Play Behavior

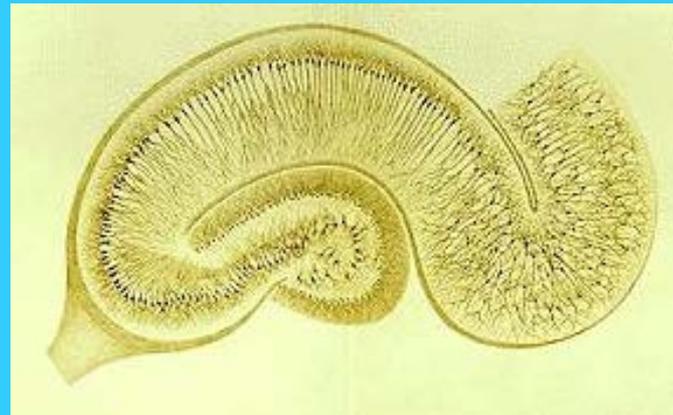


## Cell Culture!

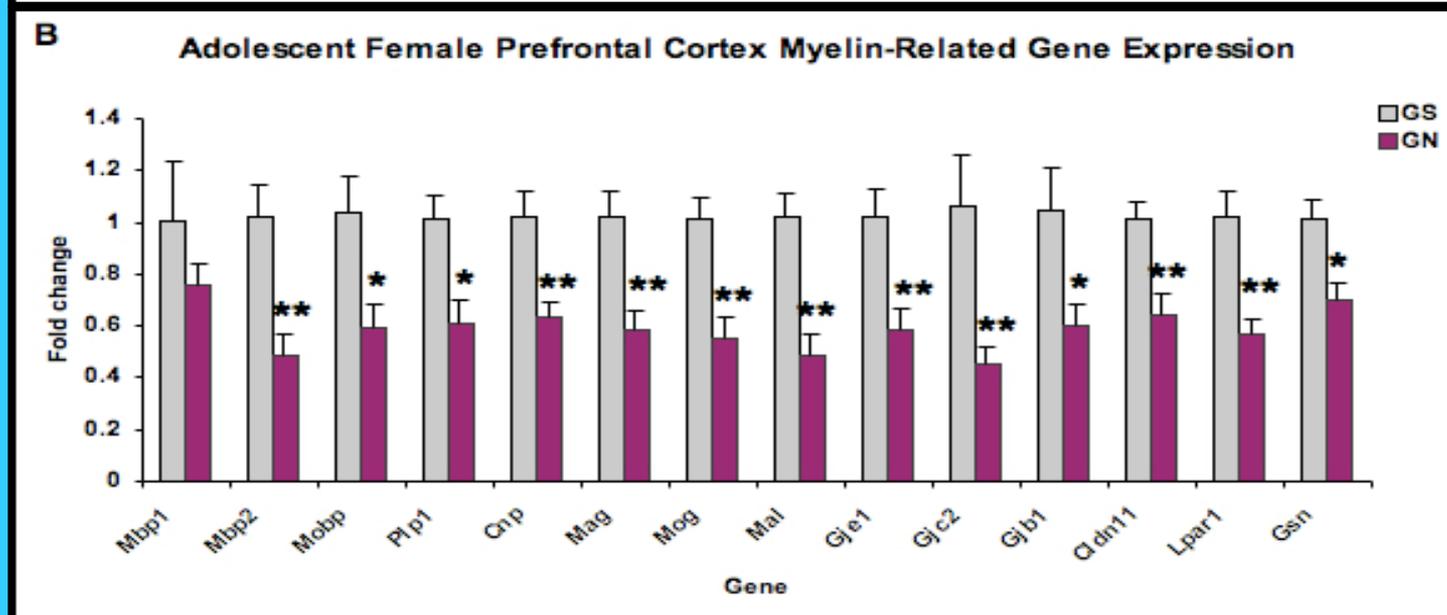
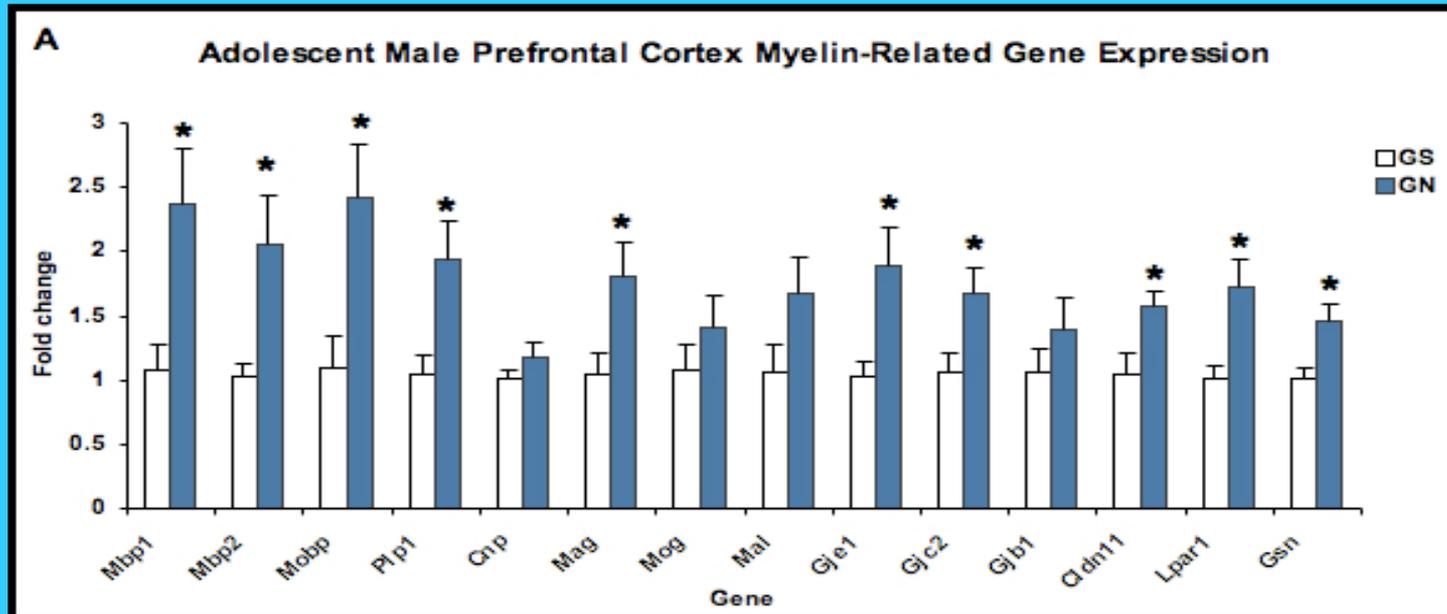
## Transgenic Mice

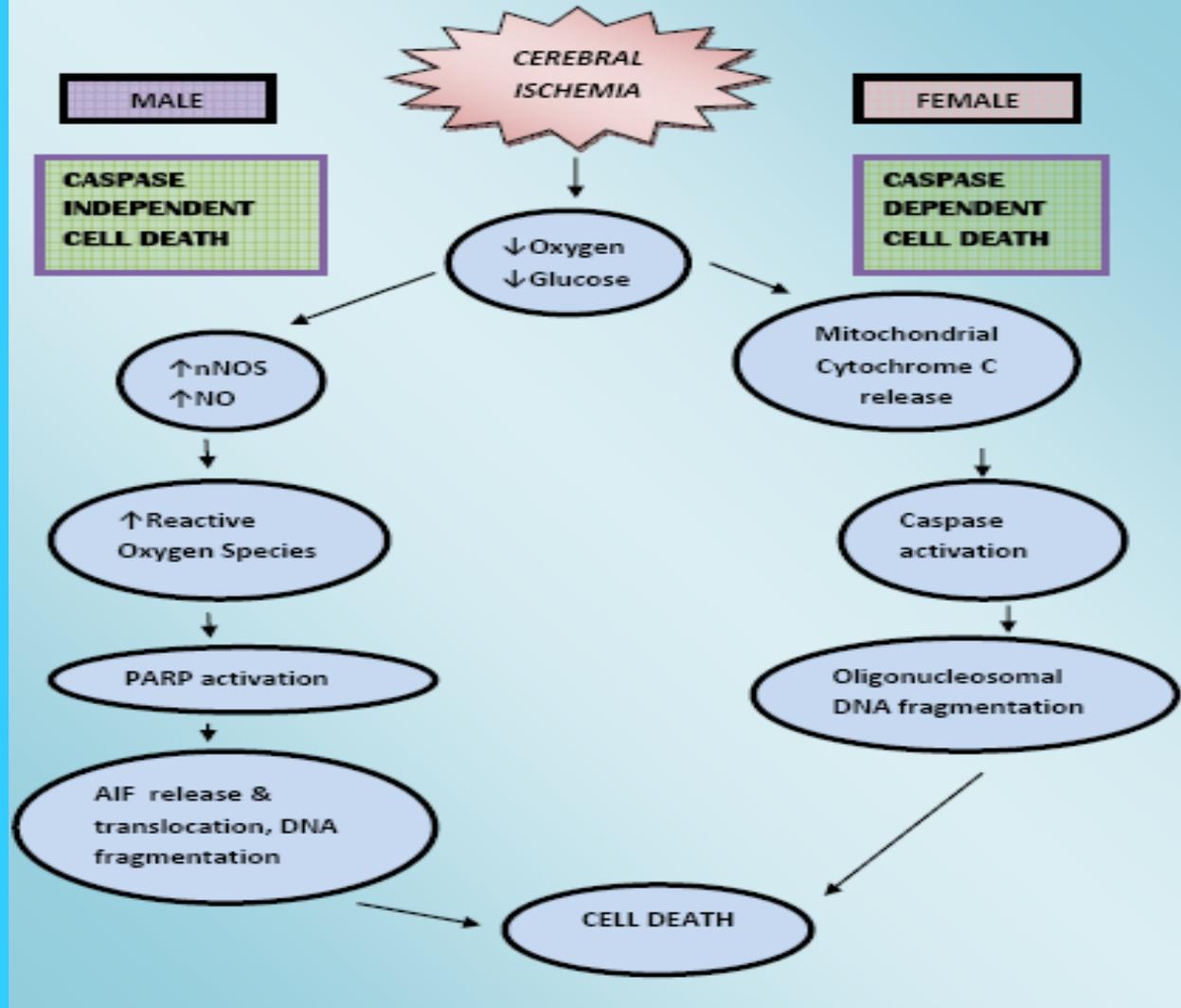


## Hippocampus



# GN increases myelin-related genes in the male PrL but decreases them in the female PrL





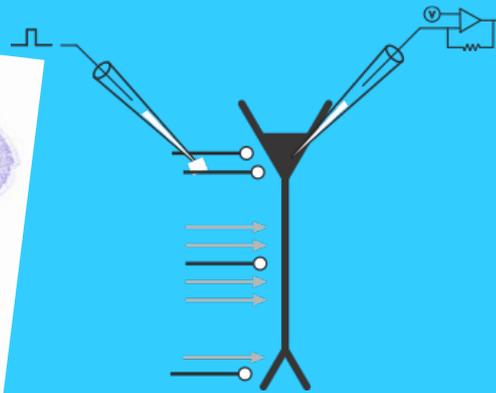
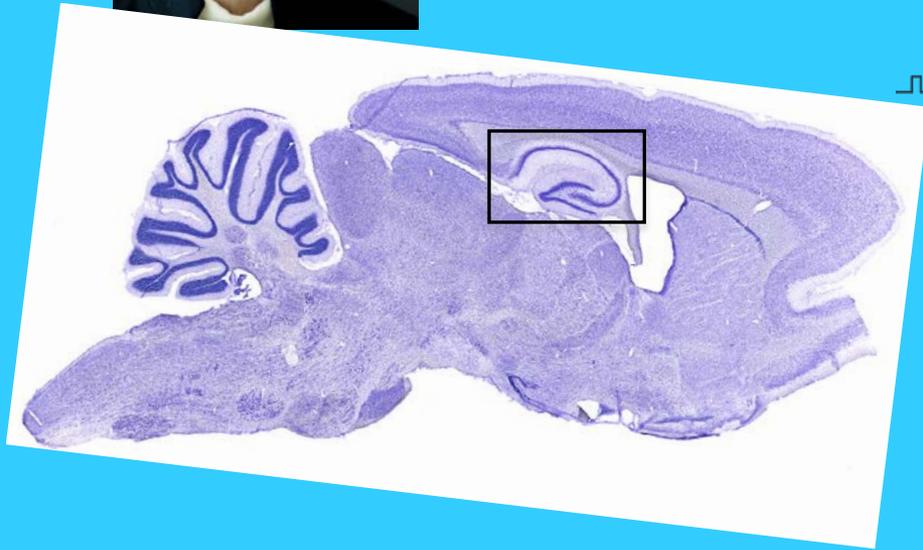
### Sexual dimorphism in ischemic stroke: lessons from the laboratory

Womens Health (Lond Engl). 2011 May ; 7(3): 319–339.

# Sex Difference in Endocannabinoid Tone in the Hippocampus



Catherine Woolley and her group at Northwestern University in Evanston, IL use electrophysiology to study synaptic modulation in the hippocampus.



**GABA<sub>A</sub>-mediated synaptic currents**

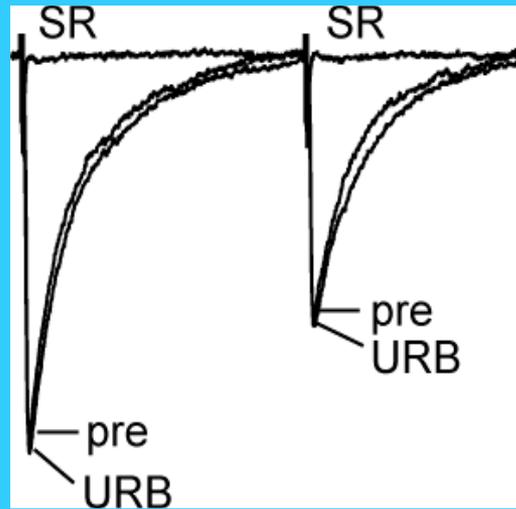


**They tested the effects of a fatty acid amide hydrolase (FAAH) inhibitor, which blocks breakdown of the endocannabinoid, anandamide.**

# Sex-Specific Endocannabinoid Action in the Hippocampus



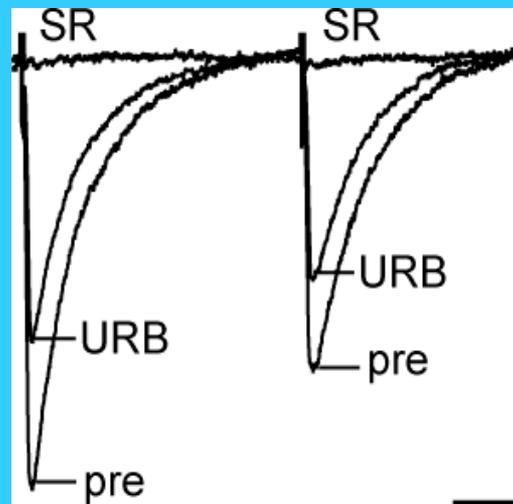
males



The FAAH inhibitor  
“URB597” -- no effect on  
synaptic inhibition in  
males...



females



...but URB597 suppresses  
inhibitory synapses in more  
than 50% of cells in  
females.

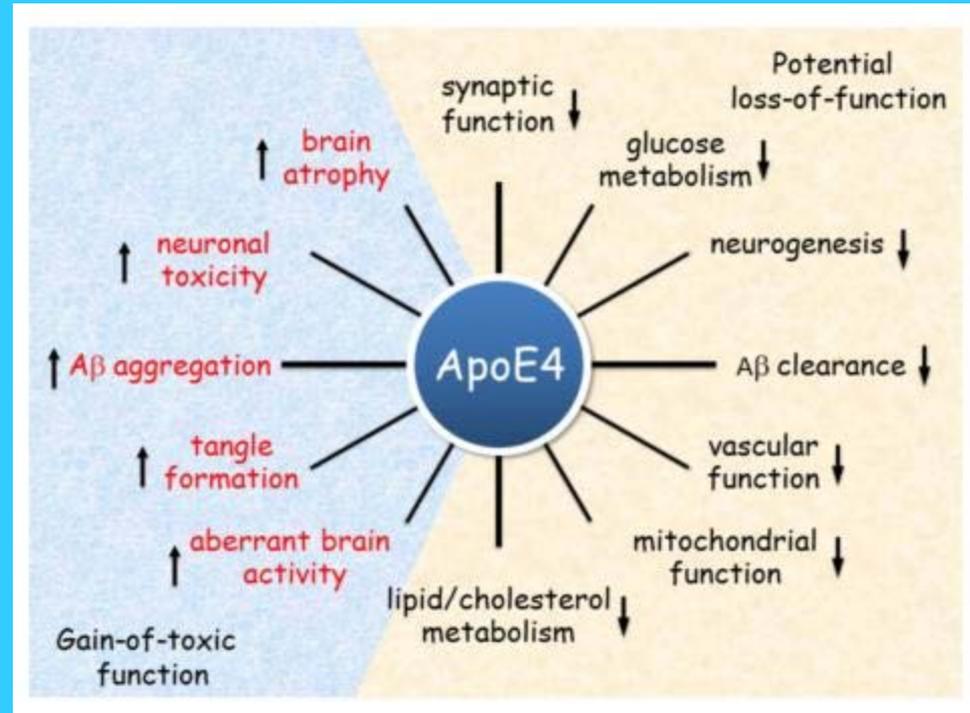
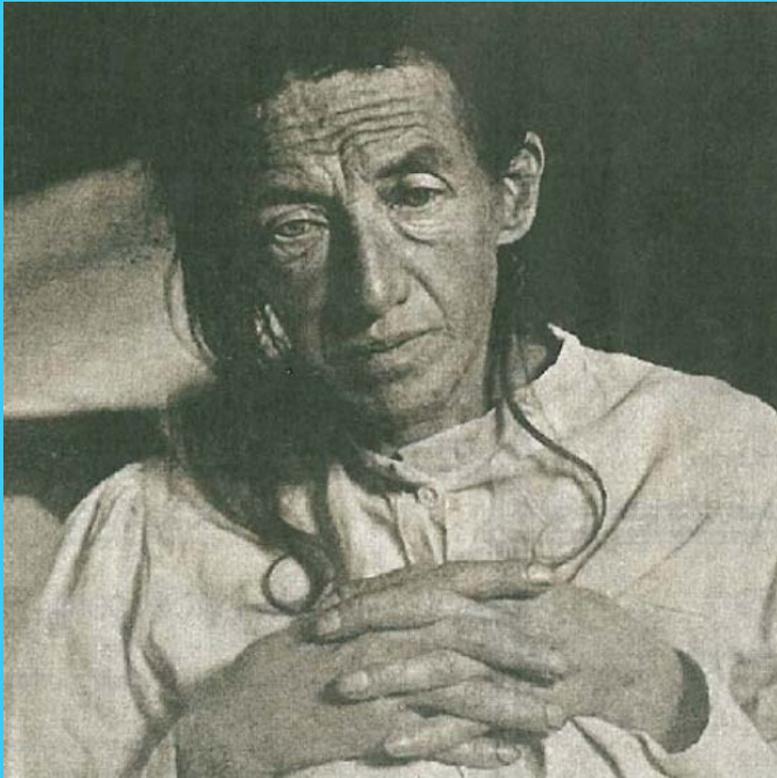
Inhibitory synapses in the hippocampus females are under tonic suppression by anandamide, which is lacking in males.

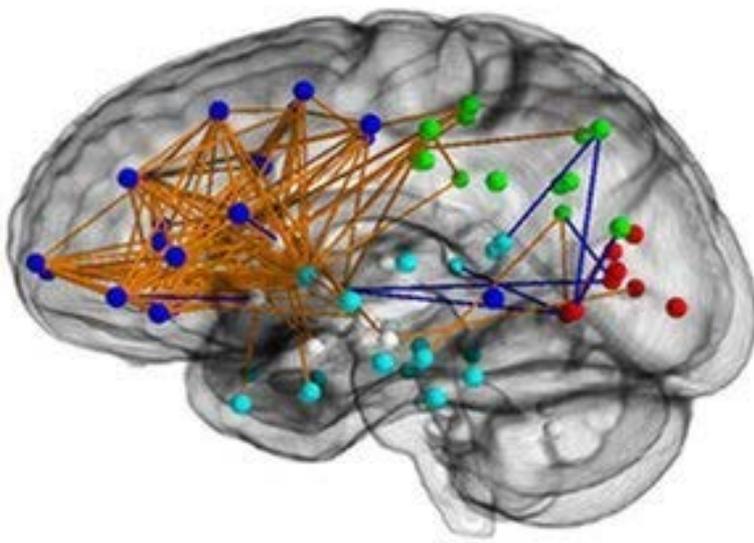
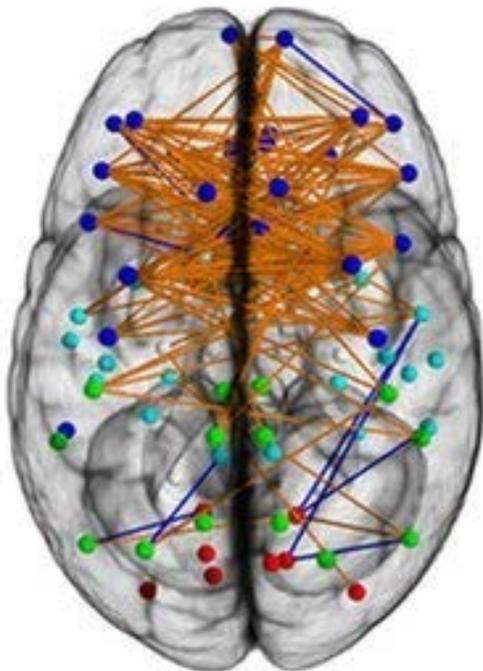
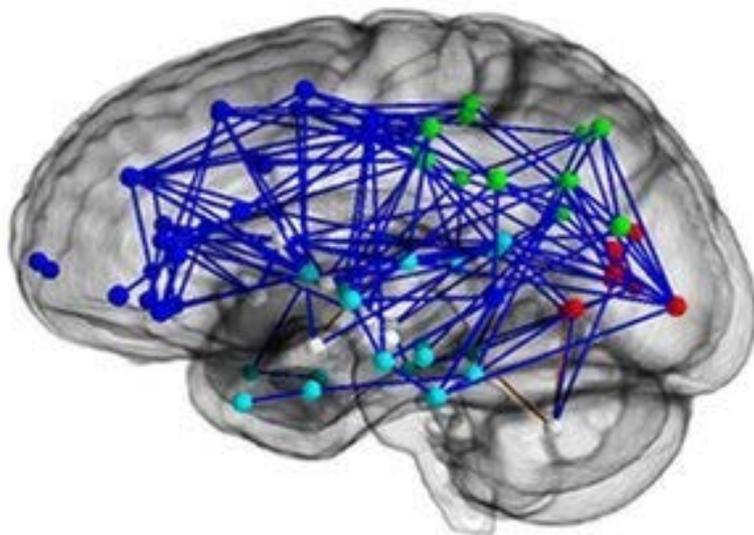
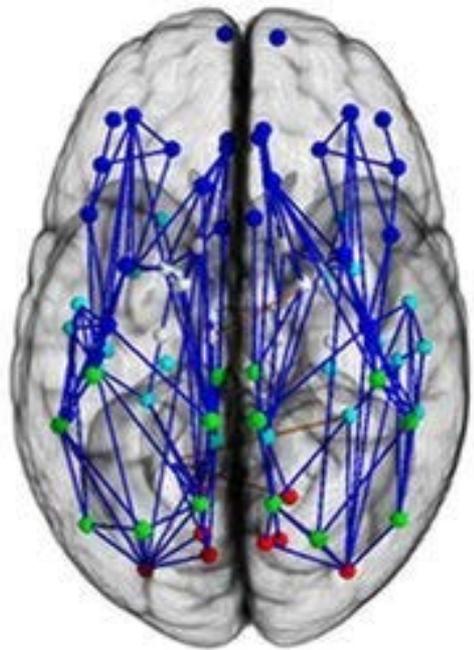


# Humans?

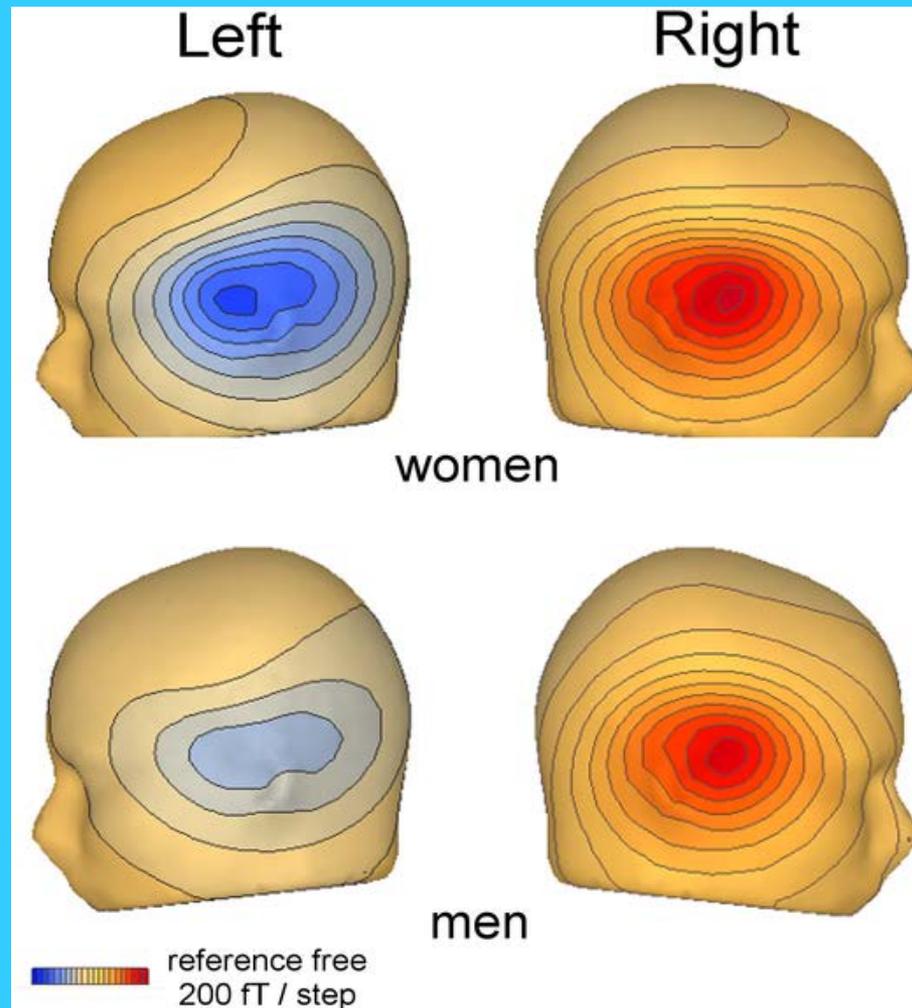


# ApoE4?



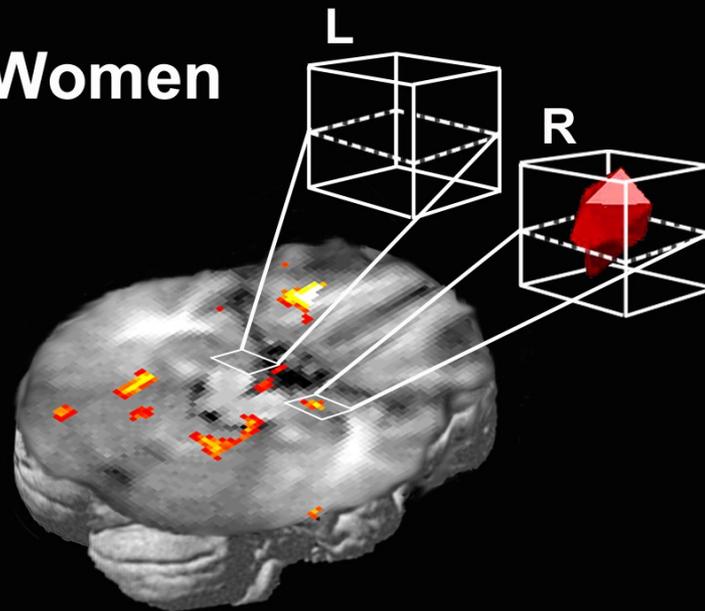


**Figure 2. Field topography corresponding to the M170 peak-amplitude in each hemisphere and for men and women separately.**

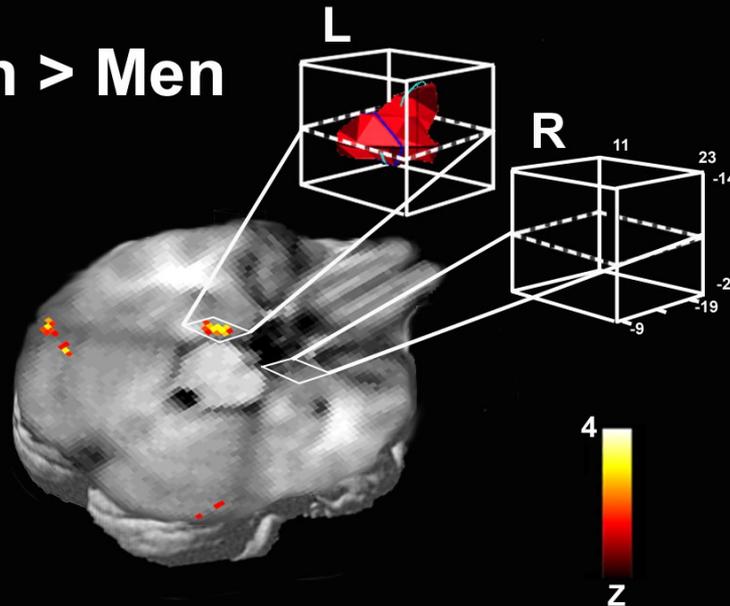


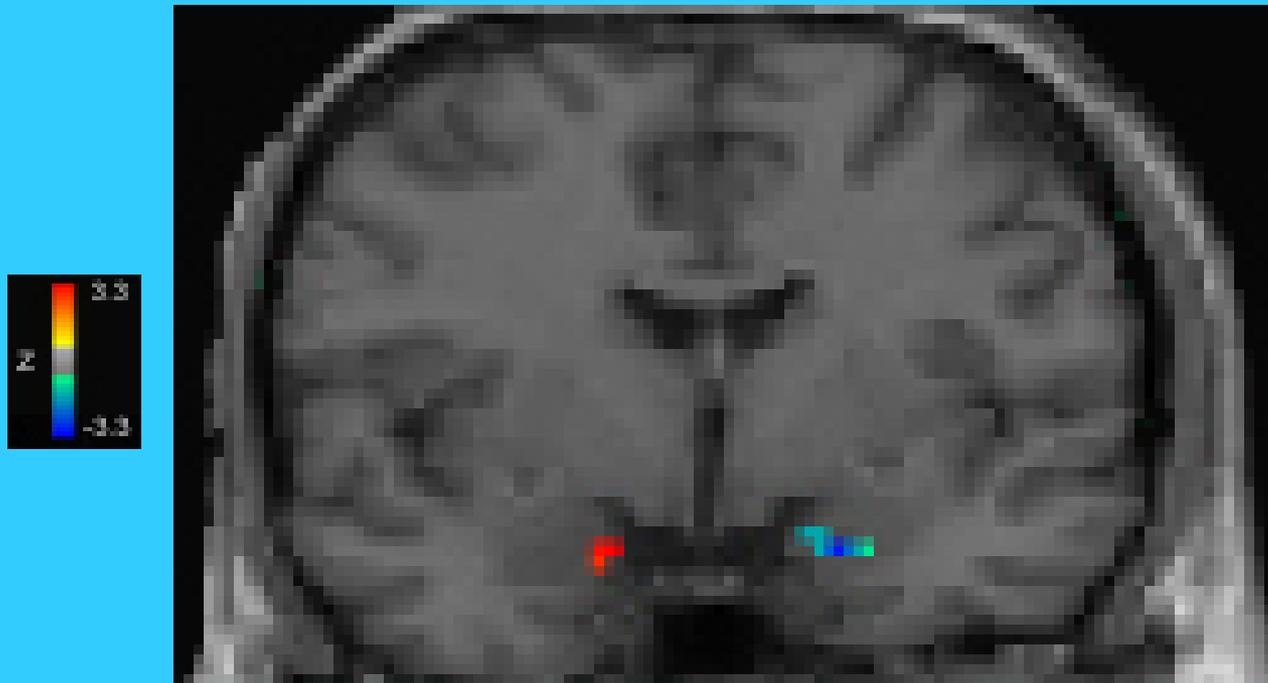
Tiedt HO, Weber JE, Pauls A, Beier KM, et al. (2013) Sex-Differences of Face Coding: Evidence from Larger Right Hemispheric M170 in Men and Dipole Source Modelling. PLoS ONE 8(7): e69107. doi:10.1371/journal.pone.0069107  
<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0069107>

**Men > Women**



**Women > Men**





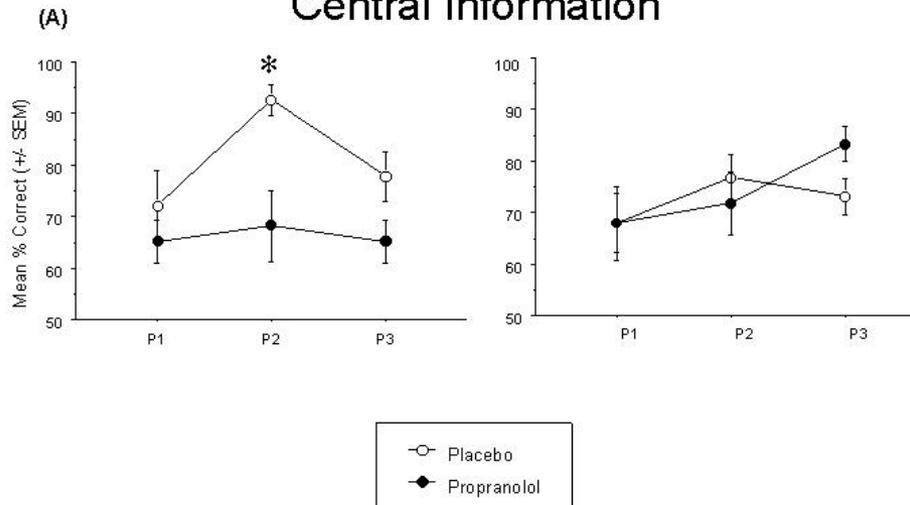
**Location of Amygdala Seed Voxels Displaying Significant Sex-related Differences in Amygdala Functional Connectivity during Resting Conditions**

Red areas are associated with greater functional connectivity in women than in men. Blue areas are associated with greater functional connectivity in men than in women.

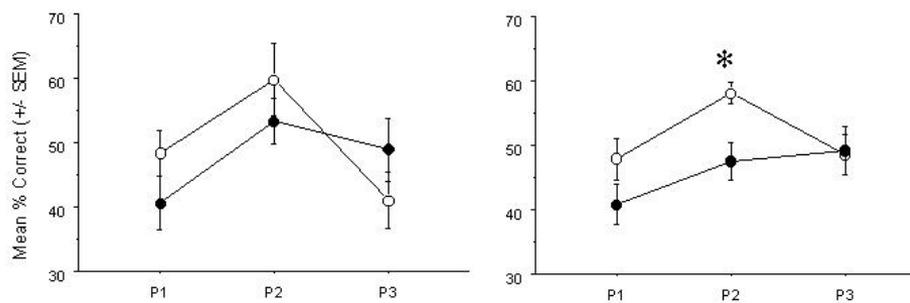
# Men

# Women

## Central Information

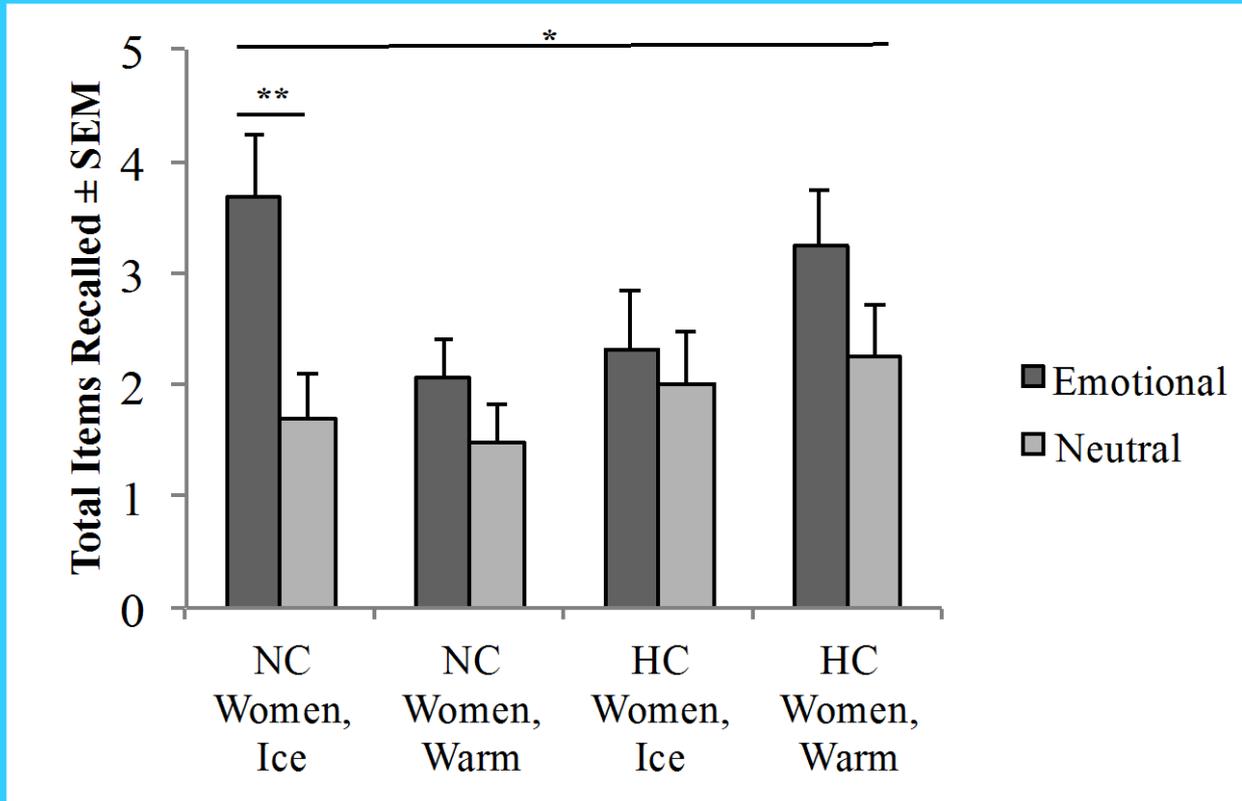


## Peripheral Detail

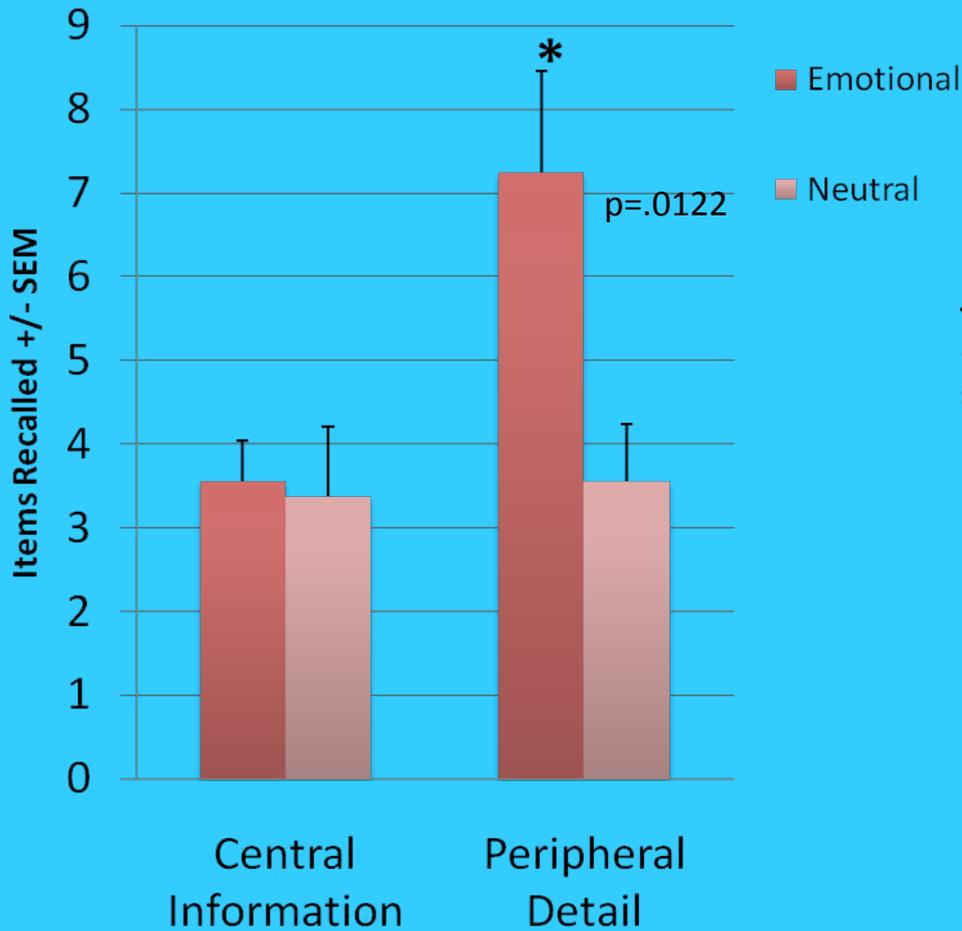


(3-phase story– arm in ice water– 1 week- Memory test)

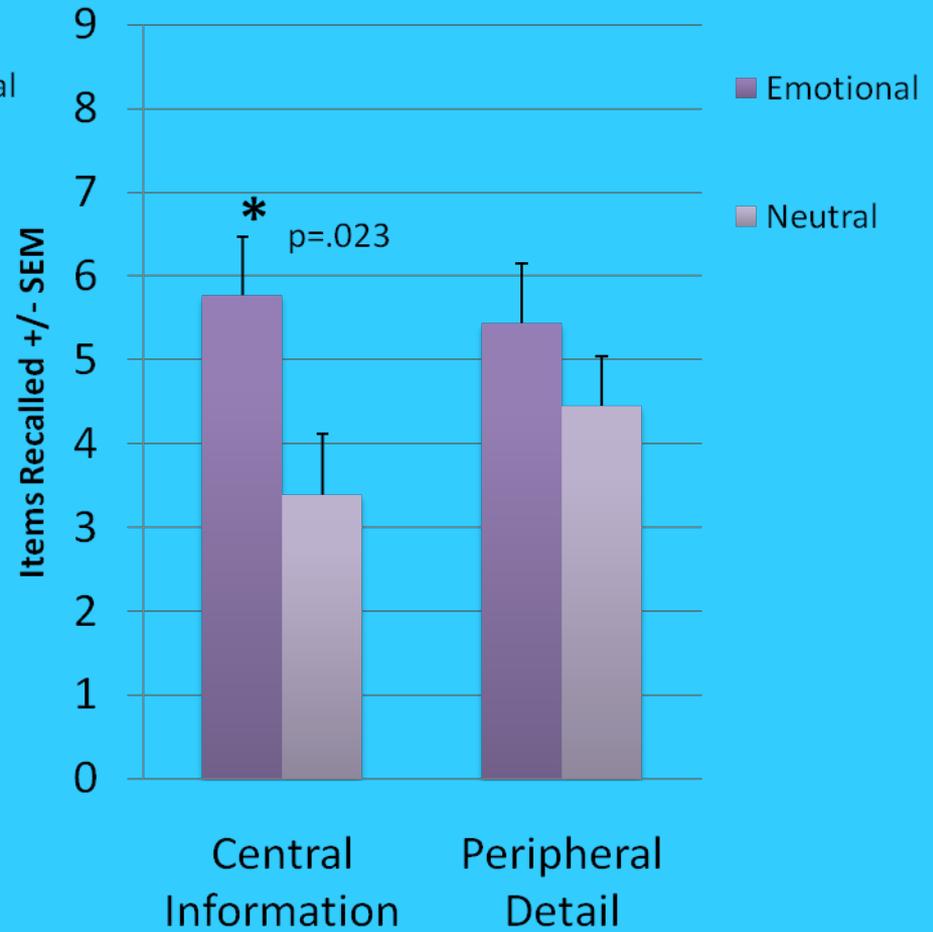
## DETAILS RECALLED



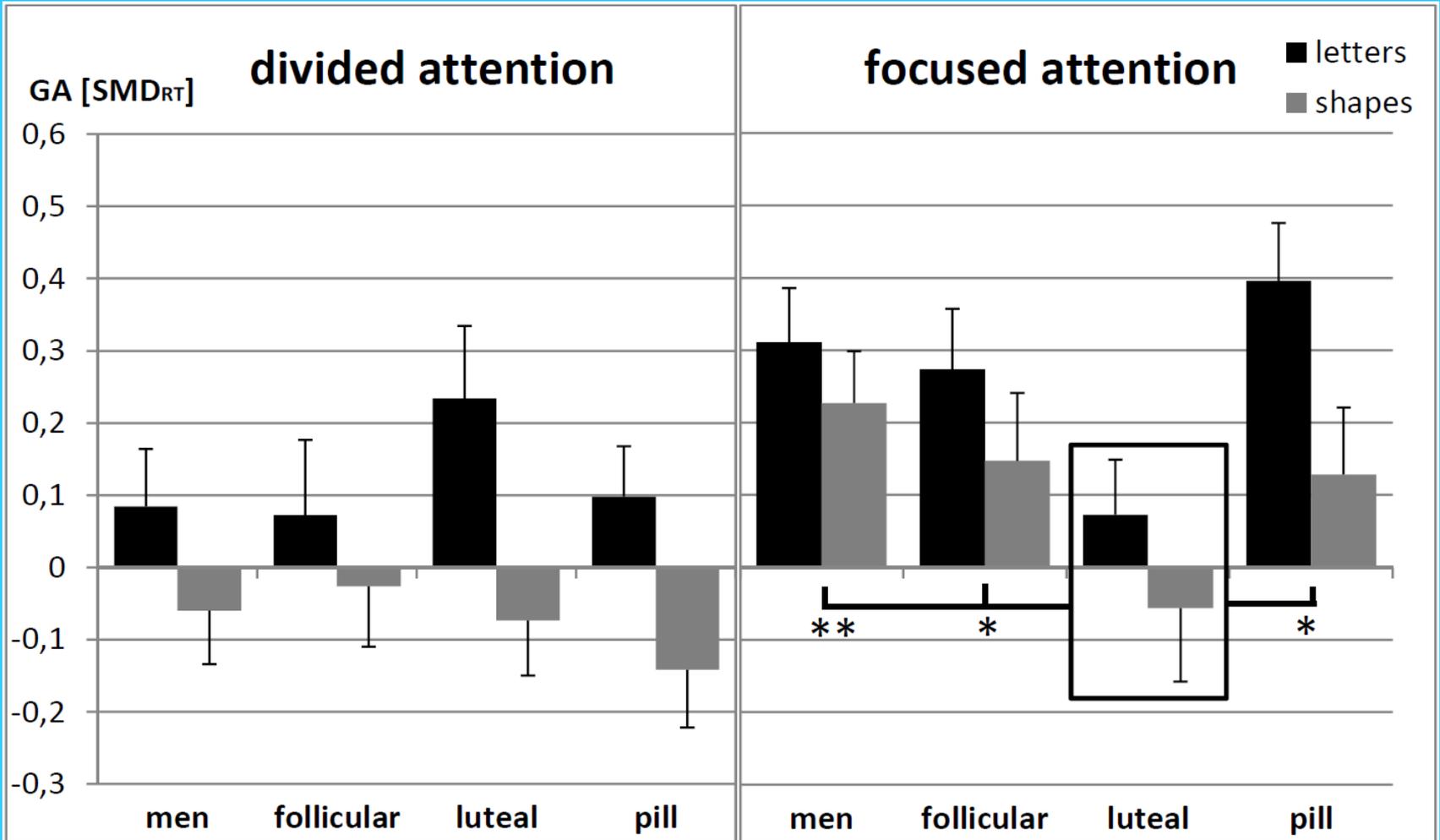
## Naturally Cycling Women



## Women on Hormonal Contraception



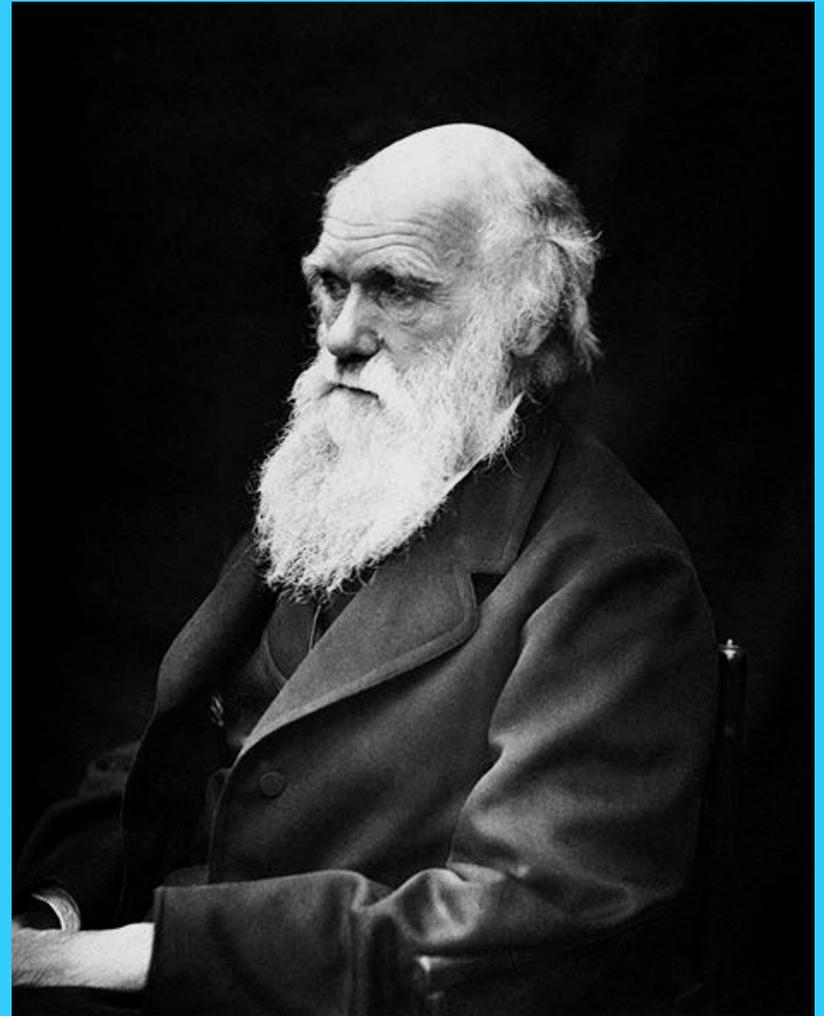
# Reduced Global Advantage



Natural  
Selection

Did NOT

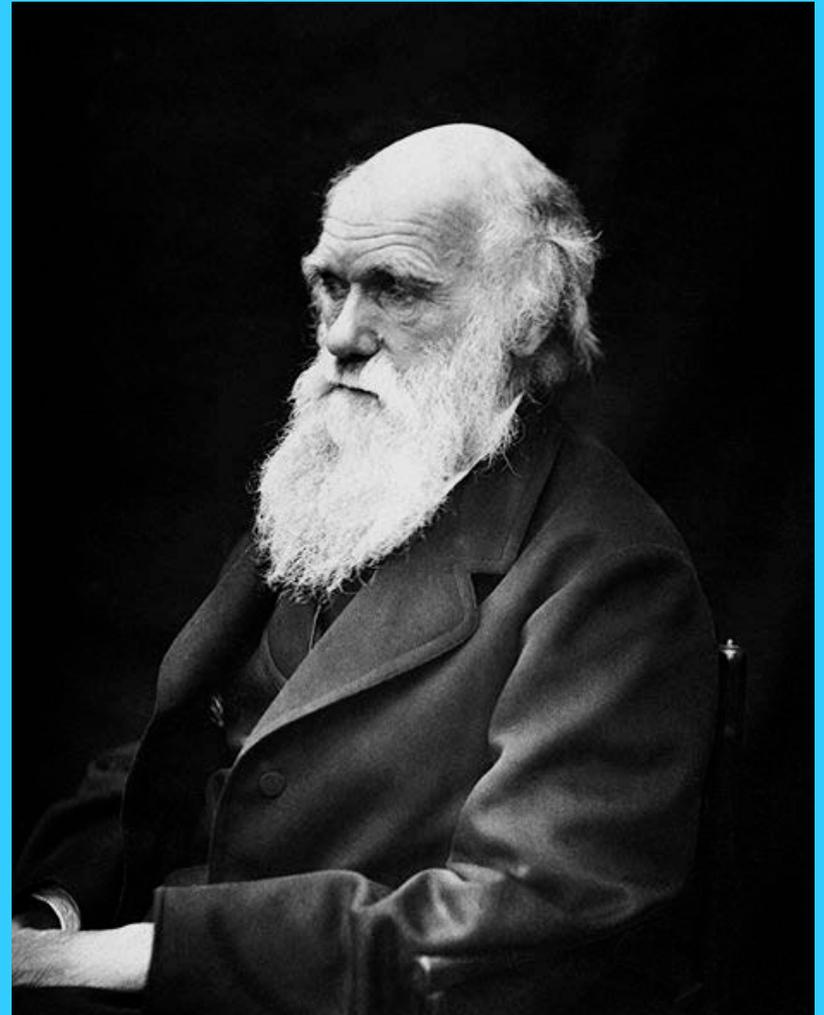
Drive  
Evolution

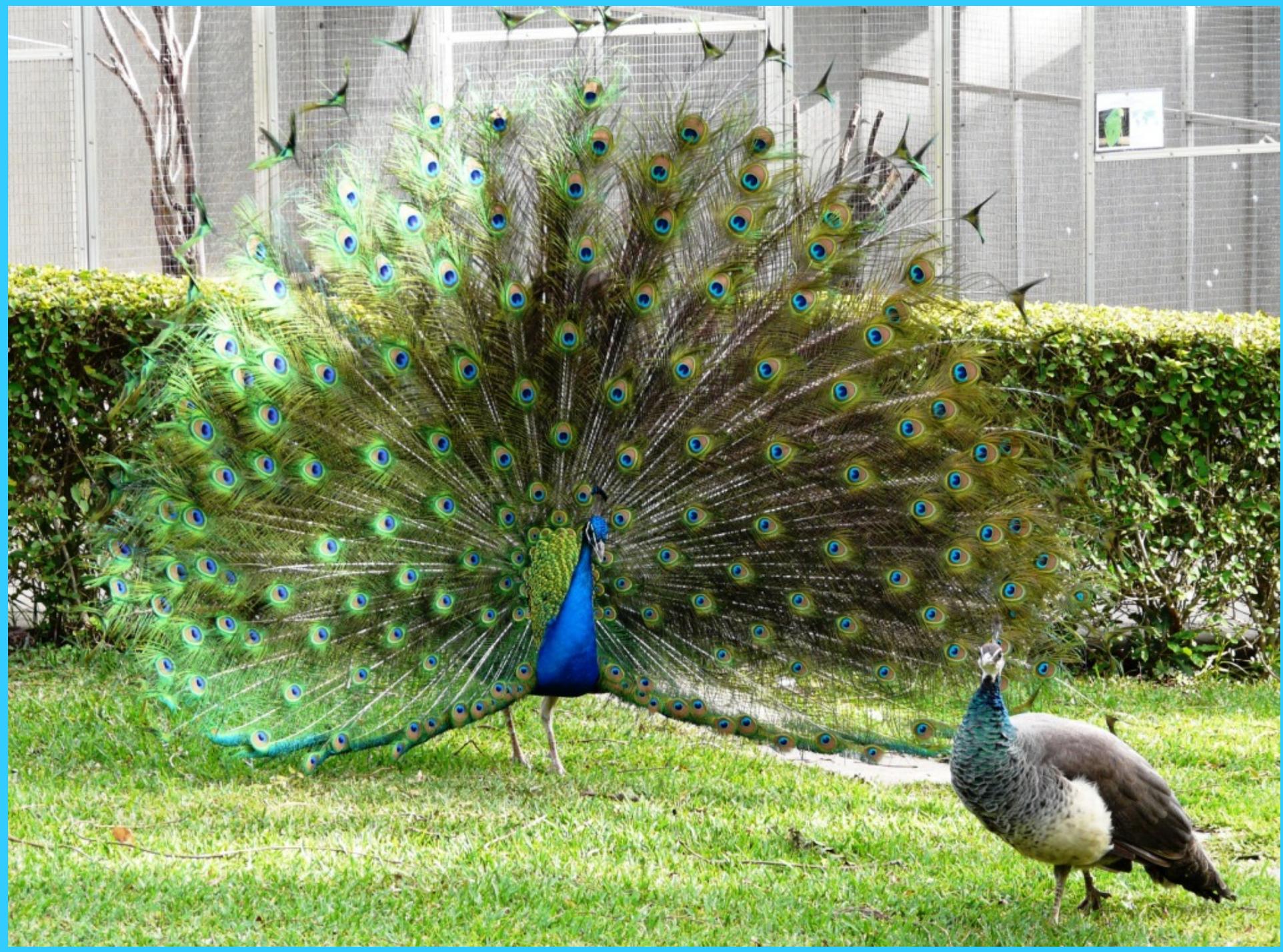


Natural  
Selection

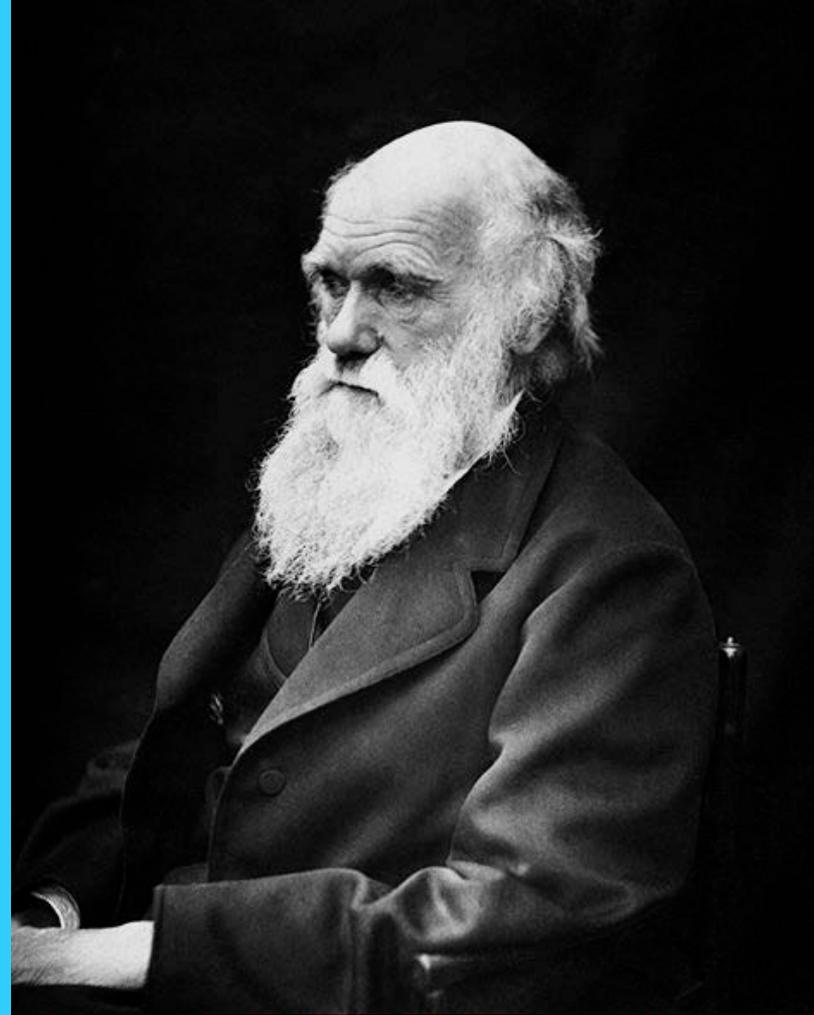
And  
Sexual  
Selection

Drove  
Evolution



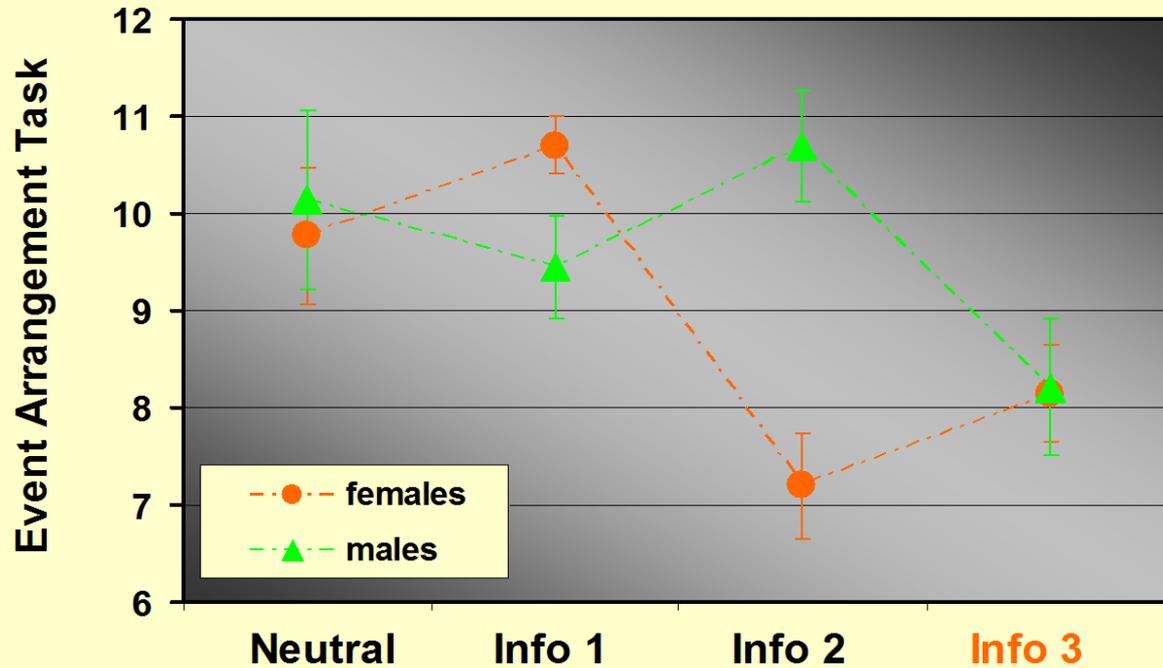


“It has been said by several critics that when I found that many details of the structure of man could not be explained by natural selection, I invented sexual selection; I gave, however, a tolerably clear sketch of this principle in the first edition of “Origin of Species,” and there I stated it was applicable to man...I have been struck with the likeness of many of the half-favourable criticisms on sexual selection, with those which appeared at first on natural selection; such as, that it would explain some few details, but certainly was not applicable to the extent to which I have employed it. **My conviction in the power of sexual selection remains unshaken.**”



“Descent of Man and Selection in Relation to Sex”, 2nd Ed, 1875, Preface to the Second Edition, page vi.

# STEREOTYPE EFFECT



INFO 1: **Females** are usually better  
INFO 2: **Males** are usually better  
INFO 3: **Males** are usually worse



# 5 QUESTIONS

- 1) Is the degree of sex bias in animal/cell research really all that bad?
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# PTSD

## ARTICLE

doi:10.1038/nature09856

# Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor

Kerry J. Ressler<sup>1,2,4</sup>, Kristina B. Mercer<sup>1</sup>, Bekh Bradley<sup>2,3</sup>, Tanja Jovanovic<sup>2</sup>, Amy Mahan<sup>4</sup>, Kimberly Kerley<sup>1</sup>, Seth D. Norrholm<sup>2,3</sup>, Varun Kilaru<sup>2</sup>, Alicia K. Smith<sup>2</sup>, Amanda J. Myers<sup>5</sup>, Manuel Ramirez<sup>5</sup>, Anzhelika Engel<sup>5</sup>, Sayamwong E. Hammack<sup>6</sup>, Donna Toufexis<sup>4,6</sup>, Karen M. Braas<sup>7</sup>, Elisabeth B. Binder<sup>2,8</sup> & Victor May<sup>7</sup>

Nature, 2011

# ARTICLE

doi:10.1038/nature09856

## Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor <sup>^</sup> in women, not men

Kerry J. Ressler<sup>1,2,4</sup>, Kristina B. Mercer<sup>1</sup>, Bekh Bradley<sup>2,3</sup>, Tanja Jovanovic<sup>2</sup>, Amy Mahan<sup>4</sup>, Kimberly Kerley<sup>1</sup>, Seth D. Norrholm<sup>2,3</sup>, Varun Kilaru<sup>2</sup>, Alicia K. Smith<sup>2</sup>, Amanda J. Myers<sup>5</sup>, Manuel Ramirez<sup>5</sup>, Anzhelika Engel<sup>5</sup>, Sayamwong E. Hammack<sup>6</sup>, Donna Toufexis<sup>4,6</sup>, Karen M. Braas<sup>7</sup>, Elisabeth B. Binder<sup>2,8</sup> & Victor May<sup>7</sup>

Nature, 2011

# PTSD

Behavioral/Cognitive

## Epigenetic Modification of the Glucocorticoid Receptor Gene Is Linked to Traumatic Memory and Post-Traumatic Stress Disorder Risk in Genocide Survivors

Vanja Vukojevic,<sup>1,2</sup> Iris-T. Kolassa,<sup>3</sup> Matthias Fastenrath,<sup>1,4</sup> Leo Gschwind,<sup>1,4</sup> Klara Spalek,<sup>1,4</sup> Annette Milnik,<sup>1,5</sup> Angela Heck,<sup>1,5,6</sup> Christian Vogler,<sup>1,5,6</sup>  Sarah Wilker,<sup>3</sup> Philippe Demougin,<sup>1,2</sup> Fabian Peter,<sup>1,2</sup> Erika Atucha,<sup>7</sup> Attila Stetak,<sup>1,2,5</sup> Benno Roozendaal,<sup>7</sup>  Thomas Elbert,<sup>8</sup> Andreas Papassotiropoulos,<sup>1,2,5,6</sup> and Dominique J.-F. de Quervain<sup>4,5,6</sup>

Journal of Neuroscience, 2014

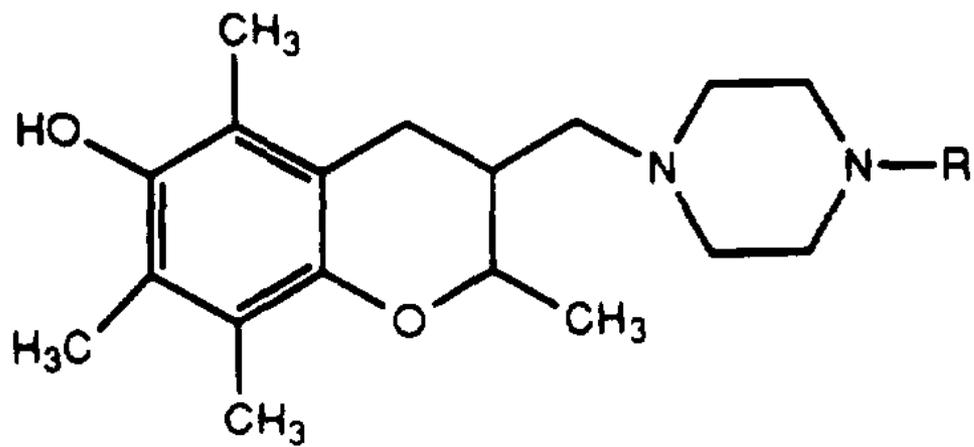
Behavioral/Cognitive

# Epigenetic Modification of the Glucocorticoid Receptor Gene Is Linked to Traumatic Memory and Post-Traumatic Stress Disorder Risk in Genocide Survivors <sup>^</sup> **in men, not women**

Vanja Vukojevic,<sup>1,2</sup> Iris-T. Kolassa,<sup>3</sup> Matthias Fastenrath,<sup>1,4</sup> Leo Gschwind,<sup>1,4</sup> Klara Spalek,<sup>1,4</sup> Annette Milnik,<sup>1,5</sup> Angela Heck,<sup>1,5,6</sup> Christian Vogler,<sup>1,5,6</sup>  Sarah Wilker,<sup>3</sup> Philippe Demougin,<sup>1,2</sup> Fabian Peter,<sup>1,2</sup> Erika Atucha,<sup>7</sup> Attila Stetak,<sup>1,2,5</sup> Benno Roozendaal,<sup>7</sup>  Thomas Elbert,<sup>8</sup> Andreas Papassotiropoulos,<sup>1,2,5,6</sup> and Dominique J.-F. de Quervain<sup>4,5,6</sup>

Journal of Neuroscience, 2014

# “Lazaroids”



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# 5 QUESTIONS

- 1) Is the degree of sex bias in animal/cell research really all that bad?
- 2) Why the resistance to studying sex influences?
- 3) Where are these sex influences?
- 4) Does all this really matter for the clinic?
- 5) So what should we do about it?



**Marjorie Jenkins MD**  
**Texas Tech University**  
**Health Sciences Center**



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**SGBM**   **SEX AND GENDER BASED MEDICINE**

This project is supported by the Office of the President, Offices of the Deans of the Schools of Medicine, Pharmacy, Allied Health Sciences and Nursing, and the Laura W. Bush Institute for Women's Health.



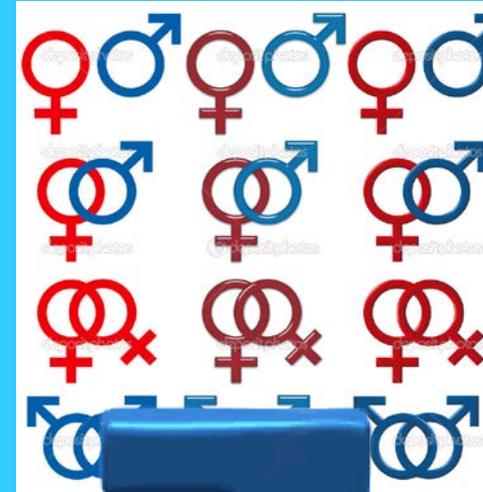
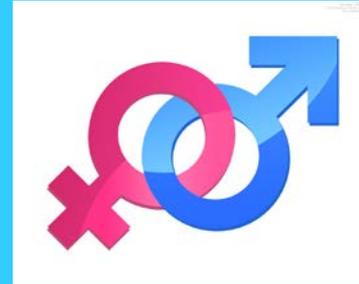
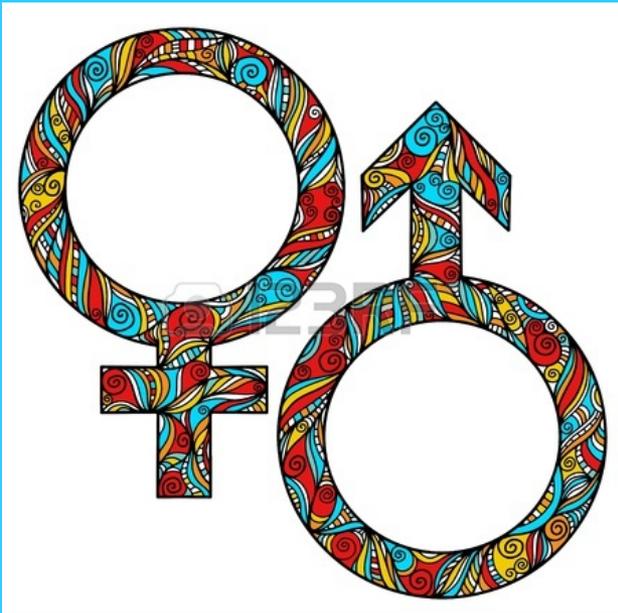
**A. WHAT IS SGBM?**  
Sex and gender are both basic human variables and important health determinants.

**B. PROJECT SUMMARY**  
The TTUHSC SGBMC project began in the School of Medicine in 2010

**C. ABOUT US**  
Texas Tech Health Sciences Center  
Laura W. Bush Institute for Women's Health

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# “Clarity about Sex” Rule



# “Clarity about Sex” Rule

All Titles

“..... in males”



# “Clarity about Sex” Rule

## All Titles

“..... in males”



“.....in females”



# Same or Different?



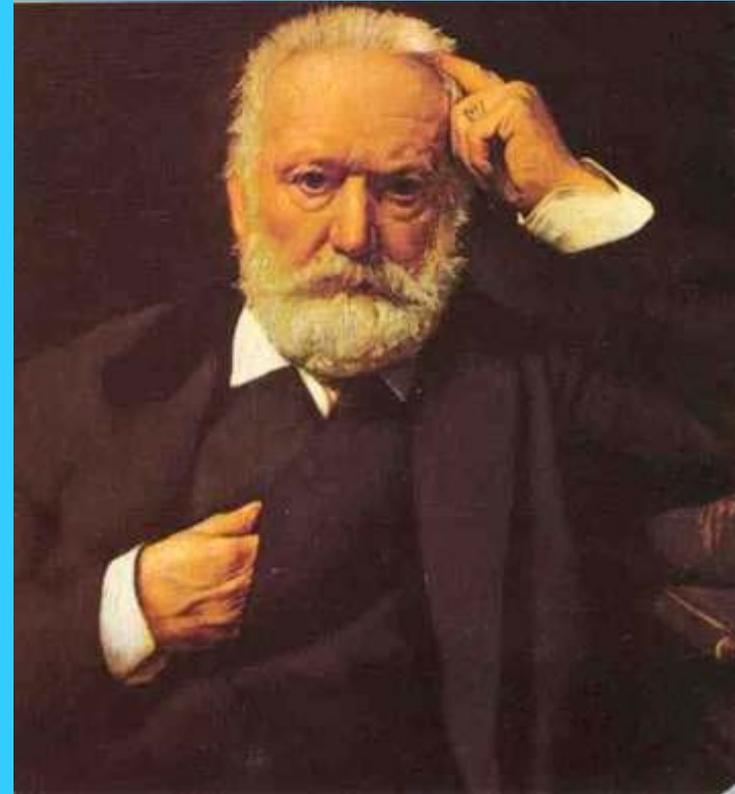
# Same or Different?



Same and Different

There is one thing  
stronger than all the  
armies in the world,  
and that is an idea  
whose time has come

Victor Hugo  
1802-1885



# Sex Matters

