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
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
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

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

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**
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

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**
3) Where are these sex influences? **Pretty Much Everywhere**
4) Does all this really matter for the clinic?
5) So what should we do about it?
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**
3) Where are these sex influences? **Pretty Much Everywhere**
4) Does all this really matter for the clinic? **YES**
5) So what should we do about it?
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**
3) Where are these sex influences? **Pretty Much Everywhere**
4) Does all this really matter for the clinic? **YES**
5) So what should we do about it? **Some Suggestions**
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?
Sex bias in neuroscience and biomedical research

Annaliese K. Beery\textsuperscript{a}, Irving Zucker\textsuperscript{b,c,*}

\textsuperscript{a} Robert Wood Johnson Health & Society Scholar at University of California, San Francisco and University of California, Berkeley, CA, USA
\textsuperscript{b} Department of Psychology, and Helen Wills Neuroscience Institute, University of California, 3210 Tolman Hall, 1650 Berkeley, 94720 CA, USA
\textsuperscript{c} 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

![Bar chart showing the number of manuscripts by gender: 80% male, 17% female, 3% both.](chart.png)
Sex Bias Exists with *Cell* Research

![Graph showing sex bias in research manuscripts](chart.png)

- **Sex Stated**: 24%
- **Sex Not Stated**: 76%
Sex Bias Exists with *Cell* Research
More Male Animals Are Studied

![Bar Graph]

- **Male**: 84%
- **Female**: 16%

**Absolute Number of Animals Used**

- 0
- 5000
- 10000
- 15000
- 20000
For female-prevalent diseases, of those reports that stated the sex, only 12% studied female animals
Learning and Memory

Fear Conditioning

Fear Extinction

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?
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?
“Females are too variable and complex, and one has to deal with the estrous cycle”
Review

Female mice liberated for inclusion in neuroscience and biomedical research

Brian J. Prendergast\textsuperscript{a}, Kenneth G. Onishi\textsuperscript{a}, Irving Zucker\textsuperscript{b,c,*}

\textsuperscript{a} Department of Psychology and Institute for Mind and Biology, University of Chicago, United States
\textsuperscript{b} Department of Psychology, University of California, Berkeley, United States
\textsuperscript{c} 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
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

- NICHID: Budget of 1200 million dollars
- NIA: Budget of 1000 million dollars
- NIMHD: Budget of 250 million dollars
- ORWH: Budget of 50 million dollars

Budget (in Millions of Dollars)
Neurosexists!

Delusions of Gender
The Real Science Behind Sex Differences
“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

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?
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

Transgenic Mice

Hippocampus

Cell Culture!
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

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

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

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

...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.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0069107
Men > Women

Women > Men

Cahill et al., 2004  Supported by NIMH RO1 57508
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

(A)

Mean % Correct (+/- SEM)

P1 P2 P3

Placebo 
Propranolol

Peripheral Detail

(B)

Mean % Correct (+/- SEM)

P1 P2 P3

Cahill and van Stegeren, 2003
(3-phase story– arm in ice water– 1 week- Memory test)

DETAILS RECALLED

![Graph showing details recalled]

- **Total Items Recalled ± SEM**
- **Conditions**: NC Women, Ice, NC Women, Warm, HC Women, Ice, HC Women, Warm
- **Groups**: Emotional, Neutral

*Significant difference
**Very significant difference
Naturally Cycling Women

- Emotional
- Neutral

Women on Hormonal Contraception

- Emotional
- Neutral

*Significant difference (p < 0.05)

Items Recalled +/- SEM

Central Information

Peripheral Detail

Central Information

Peripheral Detail

p = 0.0122

p = 0.023
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.”

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

Pavlova et al., *Brain Research* 2010
Pavlova et al., *Deutsche Zeitschrift für Klinische Forschung* 5/6-2010
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?
PTSD

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


Nature, 2011
Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor ~ in women, not men
Epigenetic Modification of the Glucocorticoid Receptor Gene Is Linked to Traumatic Memory and Post-Traumatic Stress Disorder Risk in Genocide Survivors


Journal of Neuroscience, 2014
Epigenetic Modification of the Glucocorticoid Receptor Gene Is Linked to Traumatic Memory and Post-Traumatic Stress Disorder Risk in Genocide Survivors ^ in men, not women


Journal of Neuroscience, 2014
“Lazaroids”
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

www.texastechsgbm.org

SEASONAL ALIMENTATION

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
“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