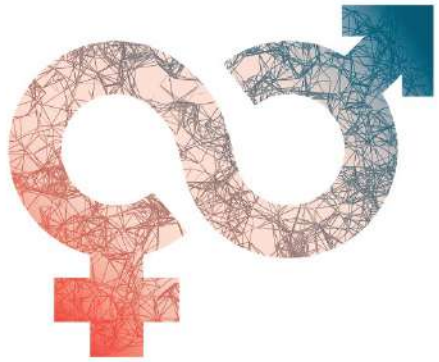
Gender-In

Integrating Gender-In Interdisciplinary Research



How can we incorporate sex and gender in preclinical and clinical research?

CHRISTINA DALLA, *PhD*

Associate Professor

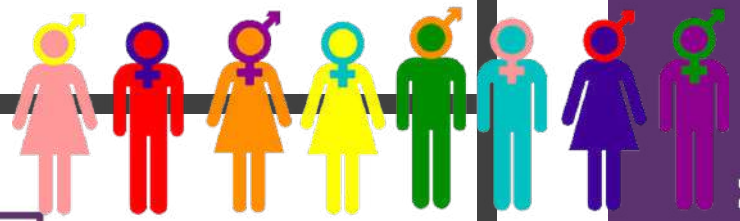
Department of Pharmacology, Medical School, National and Kapodistrian University of Athens,

President-elect of the Mediterranean Neuroscience Society

WHY INTEGRATING SEX, GENDER AND INTERSECTIONAL ANALYSIS INTO RESEARCH AND INNOVATION CONTENT MATTERS

Taking into account sex, gender and intersecting factors in the design and delivery of R&I leads to:

- added value of research in terms of excellence, creativity and business opportunities
- an in-depth understanding of all people's needs, behaviours and attitudes
- goods and services better suited to the needs of all people
- enhanced societal relevance of research and innovation.



>> **SEX** refers to biological characteristics that distinguish between male, female, and intersex (in humans) or hermaphrodite (in animals).

>> **GENDER** refers to socio-cultural norms, identities and relations that, together, shape and sanction "feminine" and "masculine" behaviours, and which are complex and change across time and place.

>> **INTERSECTIONAL FACTORS**, such as racial or ethnic origin, age, socioeconomic status, sexual orientation, or disability, combine with sex and gender to shape a person's or a group's experience and social opportunities, thereby influencing the form of discrimination and inequality they encounter.

GUIDANCE FOR COLLECTING SEX/GENDER DATA IN RESEARCH

Joshua D. Safer, MD, FACP, FACE[1]; Vin Tangpricha, MD, PhD, FACE[2]

ENDOCRINE PRACTICE Vol 26 No. 10 October 2020 1225

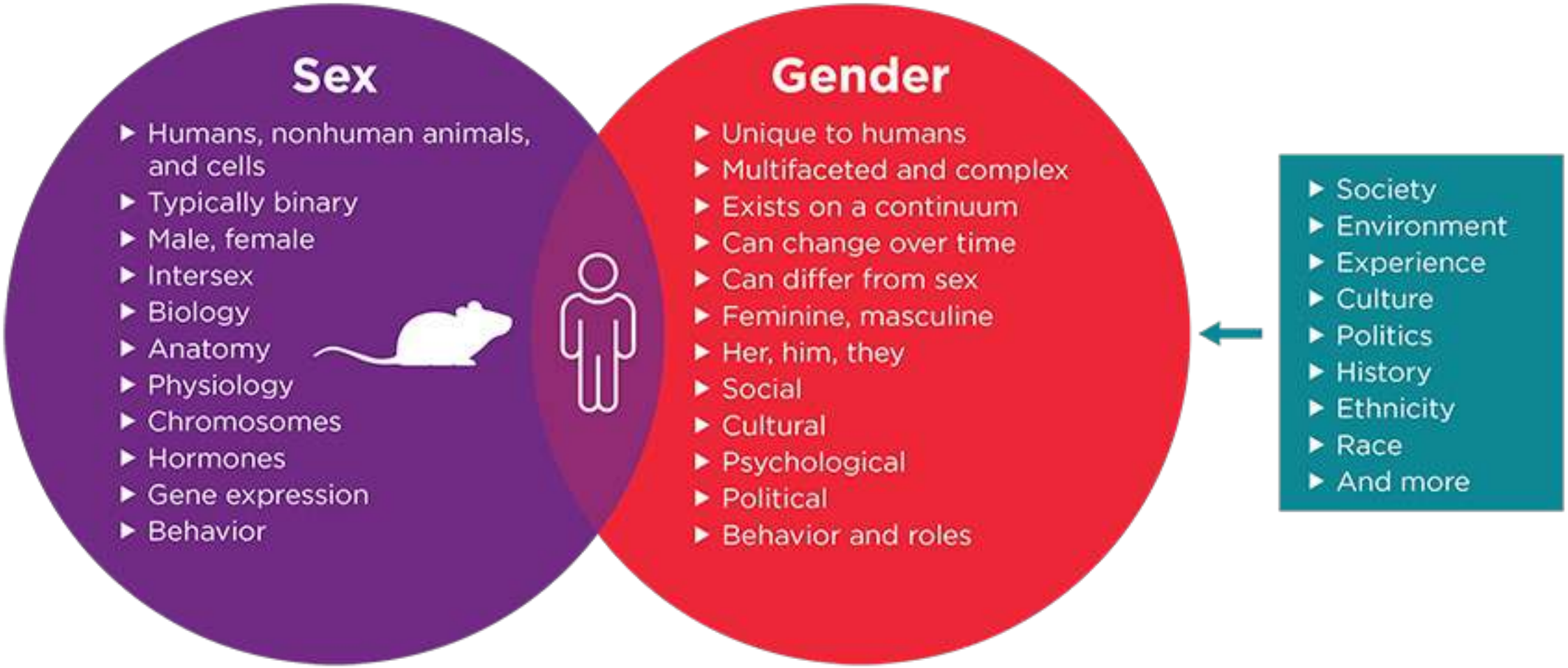
Human studies

Table 1
Definitions

Sex/gender:	Umbrella terms for biologic characteristics and behaviors that are typically considered male, female, or some variation.
Gender identity:	The internal sense of being male, female, both, or neither.
Transgender, transsexual, trans, gender nonbinary, gender incongruent, genderqueer:	Adjectives for people with gender identity that is not aligned with sex recorded at birth.
Cisgender, nontransgender:	Adjectives for people with gender identities aligned with sex recorded at birth.
Transgender male, trans masculine, masculine spectrum:	Terms for people recorded female at birth who have a more masculine gender identity.
Transgender female, trans feminine, feminine spectrum:	Terms for people recorded male at birth who have a more feminine gender identity.
Nonbinary:	Term for individuals with a gender identity that is both male and female or neither male nor female.

Table 2
Sample Framework to Replace Sex/Gender Query When Collecting Demographic Data

1. **What is the sex/gender recorded on your original birth certificate?**
   a. Male
   b. Female
   c. X, none, or other
2. **What is your sex/gender/gender identity?**
   a. Male, transgender male, trans masculine, masculine spectrum
   b. Female, transgender female, trans feminine, feminine spectrum
   c. Nonbinary
   d. None or other



https://www.taconic.com/taconic-insights/quality/sex-vs-gender-preclinical-research.html

HOW THEY HAPPENED

The guidelines were developed by a panel of 13 experts representing nine countries through a series of teleconferences, conference presentations and a 2-day workshop. The panel conducted an internet survey of 716 journal editors, scientists and others in the international publishing community and a literature search on sex and gender policies in scientific publishing.

HOW THEY WORK

The resulting guidelines are a comprehensive procedure for reporting of sex and gender information in study design, data analyses, results and interpretation of findings.

13 EXPERTS FROM

9 COUNTRIES

AND WHO SHARES RESPONSIBILITY

The use of the guidelines by authors and reviewers, their adoption by editors as gatekeepers of science, and their respect by funders all contribute to integrating the assessment of sex and gender into manuscripts as an integral part of the editorial process.

716 JOURNAL EDITORS, SCIENTISTS, AND PUBLISHERS SURVEYED

DOI: 10.1111/bph.14761

EDITORIAL

BJP BRITISH PHARMACOLOGICAL SOCIETY

Sex: A change in our guidelines to authors to ensure that this is no longer an ignored experimental variable

- Our contributors
- Our support
- Get involved
- Contact us
- Migrant Health Subgroup
- Sex/Gender Methods Gro
  - Publications
  - Current Projects

Sex and Gender in Systematic Reviews Planning Tool

A considerable body of research shows that the effects / outcomes of drugs and other health interventions differ between men and women. Questions about possible sex and gender differences should be asked and the particular relevance determined or ruled out.

This tool will help reviewers ask and answer these questions when planning a systematic review.

When a hand appears in the tool – it is a cue to stop & consider sex/gender. This consideration is intended to lead you to: (1) revise your approach; (2) highlight key gaps; (3) contextualize your findings.

PLANNING A SYSTEMATIC REVIEW

1. Review Section: Background

1a. Are sex and/or gender relevant or not relevant to the SR question?	**YES** ☐	**NO** ☐
1b. Have you discussed why sex and/or gender differences may or may not be expected?	**YES** ☐	**NO** ☐

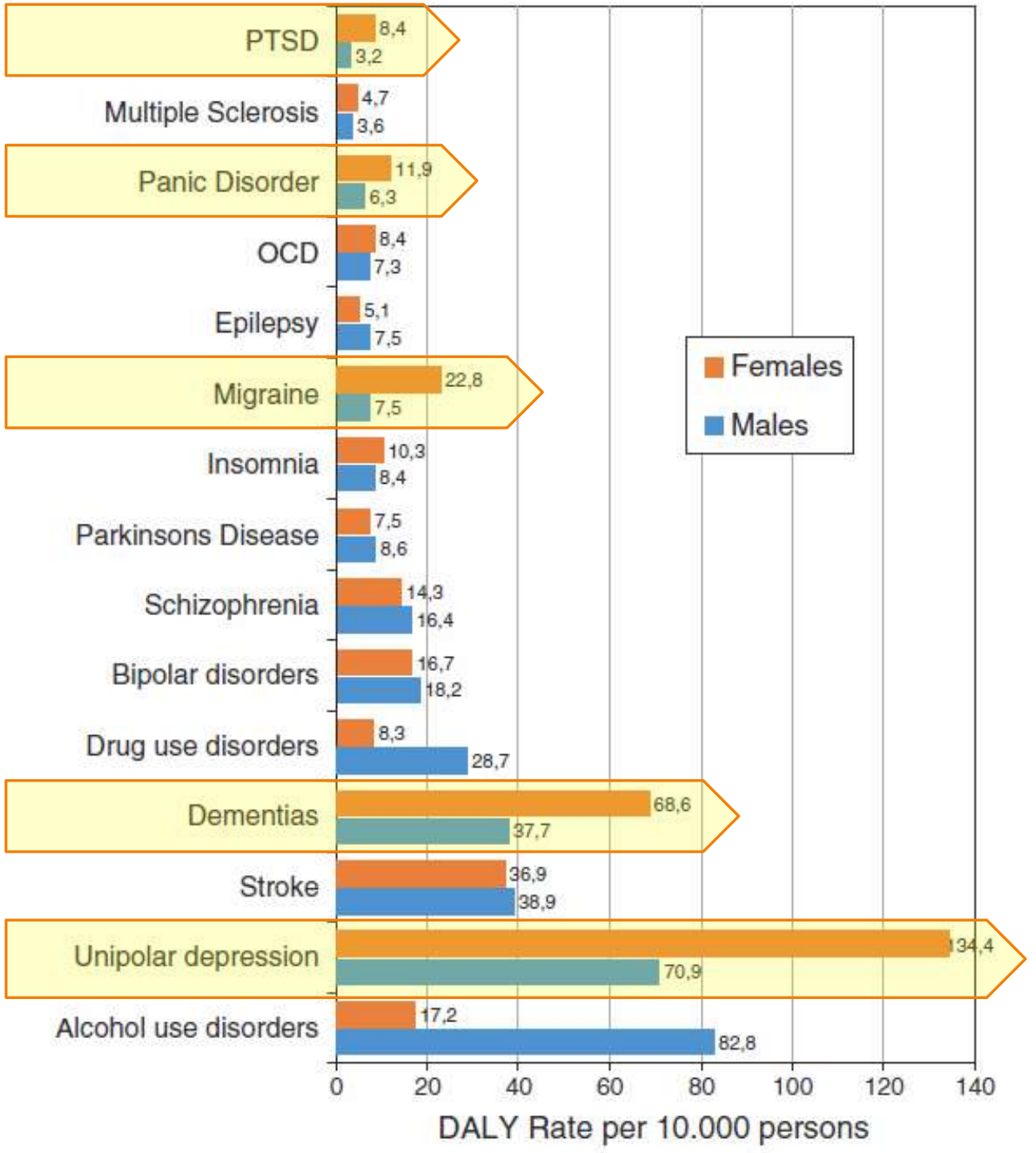
Sex Differences in Neurology & Psychiatry

European Neuropsychopharmacology
Volume 21, Issue 9, September 2011, Pages 655-679

ECNP/EBC Report 2011

The size and burden of mental disorders and other disorders of the brain in Europe 2010

H.U. Wittchen [a,1], F. Jacobi [a,1,2], J. Rehm [a,b], A. Gustavsson [c], M. Svensson [d], B. Jönsson [e], J. Olesen [f], C. Allgulander [g], J. Alonso [h], C. Faravelli [i], L. Fratiglioni [j], P. Jennum [k], R. Lieb [l], A. Maercker [m], J. van Os [n], M. Preisig [o], L. Salvador-Carulla [p], R. Simon [q], H.-C. Steinhausen [l,r,s]



frontiers in Psychology

SYSTEMATIC REVIEW
published: 25 June 2019
doi: 10.3389/fpsyg.2019.01453

Health of Non-binary and Genderqueer People: A Systematic Review

Cristiano Scandurra[1], Fabrizio Mezza[2], Nelson Mauro Maldonato[1], Mario Bottone[1], Vincenzo Bochicchio[3], Paolo Valerio[1] and Roberto Vitelli[1]*

[1] Department of Neuroscience, Reproductive Sciences and Dentistry, University of Naples Federico II, Naples, Italy, [2] Center SInAPSi, University of Naples Federico II, Naples, Italy, [3] Department of Humanistic Studies, University of Calabria, Cosenza, Italy

Background: Non-binary and genderqueer (NBGQ) people are those who do not identify within the gender binary system (male vs. female), not falling exclusively in man/male or woman/female normative categories. A higher proportion of NBGQ people is usually found within young persons. This population is marginalized and, as such, is at risk of stigmatization and of developing negative health outcomes. As literature on the health of NBGQ people is sparse, this study aims at systematically review the limited studies on this field.

REVIEWS AND OVERVIEWS
Mechanisms of Psychiatric Illness

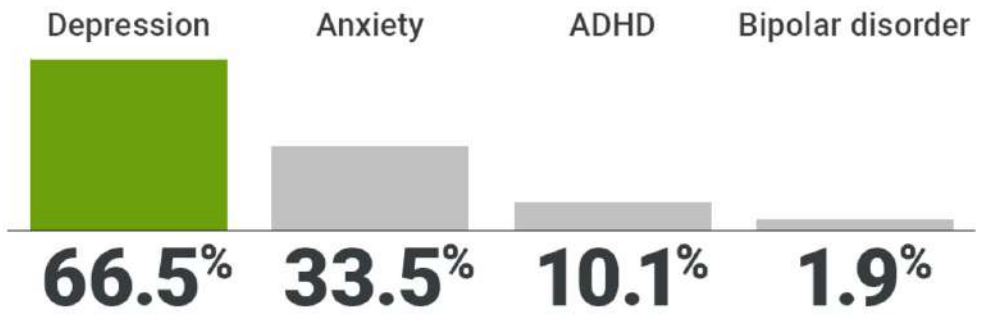
Transgender Research in the 21st Century: A Selective Critical Review From a Neurocognitive Perspective

Sven C. Mueller, Ph.D., Griet De Cuypere, M.D., Ph.D., Guy T'Sjoen, M.D.

Gender dysphoria describes the psychological distress caused by identifying with the sex opposite to the one assigned at birth. In recent years, much progress has been made in characterizing the needs of transgender persons wishing to transition to their preferred gender, thus helping to optimize care. This critical review of the literature examines their common mental health issues, several individual risk factors for psychiatric comorbidity, and current research on the underlying neurobiology. Prevalence rates of persons identifying as transgender and seeking help with transition have been rising steeply since 2000 across Western countries; the current U.S. estimate is 0.6%. Anxiety and depression are frequently observed both before and after transition, although there is some decrease afterward. Recent research has identified autistic traits in some transgender persons. Forty percent of transgender persons endorse suicidality, and the rate of self-injurious behavior and suicide are markedly higher than in the general population. Individual factors contributing to mental health in transgender persons include community attitudes, societal acceptance, and posttransition physical attractiveness. Neurobiologically, whereas structural MRI data are thus far inconsistent, functional MRI evidence in trans persons suggests changes in some brain areas concerned with olfaction and voice perception consistent with sexual identification, but here too, a definitive picture has yet to emerge. Mental health clinicians, together with other health specialists, have an increasing role in the assessment and treatment of gender dysphoria in transgender individuals.

Am J Psychiatry 2017; 174:1155–1162; doi: 10.1176/appi.ajp.2017.17060626

Prevalence of psychiatric comorbidities among transgender adolescents:



Healio

Many adolescents who identify as transgender or gender nonconforming were identified as experiencing psychological comorbidities, such as depression, anxiety and suicidal ideation, with a greater burden observed among transgender males vs. transgender females.

1 *in* 3

trans youth attempted suicide in the past year (Veale et al., 2015).

Trans people are

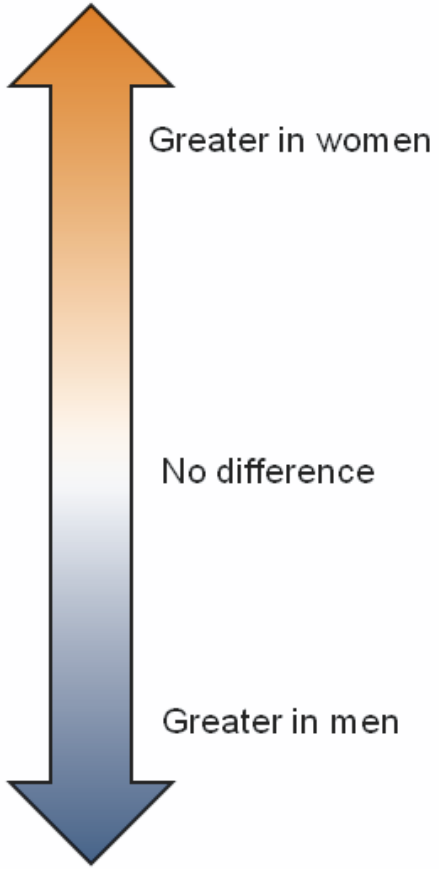
2*x*

more likely to think about and attempt suicide than LGB people (Irwin et al., 2014).

centre *for* suicide prevention

Sex bias in disorders

Disorder	Women/Men Lifetime Incidence Ratio
PTSD	2.08[a]
Panic Disorder	1.96[b]
Generalized Anxiety	1.88[b]
Major Depressive Disorder	1.75[b]
OCD	1.6[c]
Alzheimer's Disease	1.30[d]
Bipolar Disorder	~1.0[e]
Schizophrenia	1.4[f]
Parkinson's Disease	1.92[g]
Drug Use Disorder	1.94[h]
ADHD	~2.0[i]
Alcohol Dependence	2.18[b]



Cover, et al. Milad (2014) Transl. Psychiatry

Sex differences in Alzheimer disease — the gateway to precision medicine

Maria Teresa Ferretti[1,2], Maria Florencia Iulita[3,4], Enrica Cavedo[5,6,7,8,9], Patrizia Andrea Chiesa[5,6,7,8], Annemarie Schumacher Dimech[10], Antonella Santuccione Chadha[11], Francesca Baracchi[12], Hélène Girouard[4,13,14], Sabina Misoch[10], Ezio Giacobini[15], Herman Depypere[16] and Harald Hampel[5,6,7,8], for the Women's Brain Project and the Alzheimer Precision Medicine Initiative*

Abstract | Alzheimer disease (AD) is characterized by wide heterogeneity in cognitive and behavioural syndromes, risk factors and pathophysiological mechanisms. Addressing this phenotypic variation will be crucial for the development of precise and effective therapeutics in AD. Sex-related differences in neural anatomy and function are starting to emerge, and sex might constitute an important factor for AD patient stratification and personalized treatment. Although the effects of sex on AD epidemiology are currently the subject of intense investigation, the notion of sex-specific clinicopathological AD phenotypes is largely unexplored. In this Review, we critically discuss the evidence for sex-related differences in AD symptomatology, progression, biomarkers, risk factor profiles and treatment. The cumulative evidence reviewed indicates sex-specific patterns of disease manifestation as well as sex differences in the rates of cognitive decline and brain atrophy, suggesting that sex is a crucial variable in disease heterogeneity. We discuss critical challenges and knowledge gaps in our current understanding. Elucidating sex differences in disease phenotypes will be instrumental in the development of a 'precision medicine' approach in AD, encompassing individual, multimodal, biomarker-driven and sex-sensitive strategies for prevention, detection, drug development and treatment.

Sex differences in movement disorders

*Sara Meoni[1,2], Antonella Macerollo[3,4] and Elena Moro[1,2]**

Key points

- Sex differences in epidemiology, clinical features and/or response to treatment have been reported in several movement disorders, including Parkinson disease (PD), essential tremor, dystonia, Huntington disease, Sydenham chorea and tic disorders.
- In the case of PD, male sex is associated with higher incidence and prevalence, earlier disease onset, more severe motor symptoms and progression, and more frequent cognitive decline compared with female sex.
- Few data are available on sex differences in hyperkinetic movement disorders, although craniocervical dystonia is more prevalent in women, whereas most focal task-specific dystonias and tics are more frequent in men.
- Prospective studies specifically addressing sex differences in risk factors, symptomatology, disease progression, biomarkers and response to treatment are needed to develop tailored management strategies for patients with movement disorders.

Review Article

JCBFM

Journal of Cerebral Blood Flow & Metabolism
2018, Vol. 38(12) 2179–2191

DOI: 10.1177/0271678X18793324
journals.sagepub.com/home/jcbfm
SAGE

Sex differences in stroke: Challenges and opportunities

Cheryl D Bushnell[1], Seemant Chaturvedi[2], Kathy R Gage[3], Paco S Herson[4], Patricia D Hurn[5], Monik C Jiménez[6], Steven J Kittner[7], Tracy E Madsen[8], Louise D McCullough[9], Mollie McDermott[10], Mathew J Reeves[11] and Tatjana Rundek[2]; the PROWESS group

Neurological Disorders in Women Special Collection

Therapeutic Advances in Neurological Disorders *Original Research*

Relapsing and progressive MS: the sex-specific perspective

Ther Adv Neurol Disord
2020, Vol. 13: 1–13
DOI: 10.1177/1756286420956495

Paulus Stefan Rommer, David Ellenberger, Kerstin Hellwig, Judith Haas, Dieter Pöhlau, Alexander Stahmann, Uwe Klaus Zettl on behalf of the Scientific Advisory Group of the German MS-Register by the German MS Society

1058 ***Current Molecular Medicine* 2009, *9*, 1058-1079**

Sexual Dimorphism in Autoimmune Disease

P.A. McCombe*,[1], J.M. Greer*,[1] and I.R. Mackay[2]

[1]The University of Queensland, Centre for Clinical Research, Royal Brisbane & Women's Hospital, Brisbane, 4029, Australia; [2]Department of Biochemistry and Molecular Biology, Monash University, Clayton, Vic, 3800, Australia

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–3
doi:10.1093/eurheartj/ehab297
CARDIOPULSE

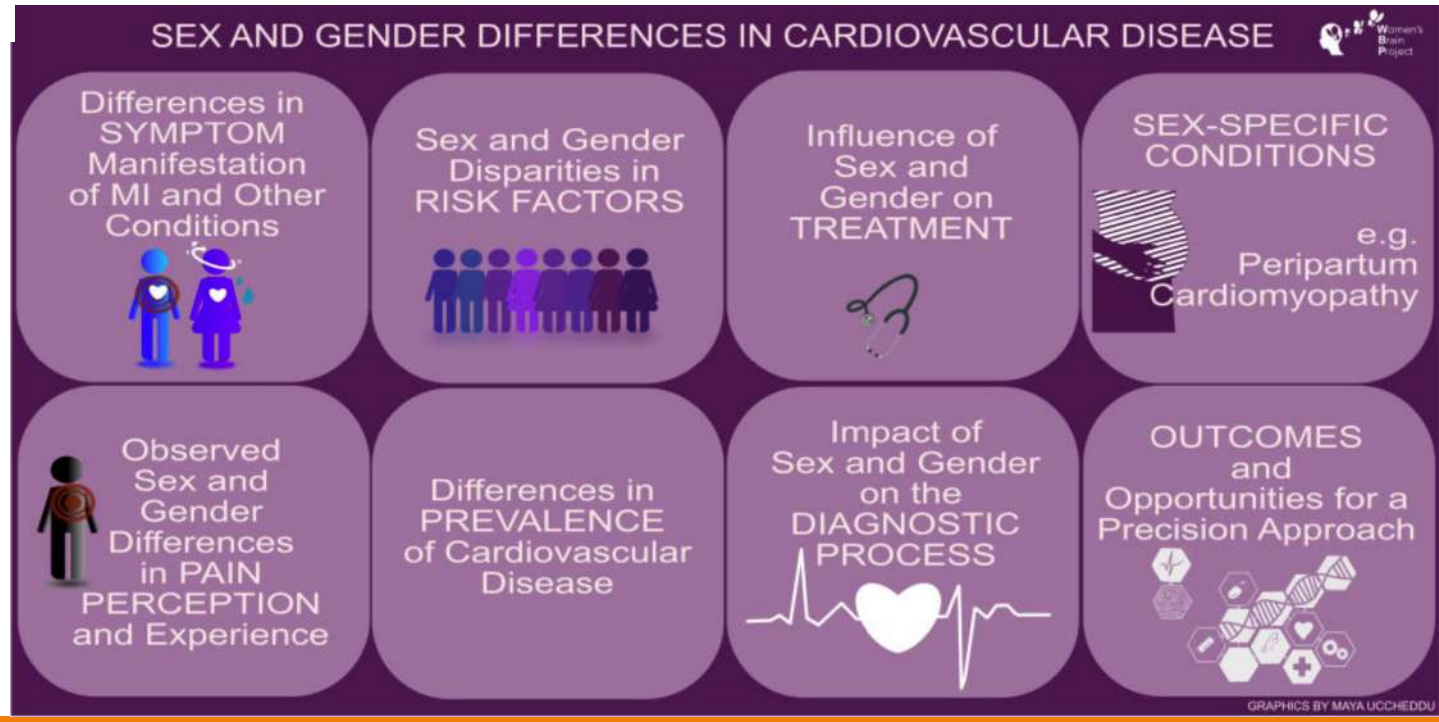
Global Spotlights

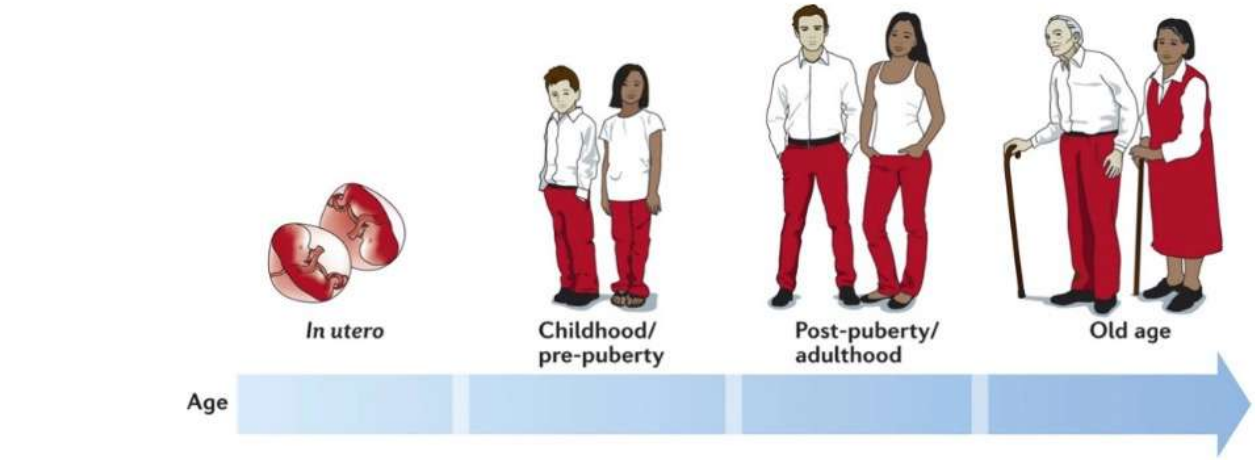
The role of sex and gender differences in precision medicine: the work of the Women's Brain Project

Annemarie Schumacher Dimech [1,2]*, Maria Teresa Ferretti [1], Else C. Sandset [3], and Antonella Santuccione Chadha [1 4]

[1]Women's Brain Project, Pfisterwisstrasse 14, 8357 Guntershausen, Switzerland; [2]University of Lucerne, Frohburgstrasse 3, 6002 Luzern, Switzerland; [3]Stroke Unit, Department of Neurology, Oslo University Hospital, Oslo, Norway; and [4]Biogen International, Baar, Switzerland

WOMEN'S BRAIN PROJECT®

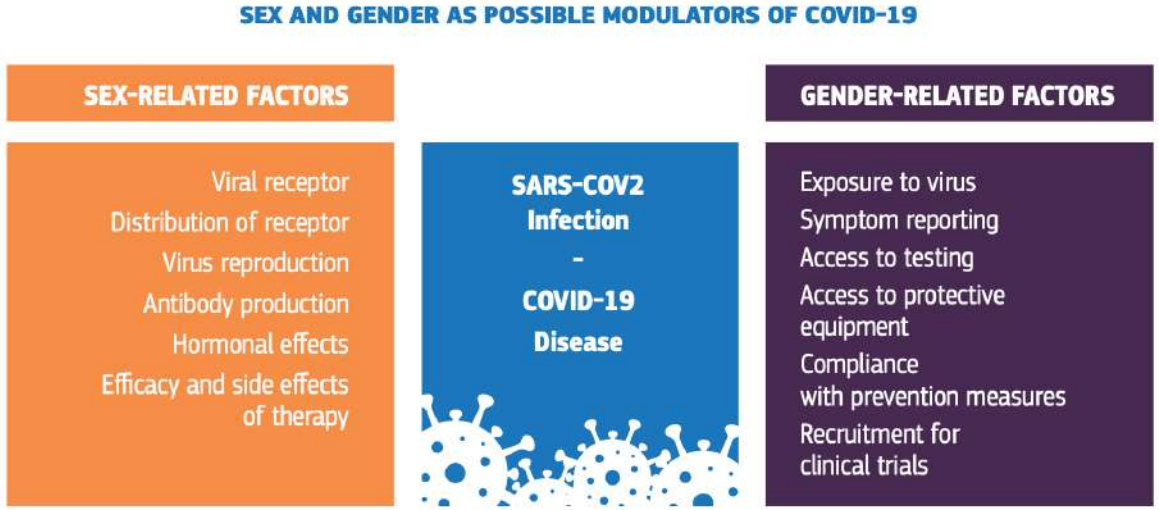




Innate immunity	• Increased inflammatory responses in males	↑ Inflammation in males ↑ NK cells in males	↑ Inflammation in females ↑ NK cells in males	↑ Inflammation in males ↑ IL-10 in females ↑ NK cells in females
Adaptive immunity	• Increased IgE levels in males	• CD4/CD8 ratios and $CD4^+$ T cell numbers equal • $CD8^+$ T cell numbers equal • IgA levels in males ≥ females • IgM levels in males ≥ females • IgG and IgM levels equal • B cell numbers equal • T_{reg} cell numbers in males ≥ females	• CD4/CD8 ratios and $CD4^+$ T cells ↑ in females • $CD8^+$ T cells ↑ in males • T cell activation/ proliferation ↑ in females • T_{reg} cells ↑ in males • B cells ↑ in females • Immunoglobulins ↑ in females	• CD4/CD8 ratios and $CD4^+$ T cells ↑ in females • $CD8^+$ T cells ↑ in males • T cell activation/ proliferation ↑ in females • T_{reg} cells ↑ in males • B cells ↑ in females • Immunoglobulins ↑ in females

Figure 1. Gender-specific differences in immune responses and inflammatory diseases. Multiple immunological factors vary between the sexes throughout the course of life. For certain factors (for example, pro-inflammatory responses), the sex differences change at puberty and then wane in later life, suggesting hormonal effects. For other factors, the sex difference remains constant from birth to old age (for example, higher numbers of $CD4^+$ T cells and CD4/CD8 T cell ratios in females). The paucity of studies in this area is notable, particularly in utero sex differences in which results are conflicting. IL-10, interleukin-10; NK, natural killer; T_{reg}, regulatory T. Reproduced with permission from [26].

Journal of *Clinical Medicine*



Sex and gender as possible modulators of COVID-19.
© Sabine Oertelt-Prigione

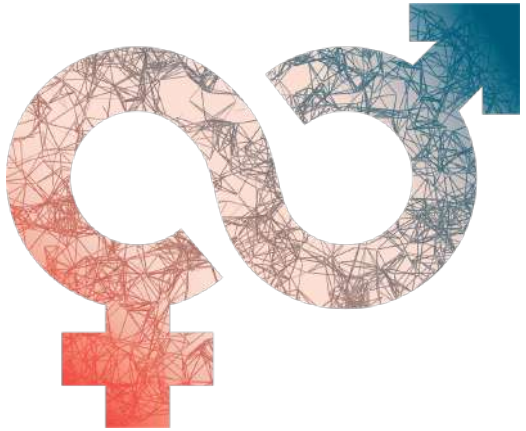
Method: analysing sex

All data related to COVID-19 morbidity and mortality should be disaggregated by sex (Wenham et al., 2020). Females generally respond more intensely to contact with viruses such as SARS-CoV2, including both natural infection and vaccination (Klein and Flanagan, 2016), and the potential impacts of these differences should be considered in:

- identifying and reporting symptoms,
- developing diagnostics and testing,
- validating therapeutics.

All study of COVID-19 needs to integrate sex as a biological variable. This includes using female and male cells and experimental animals in drug discovery and development and in preclinical research, as well as using women and men in clinical trials. Females develop side effects to medications more frequently than males (Obias-Manno et al., 2007), and all drug and vaccine trials for COVID-19 should include sex-specific analyses.

Anxiety and depression increased during COVID-19 pandemic, especially in women



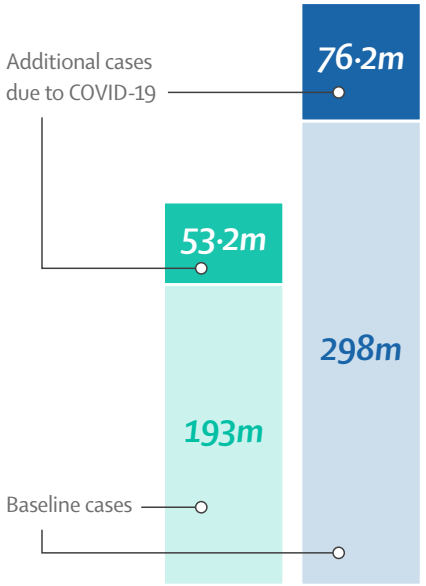
The COVID-19 pandemic has had a large and uneven impact on global mental health

Cases of mental disorders rose sharply during the pandemic

Cases in 2020

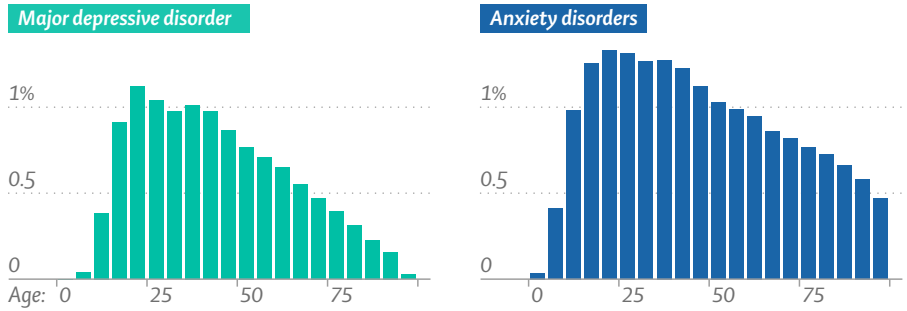
Major depressive disorder

Anxiety disorders



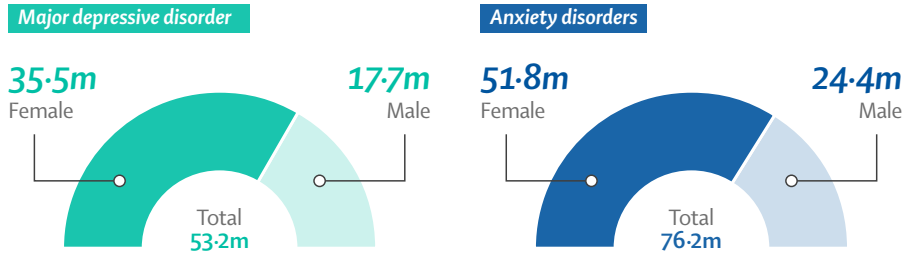
Younger people were hardest hit

Additional prevalence due to COVID-19, by age



Increases were higher among females than males

Additional cases due to COVID-19, by gender



Read the full paper: Santomauro DF, Mantilla Herrera AM, Shadid J, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. The *Lancet* 2021. Published online October 8.

THE LANCET

The University Of Queensland AUSTRALIA

QCMHR

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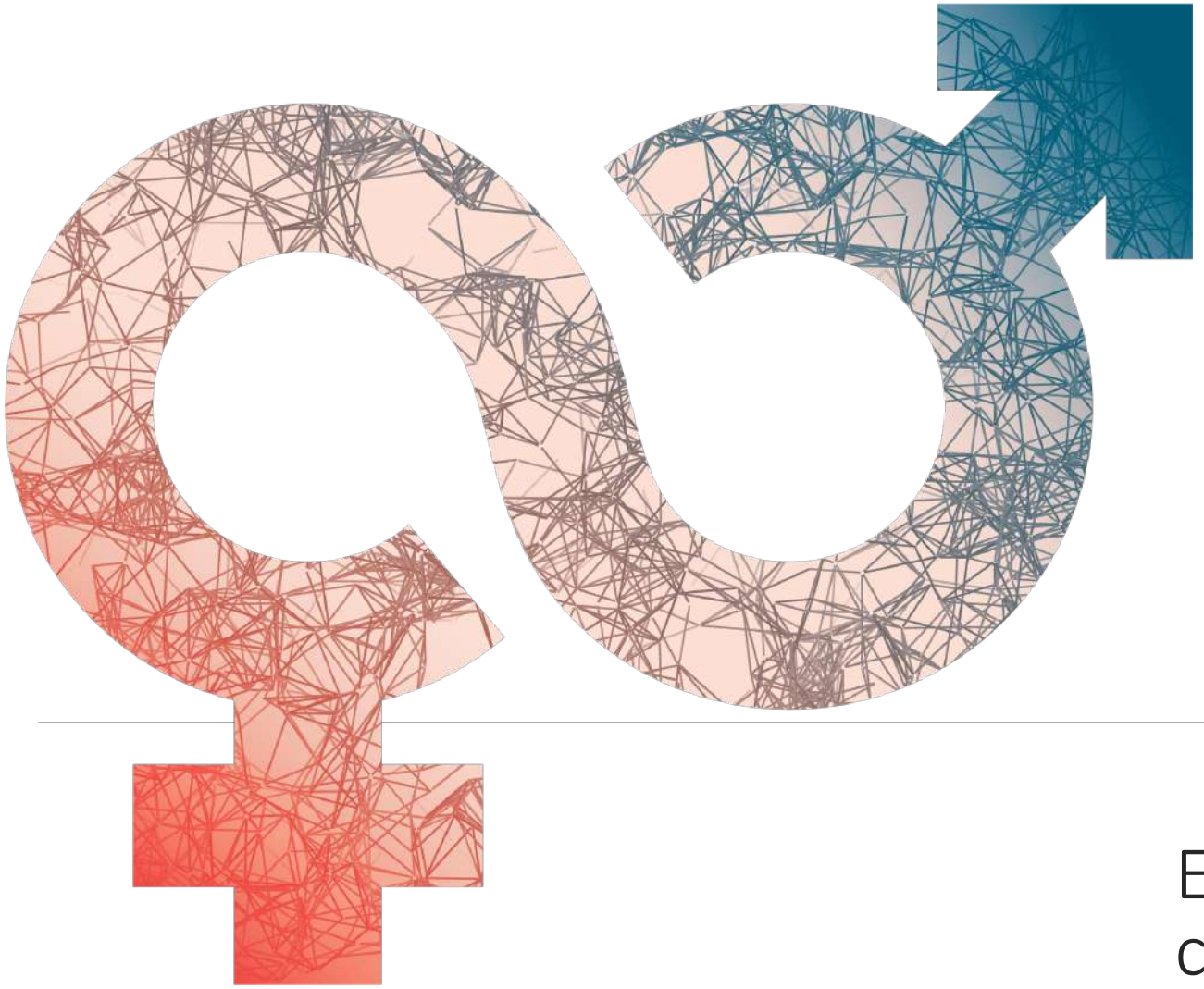
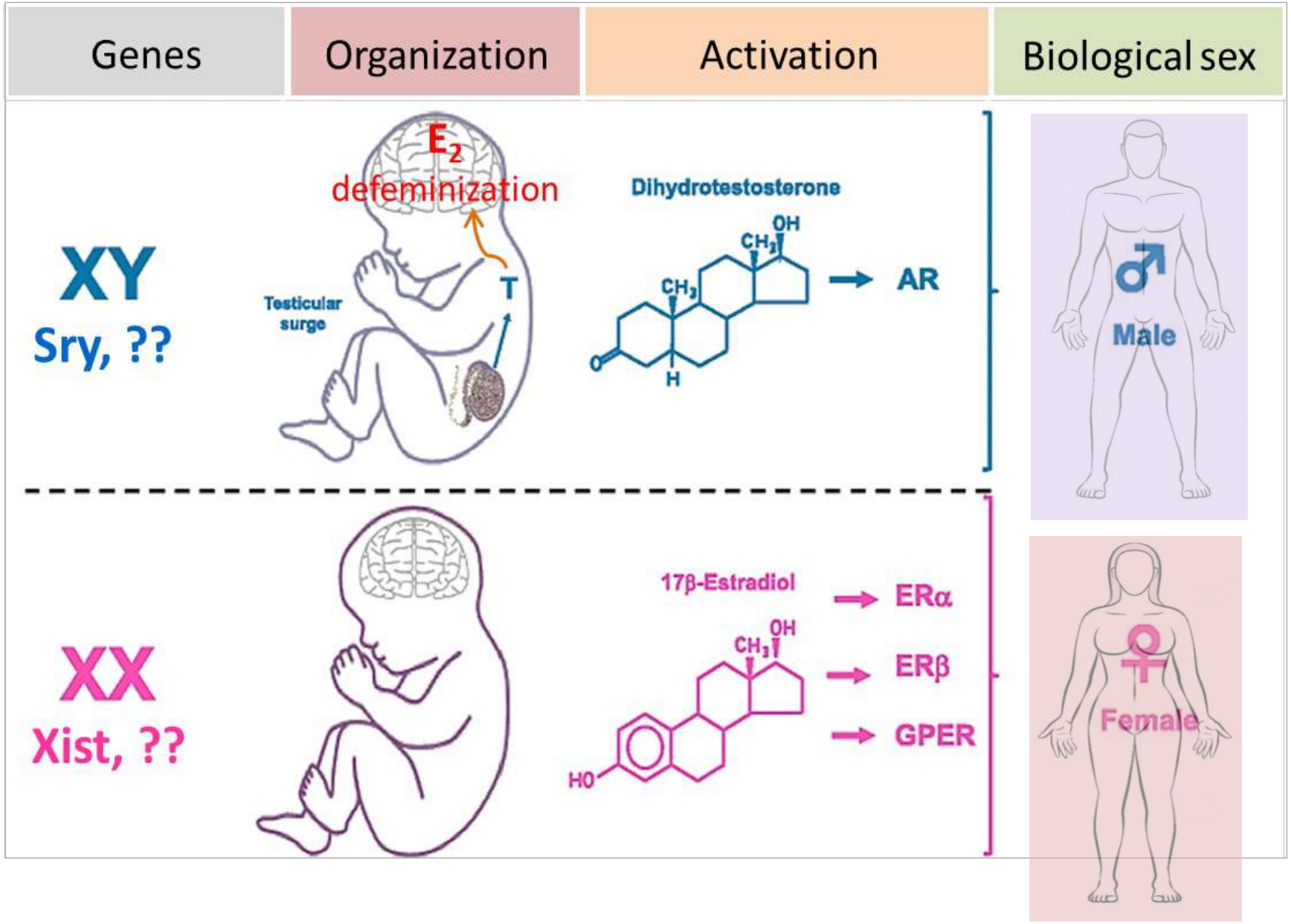
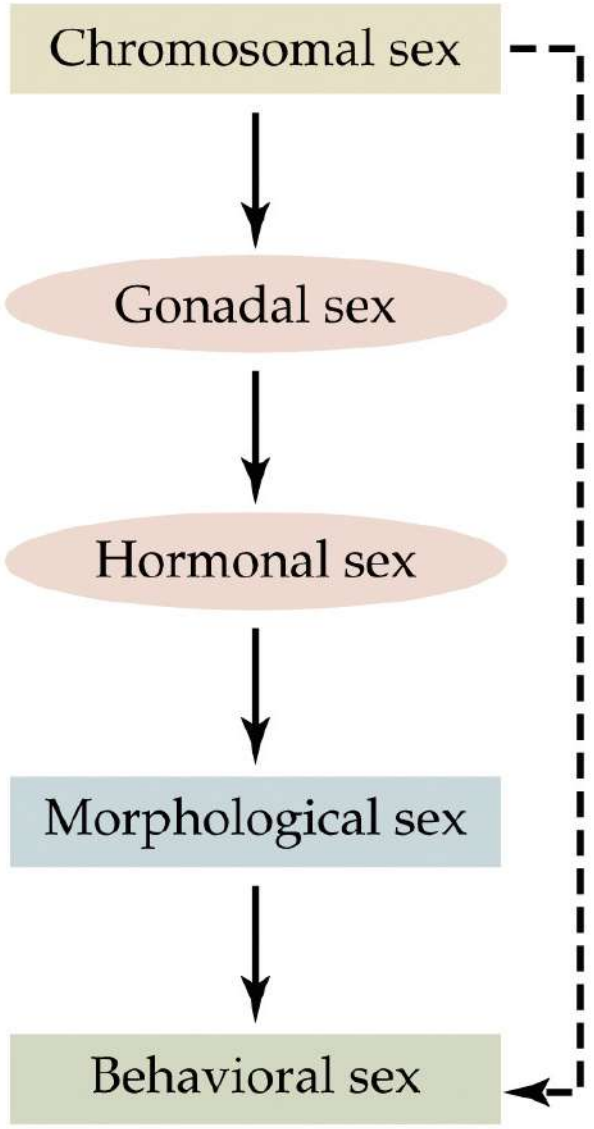


Examples of factors that could be investigated

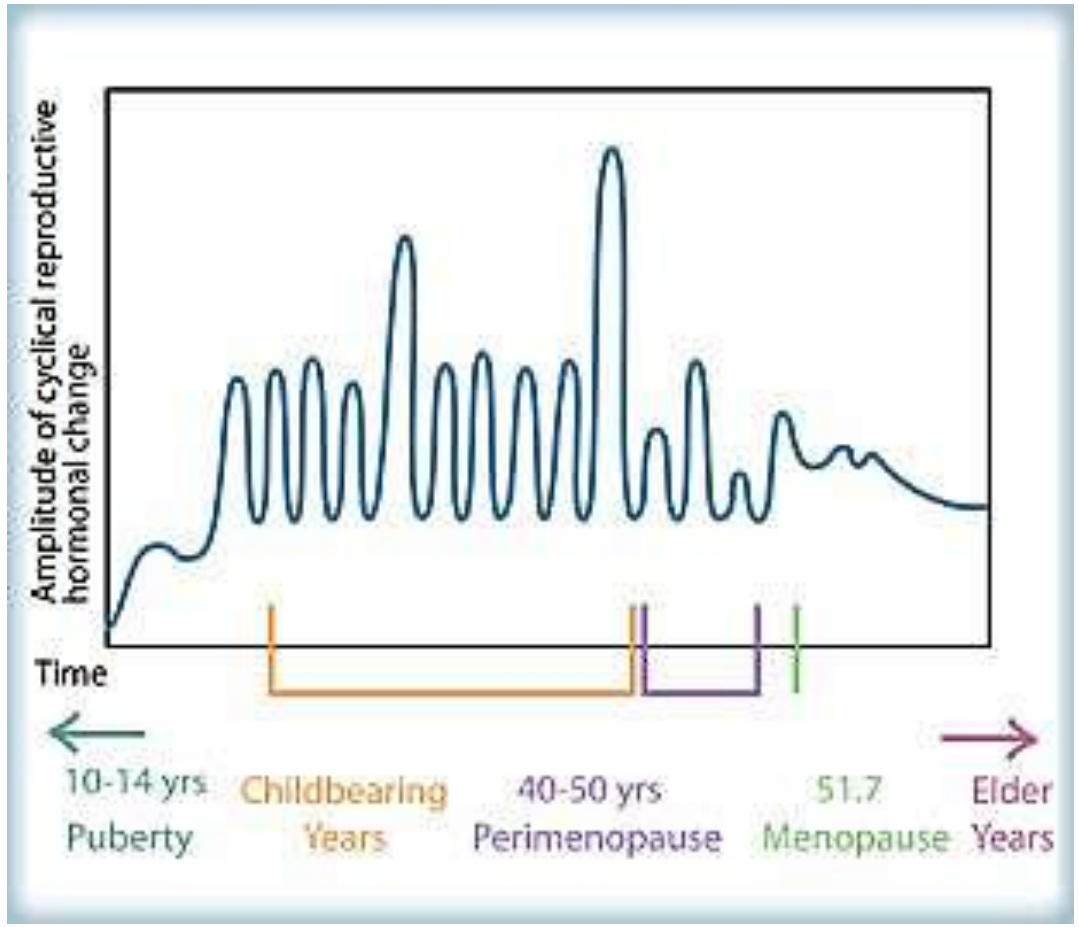


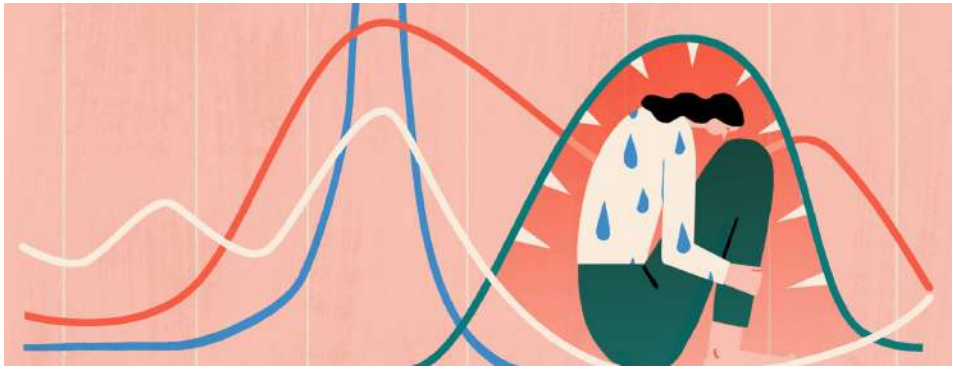


AN INTRODUCTION TO BEHAVIORAL ENDOCRINOLOGY 5e, Figure 3.5

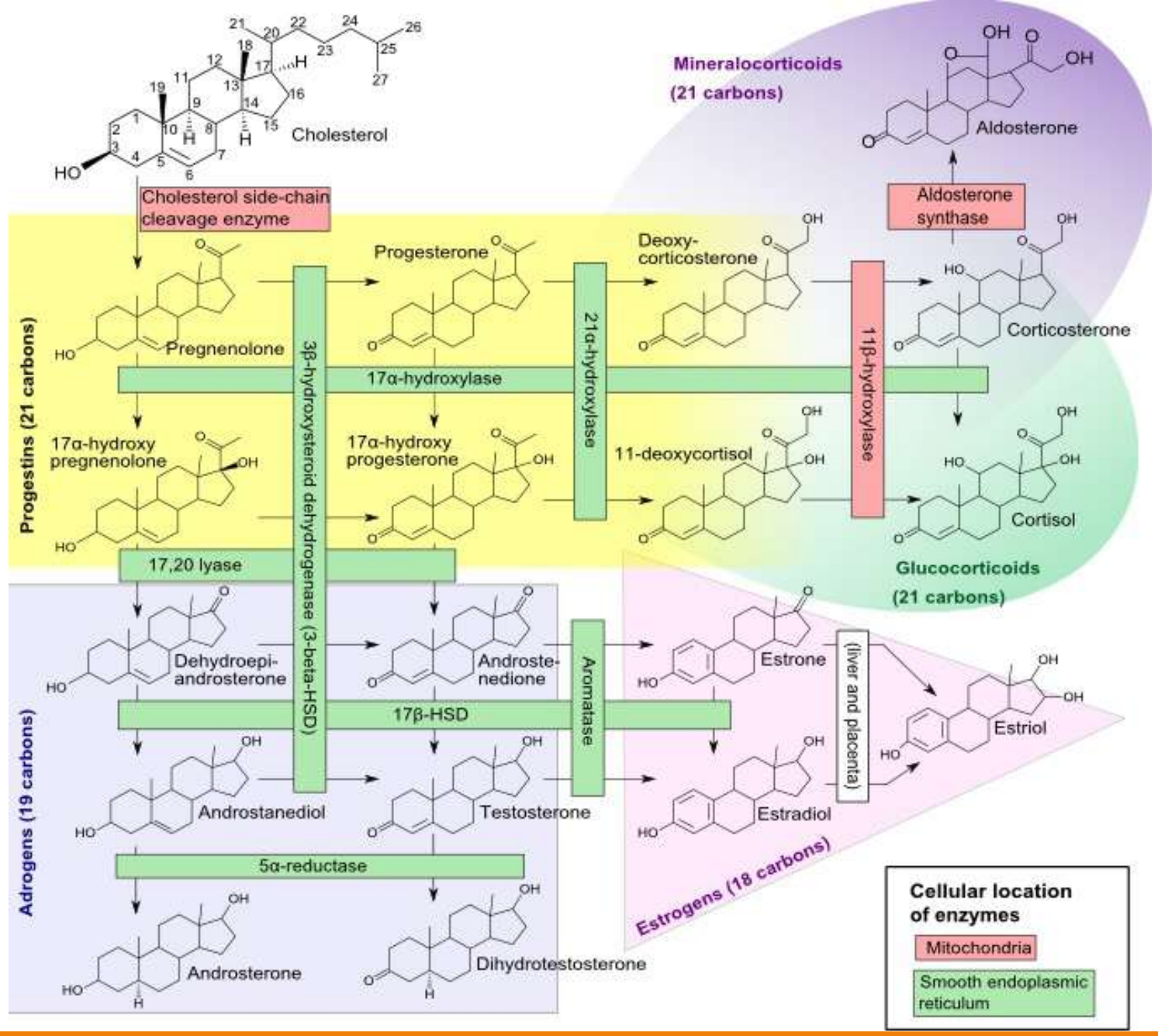
adapted from F. Mauvais-Jarvis, A. P. Arnold, K. Reue, *Cell Metab* 2017

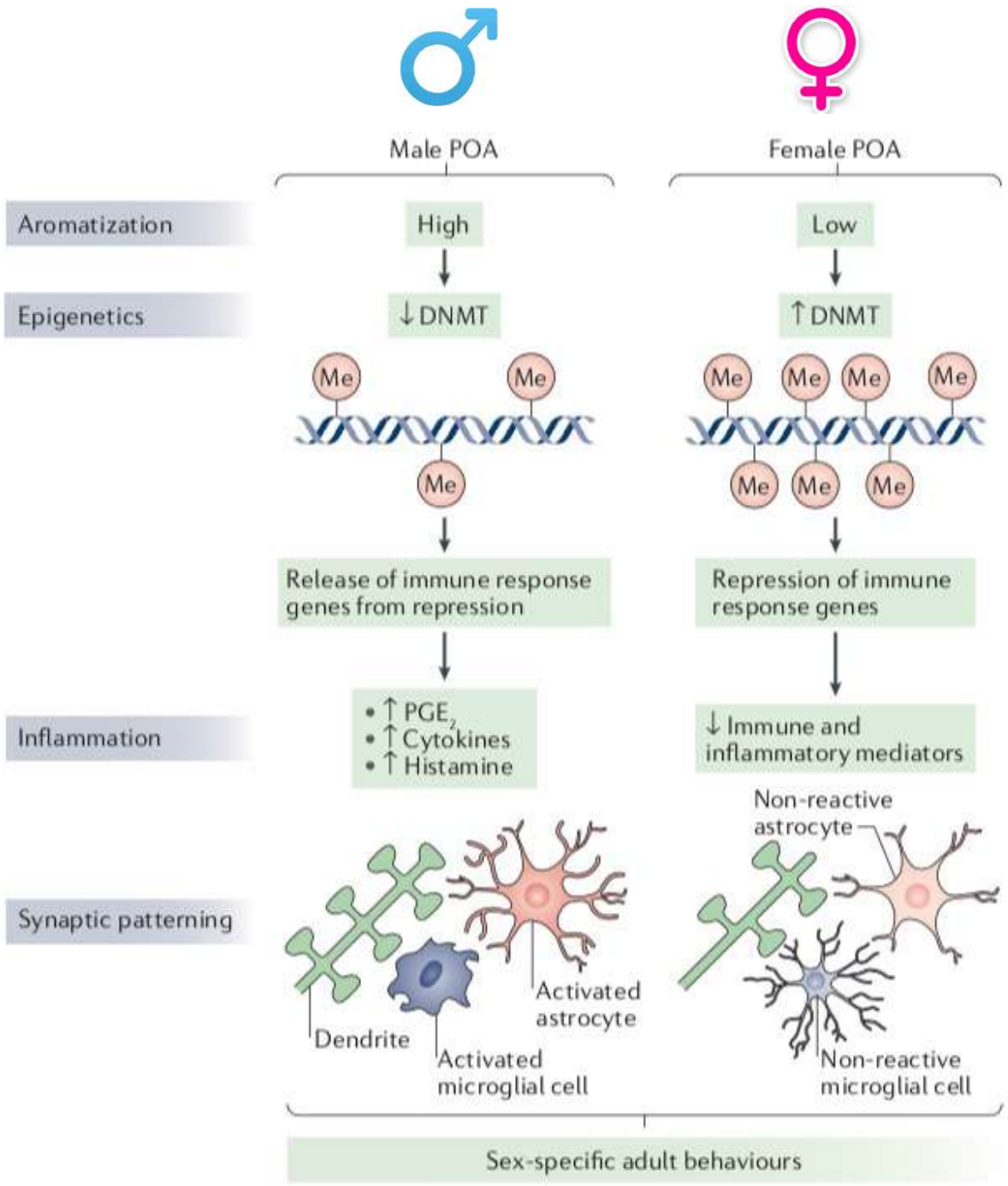
Gonadal Hormone effects

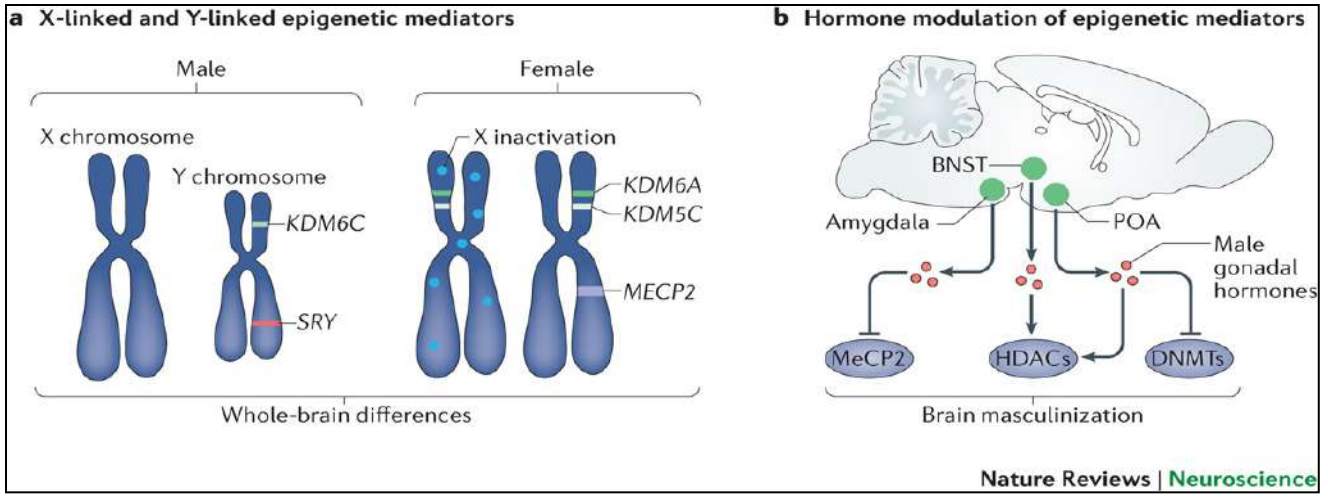




Neurosteroid's effects







Neuroimmunology and neuroepigenetics in the establishment of sex differences in the brain

Margaret M. McCarthy[1], Bridget M. Nugent[2] and Kathryn M. Lenz[3]

NATURE REVIEWS | NEUROSCIENCE

Weizmann Institute | עברית

Weizmann Wonder Wander

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Home > Topics > Life Sciences > Researchers Identify 6,500 Genes That Are Expressed Differently in Men and Wom

Researchers Identify 6,500 Genes That Are Expressed Differently in Men and Women

Genes that are mostly active in one sex or the other may play a crucial role in our evolution and health

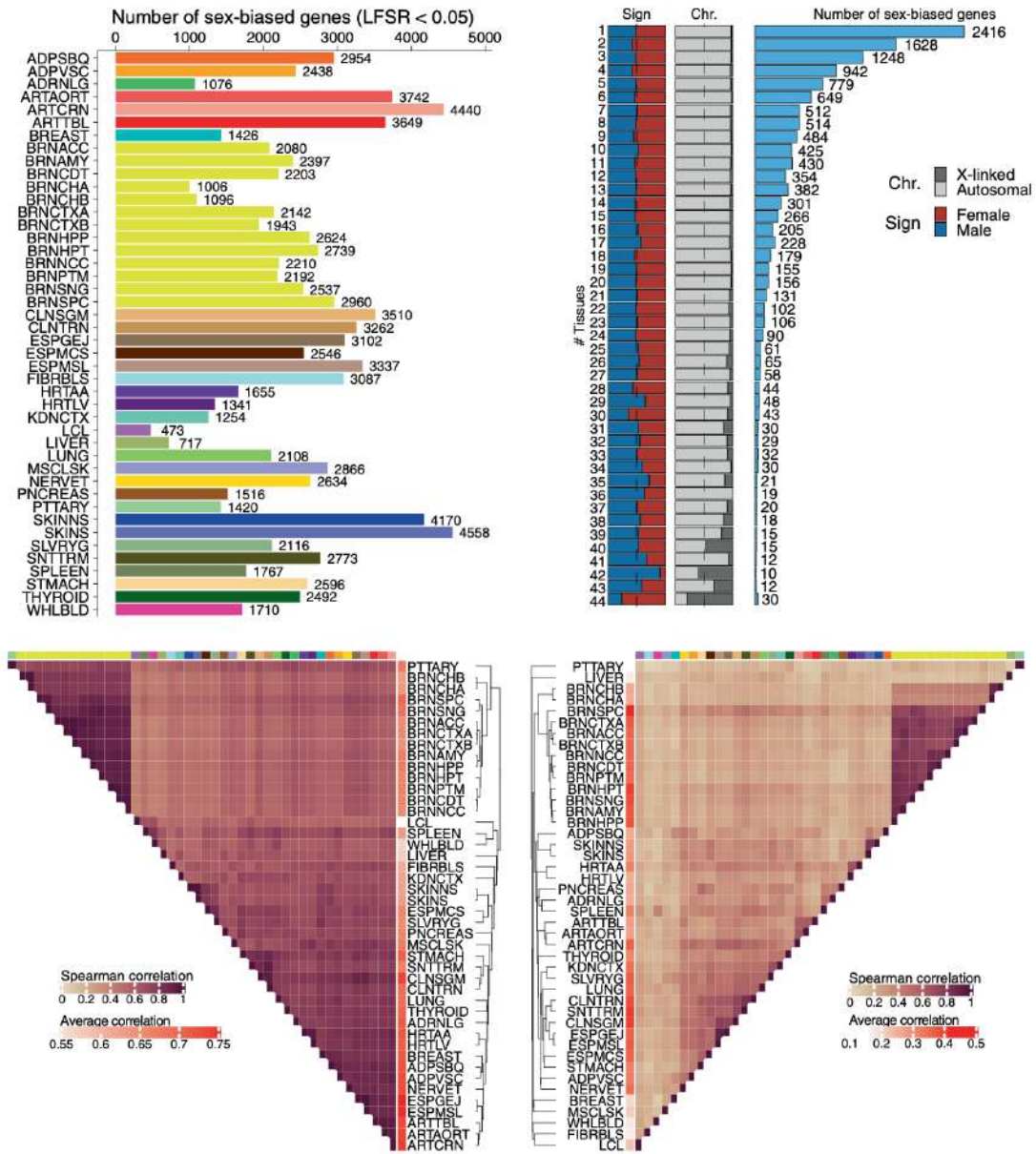


Fig. 2 | **Sex-based gene expression.** Hierarchical clustering of tissues based on gene expression (left) and the effect size of sex-biased genes (right). LFSR, local false sign rate. (Adapted with permission from ref. [13], AAAS).

Review > Biol Psychiatry. 2022 Jan 1;91(1):25-35. doi: 10.1016/j.biopsych.2021.02.003.
Epub 2021 Feb 12.

Translating the Transcriptome: Sex Differences in the Mechanisms of Depression and Stress, Revisited

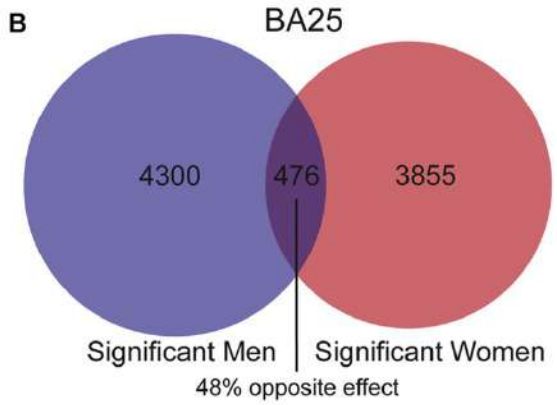
Jennifer R Rainville [1], Timothy Lipuma [1], Georgia E Hodes [2]

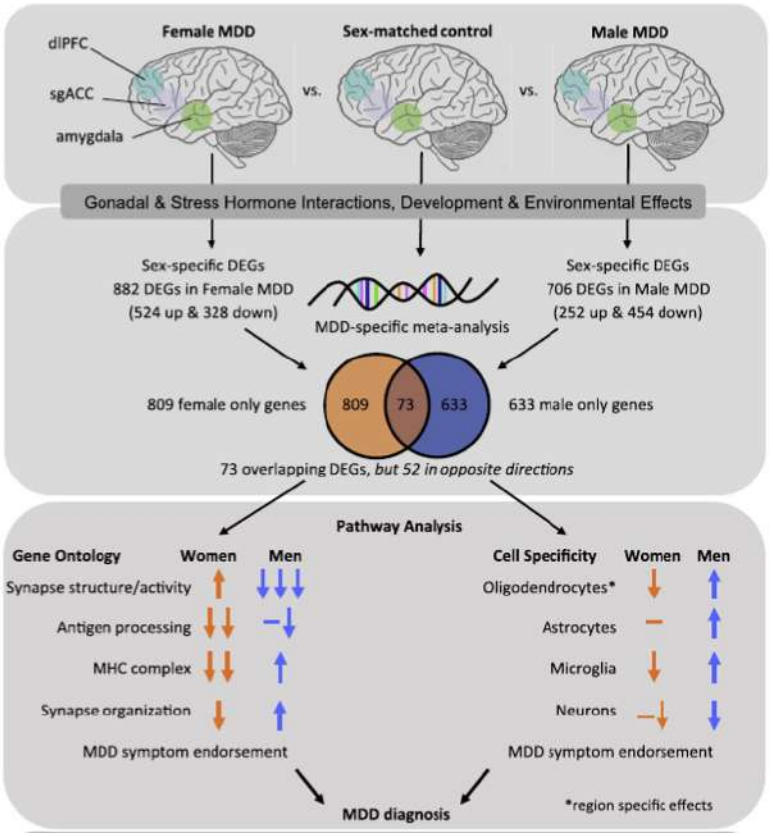
nature medicine

Nature Medicine **23**, 1102–1111(2017)

Sex-specific transcriptional signatures in human depression

Benoit Labonté, Olivia Engmann, [...] Eric J Nestler





Seney et al Biol. Psychiatry 2018

Danielle M. Gerhard and Ronald S. Duman, Biol. Psychiatry Commentary, 2018

REVIEWS

Sex differences in anxiety and depression: circuits and mechanisms

Debra A. Bangasser ✉ *and Amelia Cuarenta*

Abstract | Epidemiological sex differences in anxiety disorders and major depression are well characterized. Yet the circuits and mechanisms that contribute to these differences are understudied, because preclinical studies have historically excluded female rodents. This oversight is beginning to be addressed, and recent studies that include male and female rodents are identifying sex differences in neurobiological processes that underlie features of these disorders, including conflict anxiety, fear processing, arousal, social avoidance, learned helplessness and anhedonia. These findings allow us to conceptualize various types of sex differences in the brain, which in turn have broader implications for considering sex as a biological variable. Importantly, comparing the sexes could aid in the discovery of novel therapeutics.

NATURE REVIEWS | NEUROSCIENCE

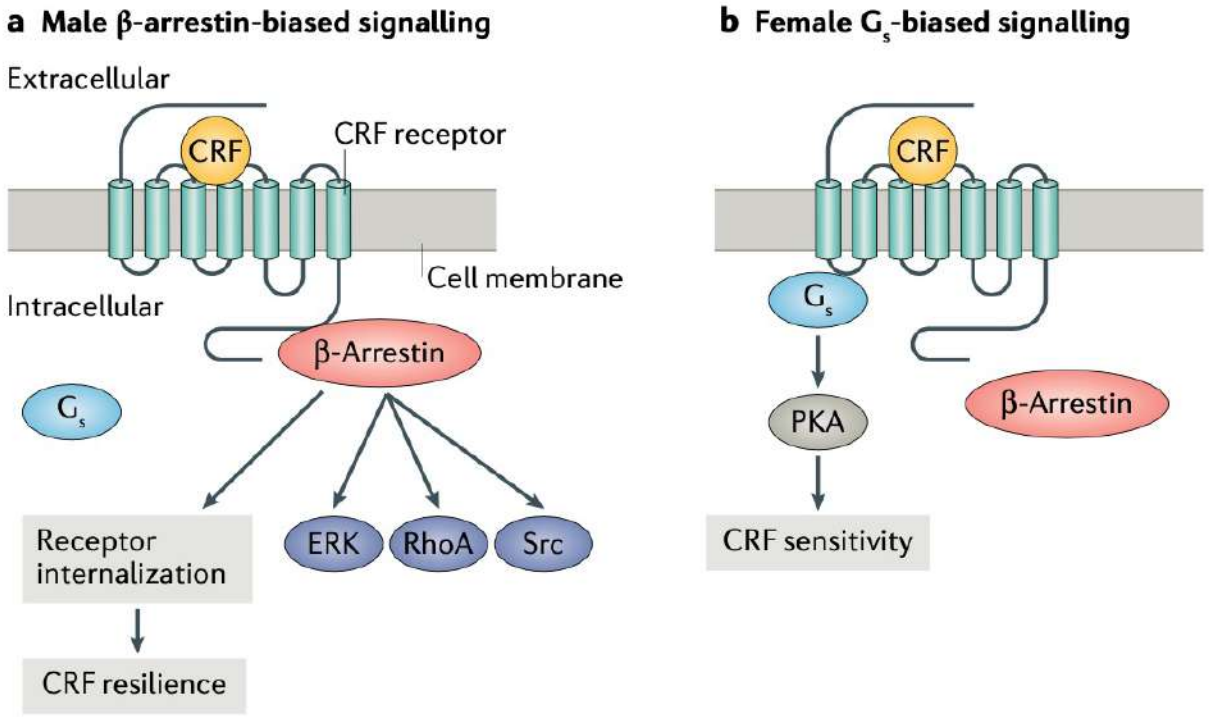
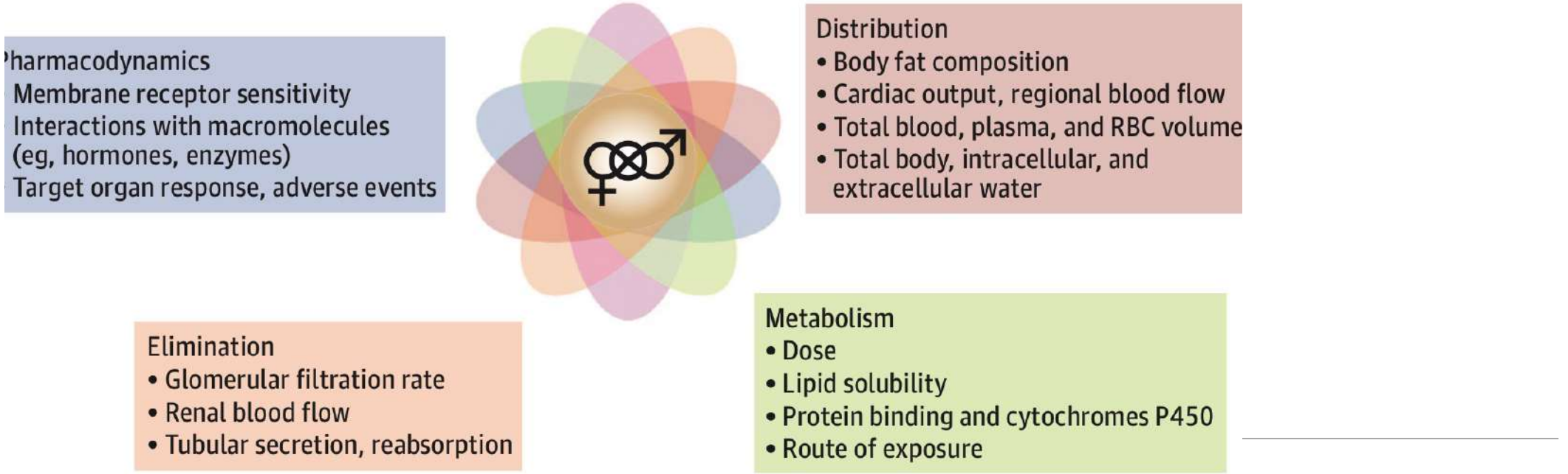


Fig. 2 | **Sex-biased receptor signalling. a** | In males, the CRF_1 receptor associates with β-arrestin, which biases signalling towards β-arrestin-mediated pathways and causes receptor internalization. **b** | In females, the CRF_1 receptor signals more through G_s-mediated pathways, which increases the sensitivity of their locus coeruleus neurons to corticotropin-releasing factor (CRF). Given reduced β-arrestin binding in females, their CRF_1 receptors do not internalize following acute stress or CRF overexpression. Adapted with permission from REF.[165], Elsevier.

JAMA Internal Medicine | Review

Clinical Advances in Sex- and Gender-Informed Medicine to Improve the Health of All

A Review



What about sex and gender in treatment?

GLOBAL PRECLINICAL DATA FORUM

Addressing Sex as a Biological Variable in Preclinical Research

Accounting for Neglected Factors and Applying Practical Solutions to Enhance Rigor and Reproducibility

Differences between males and females extend well beyond reproduction, with significant implications for human health and disease. This is particularly the case in the field of neuroscience, where differences in basic biology between men and women can lead to sex differences in the prevalence, progression, and responses to treatment of many brain disorders.

This video training series was developed by Cohen Veterans Bioscience, a non-profit research and biotechnology organization dedicated to advancing health solutions for brain disorders by ensuring that early-stage research is conducted to the highest and most rigorous standards possible. One solution is to ensure that the research community—including graduate students, postdocs, and other early career researchers—have the tools they need to enable the implementation of best practices across the experimental process.

The goal of the video training series is to provide practical guidance to preclinical researchers on how to navigate the NIH's 2015 policy on incorporating sex as a biological variable into their current and future research.

Across this video series, we will demonstrate:

- Why research inclusive of both sexes is important for increasing scientific rigor and the health of both men and women;
- Why common misconceptions arguing against the inclusion of both sexes into preclinical research are outdated;
- How including both sexes into preclinical research can open new areas of research and advance patient-centered treatment solutions.

The content of these training videos is distributed across three modules:

- Module 1: Primer of Sex Differences in Brain and Behavior
- Module 2: Incorporating Sex as a Biological Variable Throughout the Experimental Process
- Module 3: Sex as a Biological Variable in Pharmacology Studies

Watch the introduction:

NIH National Institutes of Health

https://www.preclinicaldataforum.org/addressing-sex-as-a-biological-variable-training/

Cohen Veterans
Bioscience

Introductory Video to Sex as a Biological Variable and the Video Series

Cohen Veterans
Bioscience

Human and Preclinical Evidence of Sex-Related Differences in Pharmacokinetics, Pharmacodynamics, and Toxicology

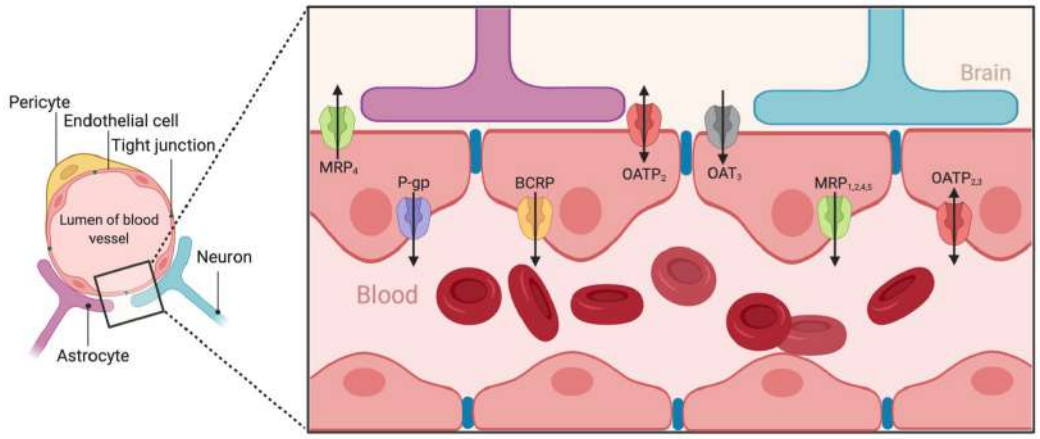


FIGURE 1 | Graphical representation of the blood–brain barrier and its transporters.

frontiers | Frontiers in Behavioral Neuroscience

MINI REVIEW
published: 23 May 2022
doi: 10.3389/fnbeh.2022.844916

Sex Differences in Blood–Brain Barrier Transport of Psychotropic Drugs

*Christina Dalla[1], Pavlina Pavlidi[1], Danai-Georgia Sakelliadou[1], Tatiana Grammatikopoulou[1] and Nikolaos Kokras[1,2]**

[1] *Department of Pharmacology, Medical School, National and Kapodistrian University of Athens, Athens, Greece,* [2] *First Department of Psychiatry, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece*

Review

Sex differences in pharmacokinetics of antidepressants

Expert Opinion

Nikolaos Kokras, Christina Dalla & Zeta Papadopoulou-Daifoti†

1521-0103/367/3/393–404$35.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

https://doi.org/10.1124/jpet.118.251652
J Pharmacol Exp Ther 367:393–404, December 2018

Sex Differences in the Pharmacokinetics of Low-dose Ketamine in Plasma and Brain of Male and Female Rats

Samantha K. Saland and Mohamed Kabbaj

Department of Biomedical Sciences, Program in Neuroscience, College of Medicine, Florida State University, Tallahassee, Florida

Received June 23, 2018; accepted September 10, 2018

Zucker and Prendergast *Biology of Sex Differences* (2020) 11:32
https://doi.org/10.1186/s13293-020-00308-5

Biology of Sex Differences

RESEARCH Open Access

Sex differences in pharmacokinetics predict adverse drug reactions in women

Irving Zucker[1,2*] and Brian J. Prendergast[3]

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Systematic Analysis of Adverse Event Reports for Sex Differences in Adverse Drug Events

Received: 11 November 2015
Accepted: 05 April 2016
Published: 22 April 2016

Yue Yu[1,2], Jun Chen[2], Dingcheng Li[2], Liwei Wang[1], Wei Wang[1] & Hongfang Liu[2]

Increasing evidence has shown that sex differences exist in Adverse Drug Events (ADEs). Identifying those sex differences in ADEs could reduce the experience of ADEs for patients and could be conducive to the development of personalized medicine. In this study, we analyzed a normalized US Food and

FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR

Different dosing in men and women? The example of zolpidem

COMMENTARY

Zolpidem and Gender: Are Women Really At Risk?

David J. Greenblatt, Jerold S. Harmatz,* and Thomas Roth†*

Towards a sex-specific Pharmacology


SPECIAL ISSUE POLICY FORUM

Women in Clinical Trials: an FDA Perspective

LINDA ANN SHERMAN, ROBERT TEMPLE, AND , RUTH B. MERKATZ Authors Info & Affiliations

SCIENCE • 11 Aug 1995 • Vol 269, Issue 5225 • pp. 793-795 • DOI: 10.1126/science.7638593

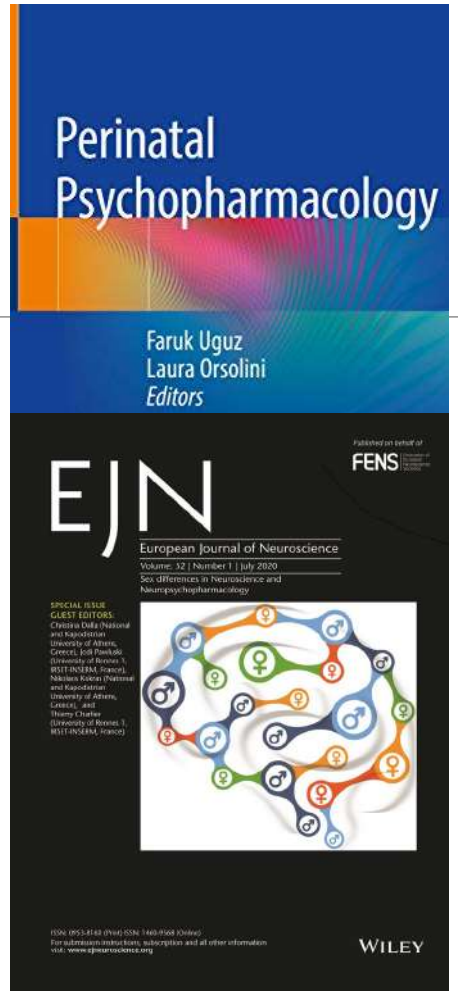
18

POLICY FORUMS

Women in Clinical Trials: An FDA Perspective

Linda Ann Sherman, Robert Temple, Ruth B. Merkatz*

men and women, the gender guideline translated what was already the common practice into a more formal expectation. Nevertheless, although women and men were included in studies in numbers that could be evaluated, there were few attempts to use the trial data to examine whether responses were different by gender. The



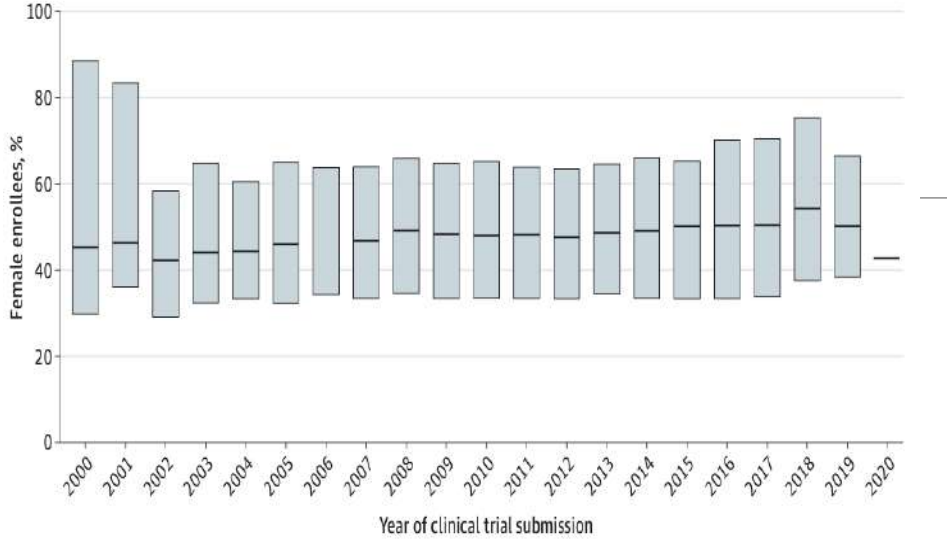
SPECIAL ISSUE EDITORIAL

EJN European Journal of Neuroscience FENS WILEY

Sex matters in neuroscience and neuropsychopharmacology

Jodi L. Pawluski[1] | Nikolaos Kokras[2,3] | Thierry D. Charlier[1] | Christina Dalla[2]

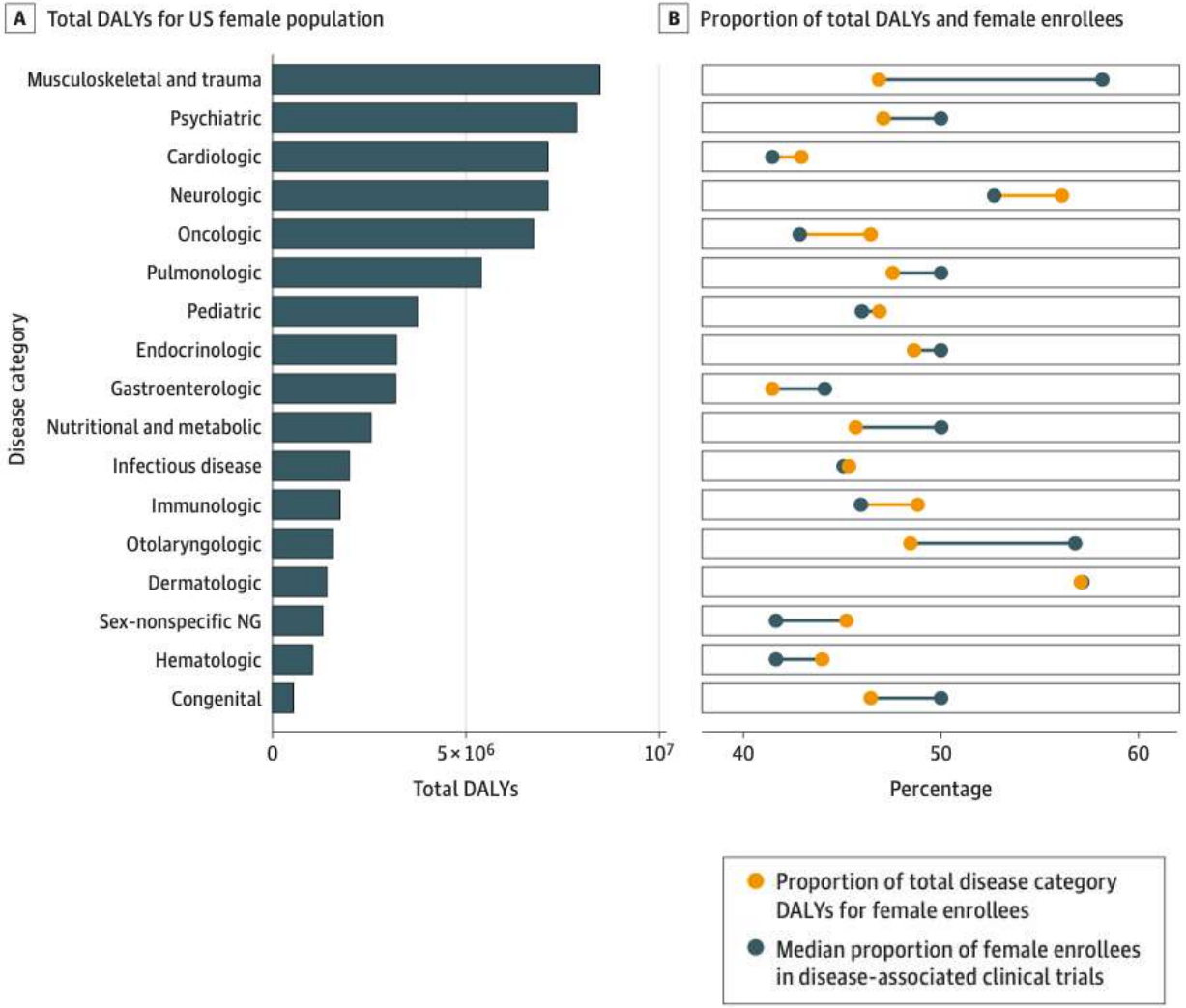
*"In 1993, a new guideline was issued that reversed the 1977 policy of exclusion of women of childbearing potential from early trials. The guideline, Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, recommended collection and analysis of data on **sex** differences for effectiveness, adverse events, and pharmacokinetics."*



Female Representation in Clinical Trials

Are women under-represented ?

If not, what is the problem?



Over !

Steinberg et al, JAMA Open, 2021

Sex Mismatch between preclinical/P-1 (males) vs PII/II (females)

JAMA Network | Open

Original Investigation | Public Health

Analysis of Female Enrollment and Participant Sex by Burden of Disease in US Clinical Trials Between 2000 and 2020

Jecca R. Steinberg, MD, MSc; Brandon E. Turner, MD, MSc; Brannon T. Weeks, MD; Christopher J. Magnani, MPhil; Bonnie O. Wong, MSc; Fatima Rodriguez, MD, MPH; Lynn M. Yee, MD, MPH; Mark R. Cullen, MD

Abstract

IMPORTANCE Although female representation has increased in clinical trials, little is known about how clinical trial representation compares with burden of disease or is associated with clinical trial features, including disease category.

OBJECTIVE To describe the rate of sex reporting (ie, the presence of clinical trial data according to sex), compare the female burden of disease with the female proportion of clinical trial enrollees, and investigate the associations of disease category and clinical trial features with the female proportion of clinical trial enrollees.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study included descriptive analyses and logistic and generalized linear regression analyses with a logit link. Data were downloaded from the Aggregate Analysis of ClinicalTrials.gov database for all studies registered between March 1, 2000, and March 9, 2020. Enrollment was compared with data from the 2016 Global Burden of Disease database. Of 328 452 clinical trials, 70 095 were excluded because they had noninterventional designs, 167 936 because they had recruitment sites outside the US, 69 084 because they had no reported results, 1003 because they received primary funding from the US military, and 314 because they had unclear sex categories. A total of 20 020 interventional studies enrolling approximately 5.11 million participants met inclusion criteria and were divided into those with and without data on participant sex.

EXPOSURES The primary exposure variable was clinical trial disease category. Secondary exposure variables included funding, study design, and study phase.

MAIN OUTCOMES AND MEASURES Sex reporting and female proportion of participants in clinical trials.

Key Points

Question How is disease burden associated with female representation in US-based clinical trials, and how are disease category and other clinical trial features associated with female representation in clinical trials?

Findings In this cross-sectional study of 20 020 clinical trials enrolling more than 5 million participants between 2000 and 2020, clinical trials in the fields of oncology, neurology, immunology, and nephrology had the lowest female participant representation relative to corresponding disability-adjusted life-years. Clinical trials in cardiology and pediatrics had the greatest negative associations with female enrollment, and clinical trials of preventive interventions had a positive association.

Meaning This study's findings suggest that sex bias persists within clinical trials, with male and female participants underrepresented in different areas of research.

frontiers in Medicine

ORIGINAL RESEARCH
published: 11 March 2021
doi: 10.3389/fmed.2021.643028

Sex Proportionality in Pre-clinical and Clinical Trials: An Evaluation of 22 Marketing Authorization Application Dossiers Submitted to the European Medicines Agency

OPEN ACCESS

Edited by:
Steffen Thirstrup, NDA Advisory Services Ltd., United Kingdom

Reviewed by:
Lise Aagaard, Independent Researcher, Copenhagen, Denmark
Domenico Criscuolo, Italian Society of Pharmaceutical Medicine, Italy

Marieke J. H. J. Dekker[1†], Sieta T. de Vries[1,2†], Carolien H. M. Versantvoort[1], Ellen G. E. Drost-van Velze[1], Mansi Bhatt[1], Peter J. K. van Meer[1], Ineke K. Havinga[1], Christine C. Gispen-de Wied[1] and Peter G. M. Mol[1,2*†]

[1] Dutch Medicines Evaluation Board, Utrecht, Netherlands, [2] Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centre Groningen, Groningen, Netherlands

Contemporary Clinical Trials 115 (2022) 106700

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Review

COVID-19 vaccines: Considering sex differences in efficacy and safety

Adelaide Jensen [a,c,*], Masha Stromme [b], Shayda Moyassari [c], Antonella Santuccione Chadha [c,d], Maria Carmela Tartaglia [c,e,f], Cassandra Szoeke [c,g], Maria Teresa Ferretti [c]

[a] School of Psychology, University of Ottawa, Canada
[b] 4HerHealth, Norway
[c] Women's Brain Project, Switzerland
[d] Biogen International, Switzerland
[e] Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Canada
[f] Krembil Brain Institute, University Health Network, Canada
[g] Centre for Medical Research (RMH), Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Australia

Table 1
Summary of regulatory safety and efficacy data for approved COVID-19 vaccines.

Vaccine	Regulatory Agency	Total participants (N)	Females (%)	Males (%)	Efficacy subgroup analyses by sex?	Safety subgroup analyses by sex?	Sources
Moderna(mRNA-1273)	EMA[a]	30,351	47.4	52.6	Yes	No	Moderna Assessment Report, EMA Moderna Product Information, EMA
	FDA[a]				Yes	Yes	Moderna VRBPAC[a], FDA
	Health Canada				Yes	No	Moderna Product Information, EMA[1]
Pfizer-BioNTech (BNT162)	EMA	43,651	49.4	50.6	Yes	No	Comirnaty Assessment Report, EMA Comirnaty Product Information, EMA
	FDA				Yes	No	Pfizer-BioNTech VRBPAC[a], FDA
	Health Canada				No	No	Pfizer-BioNTech Regulatory Decision Summary, Health Canada
Janssen(Ad26.COV·S)	EMA	44,325	45	55	Yes	Yes	Janssen Assessment Report, EMA Janssen Product Information, EMA
	FDA				Yes	No	Janssen VRBPAC[a], FDA[a]
	Health Canada				Yes	No	Regulatory Decision Summary, Health Canada
AstraZeneca (AZD1222)	EMA	11,636	55.3	44.7	No	No	AstraZeneca Assessment Report, EMA AstraZeneca Product Information, EMA
	Health Canada				No	No	Regulatory Decision Summary, Health Canada
	FDA[2]	–	–	–	–	–	–

[1] EMA and Health Canada publish clinical data used to support their authorisations of the Moderna COVID-19 vaccine. For source of Health Canada Moderna vaccine information, see EMA documents above.
[2] The AstraZeneca vaccine has not yet been approved by the U.S. FDA.
[a] EMA = European Medicines Agency, FDA = Food and Drug Administration, VRBPAC = Vaccine and Related Biological Products Advisory Committee.

The New York Times

F.D.A. Approves New H.I.V.-Prevention Drug, but Not for Everyone

Citing a lack of evidence, the agency will require Gilead to conduct additional trials in individuals 'who have receptive vaginal sex.'

Give this story

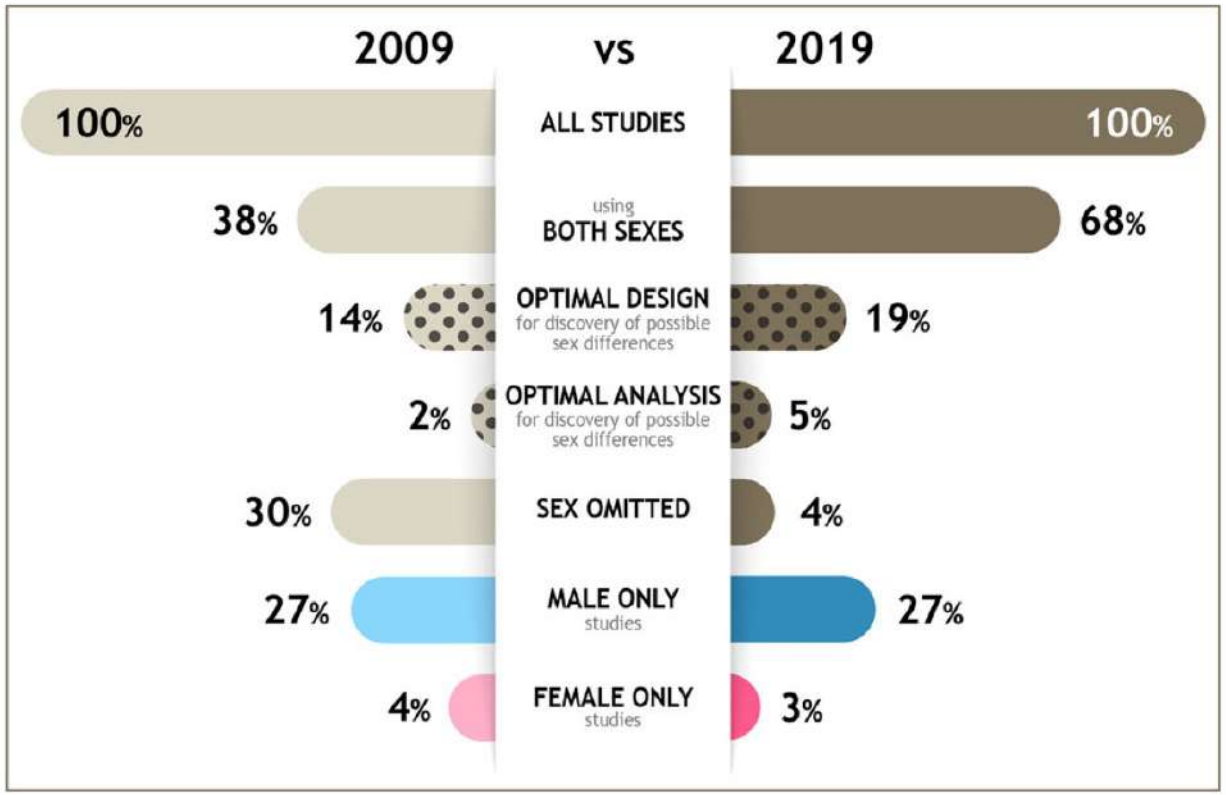


Fig. 6 An infographic depicting the change in percentages of total papers sampled reporting studies in 2009 and 2019 that used both sexes, a single sex, omitted sex, papers reporting studies that used an optimal design or analyses for the discovery of possible sex differences irrespective of discipline. Optimal design refers to relatively based sample

Table 3 Thematic rationales given in papers sampled that had studies that included one sex in study design.

Reason	Proportion
To reduce confounds/variability/ hormones	50.98% ($n = 26$)
Behaviour (i.e., aggression/fighting)	15.69 % ($n = 8$)
To avoid sex differences	11.76% ($n = 6$)
Disease prevalence	11.76% ($n = 6$)
Lack of previously observed sex difference	5.88% ($n = 3$)
Insufficient offspring	3.92% ($n = 2$)

Half (50.98%) of the sampled papers using studies that used a single sex claimed the reason was to reduce confounds or variability mainly due to fluctuating hormones. n = number of papers.

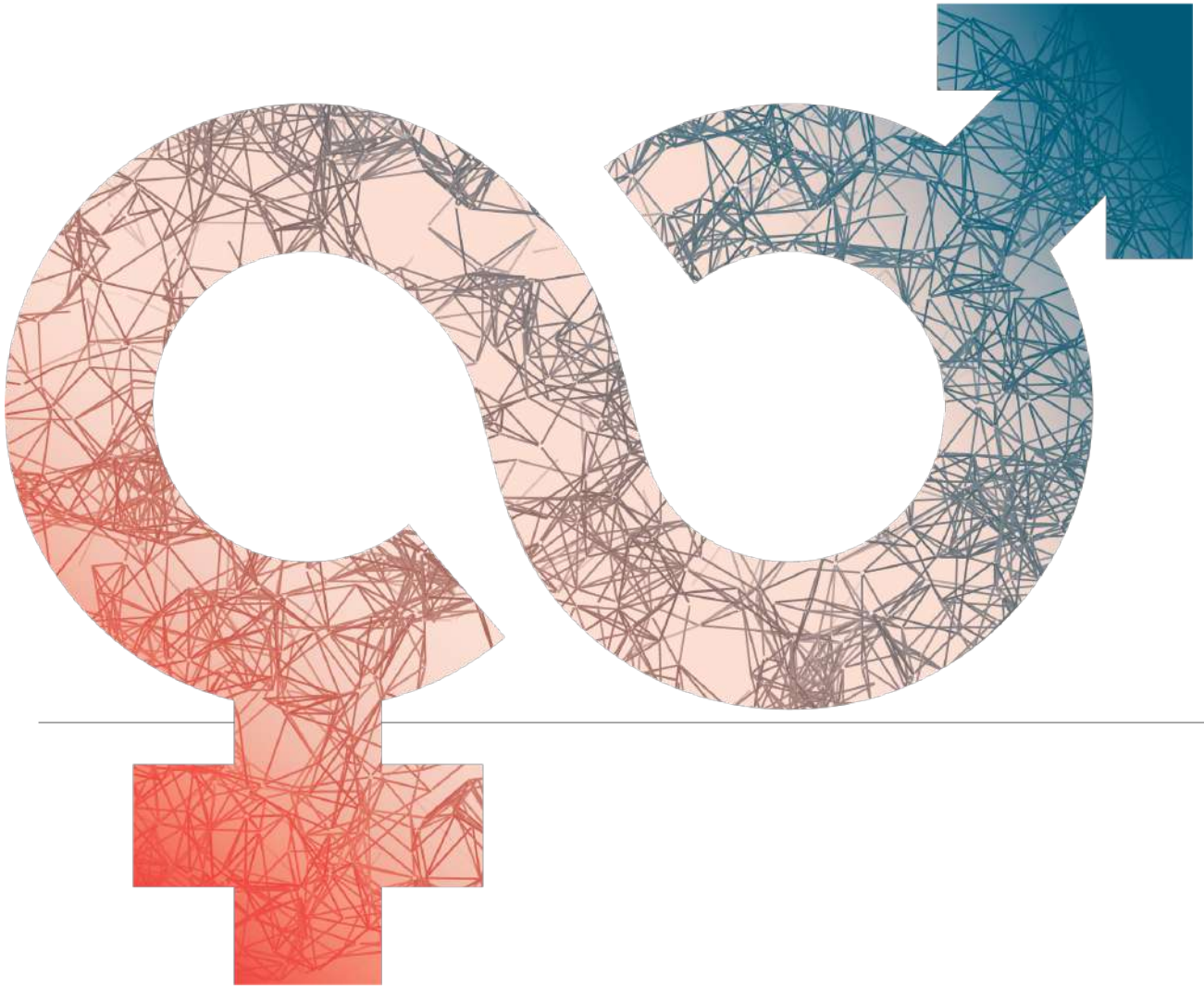
nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-022-29903-3 OPEN

An analysis of neuroscience and psychiatry papers published from 2009 and 2019 outlines opportunities for increasing discovery of sex differences

Rebecca K. Rechlin[1,2,6], Tallinn F. L. Splinter[2,3,6], Travis E. Hodges[1,2], Arianne Y. Albert[2,4] & Liisa A. M. Galea[1,2,5]✉

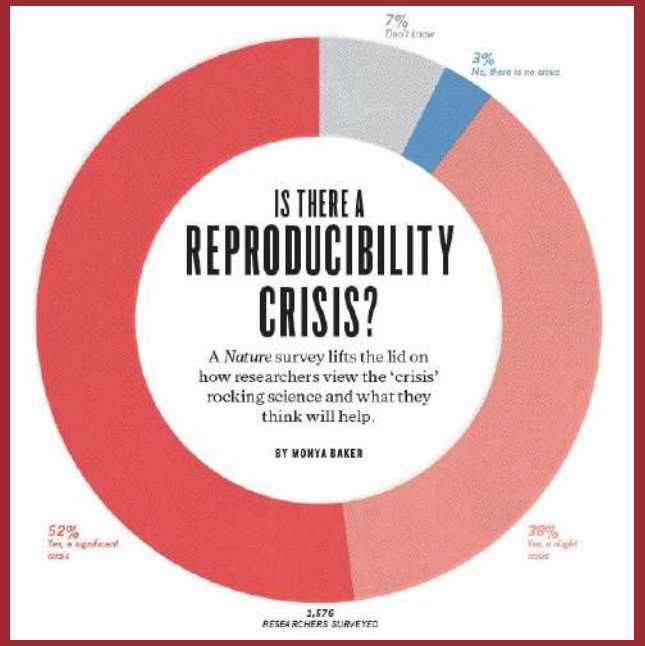


Are sex differences important for drug discovery?

Would studying both male and female animals help with better translation and how can this be achieved?

Improvement of preclinical neuroscience and drug discovery:

European College of Neuropsychopharmacology Preclinical data Network



European Neuropsychopharmacology (2015) 25, 1803-1807

ELSEVIER

www.elsevier.com/locate/euroneuro

The preclinical data forum network: A new ECNP initiative to improve data quality and robustness for (preclinical) neuroscience

HEROIC HONORABLE DEDICATED DUTY SERVICE BRAVE READY COMMITMENT COURAGEOUS SELFLESS INTEGRITY VALIANT
MISSION PATRIOTIC RESPECT ALWAYS COUNTRY SEMPER DEFEND

Cohen Veterans Bioscience

frontiers in Behavioral Neuroscience

METHODS
published: 21 October 2021
doi: 10.3389/fnbeh.2021.755812

PEERS — An Open Science "Platform for the Exchange of Experimental Research Standards" in Biomedicine

Annesha Sil[1], Anton Bespalov[2], Christina Dalla[3], Chantelle Ferland-Beckham[4], Arnoud Herremans[5], Konstantinos Karantzalos[6], Martien J. Kas[7], Nikolaos Kokras[3,8], Michael J. Parnham[9], Pavlina Pavlidi[3], Kostis Pristouris[6], Thomas Steckler[10], Gernot Riedel[11] and Christoph H. Emmerich[2†]*

PEERS

ecnp Neuroscience applied

NOT-OD-15-102*: Consideration of Sex as a Biological Variable in NIH-funded Research

"NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies."

***January 25, 2016 (effective date)**

Health

PRESCRIPTION DRUGS: ANALYSING SEX AND GENDER

© sorbetto via Getty Images

The challenge

Historically, drug development has followed a 'one size fits all' model. Drug testing has been conducted predominantly on males, from pre-clinical research in rodents to clinical trials. As a result, women report more unwanted, and sometime deadly, side effects than men.

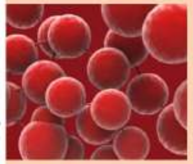
Method: analysing sex

Females and males must be included in all drug trials – from early cell and animal testing to human clinical trials – and analysed separately. Age and genetic ancestry should also be considered, as these characteristics may affect drug efficacy, safety and toxicity. Pregnancy also requires attention, as pregnant women become ill and ill women become pregnant. Information about drug safety effects on the foetus is a priority.

Method: analysing gender

Gender stereotypes can affect clinical care in several ways. First, gender and age bias can influence diagnostic questions. Physicians and researchers should pay attention to language and gender norms in diagnostic procedures. Second, gender relations between the healthcare provider and the patient can affect prescribing patterns and treatment outcomes. Age and race can also play a role.

SYSTEMS BIOLOGY: COLLECTING SEX- AND GENDER-SPECIFIC DATA



©Kittipong Jirasukhanont/Dreamstime.com

The challenge

Sex and gender roles can affect the human metabolism. Consequently, prevention and treatment of many non-communicable diseases require a sex- and gender-related approach. Systems biology aims to predict individual disease risk and enable precision treatment by mathematically modelling metabolic processes. Such models are based largely on omics data (i.e. genomics, transcriptomics, proteomics, metabolomics). Sex bias in the collection of these datasets, however, leads to sex bias in the mathematical models and their predictions.

Method: collecting sex- and gender-specific data

The amount, quality and precision of data have an essential influence on research output. The growing use of large datasets and their integration in fields such as precision medicine, pharmacotherapy and nutrition bring this aspect to the forefront. When collecting information about sex, clear decisions need to be made on how sex is operationalised (e.g. through genomic data alone or in combination with hormonal profiles and phenotypes). The same applies to the potential inclusion of gender in these analyses. Currently, the only immediately available option is the collection of data about gender identity; however, as instruments become more refined, information on gender norms and behaviours could also be collected. The integration of this information could generate new personalised therapies or preventative offers.

24 NOVEMBER 2020

"As EU Commissioner for Innovation, Research, Culture, Education and Youth, and holding gender equality matters very close to my heart, I am determined to step up our efforts on equality. I am committed to ensuring that the gender dimension is fully integrated into research and innovation content in Horizon Europe, and that it is fully acknowledged in the European Research Area."

Mariya Gabriel, Commissioner for Innovation, Research, Culture, Education and Youth

Animal studies in both sexes

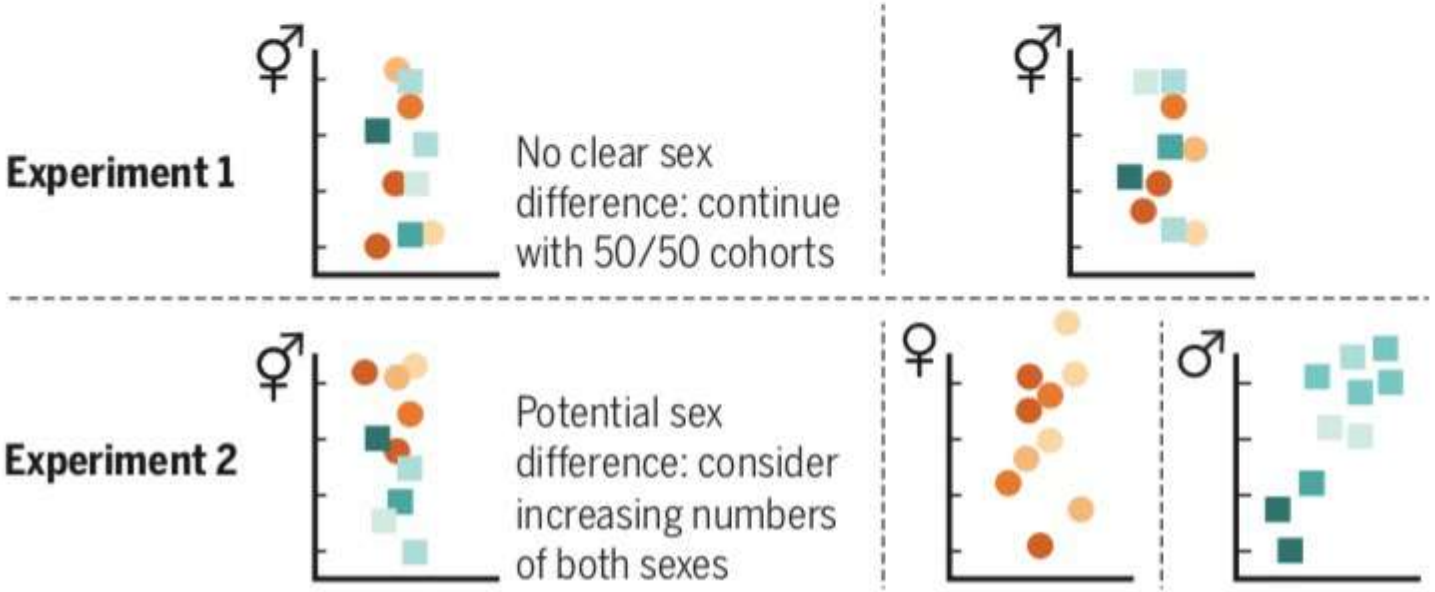
Researchers should start with mixed-sex cohorts and examine data for potential sex differences. If there are no clear sex differences (experiment 1), it is reasonable to proceed with mixed-sex cohorts. If data suggest a sex difference (experiment 2), studying cohorts of each sex may be appropriate.

♀ Proestrus Metaestrus

Estrogen

♂ Dominant Subordinate

Testosterone



PERSPECTIVES

NEUROSCIENCE

Are hormones a "female problem" for animal research?

Outdated gender stereotypes are influencing experimental design in laboratory animals

By **Rebecca M. Shansky**

very practice of preclinical animal research, it also poses a public health problem.

Laboratory of Neuroanatomy and Behavior, Department of Psychology, Northeastern University, Boston, MA, USA.
Email: r.shansky@northeastern.edu

SCIENCE sciencemag.org

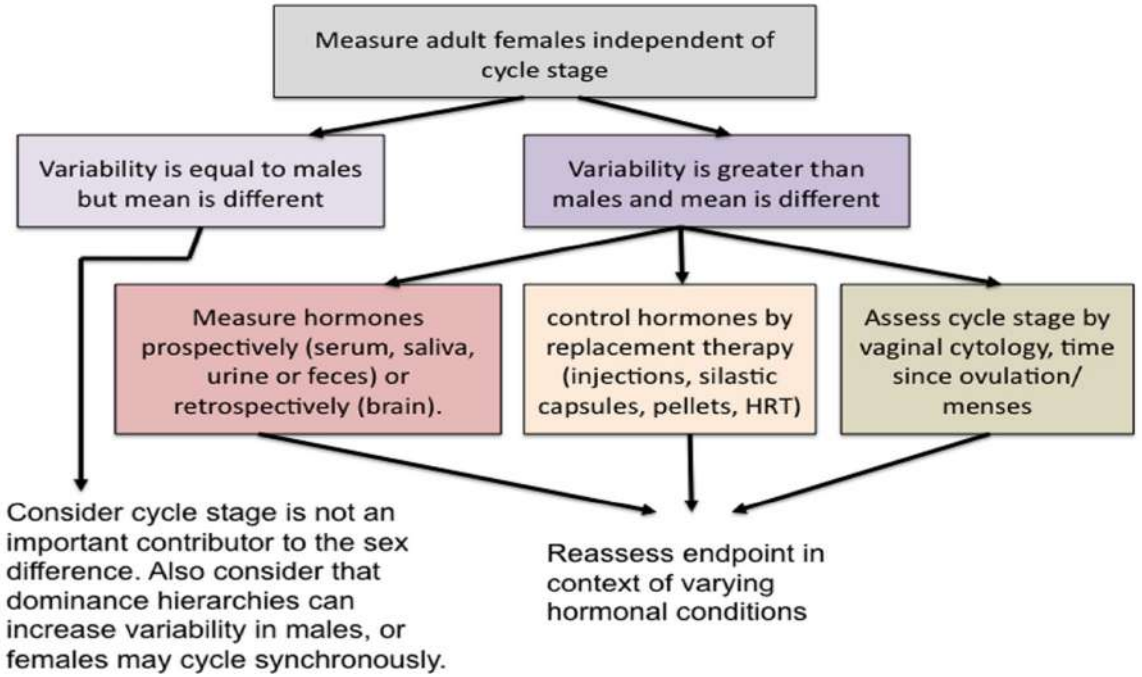
Available online at www.sciencedirect.com

ScienceDirect

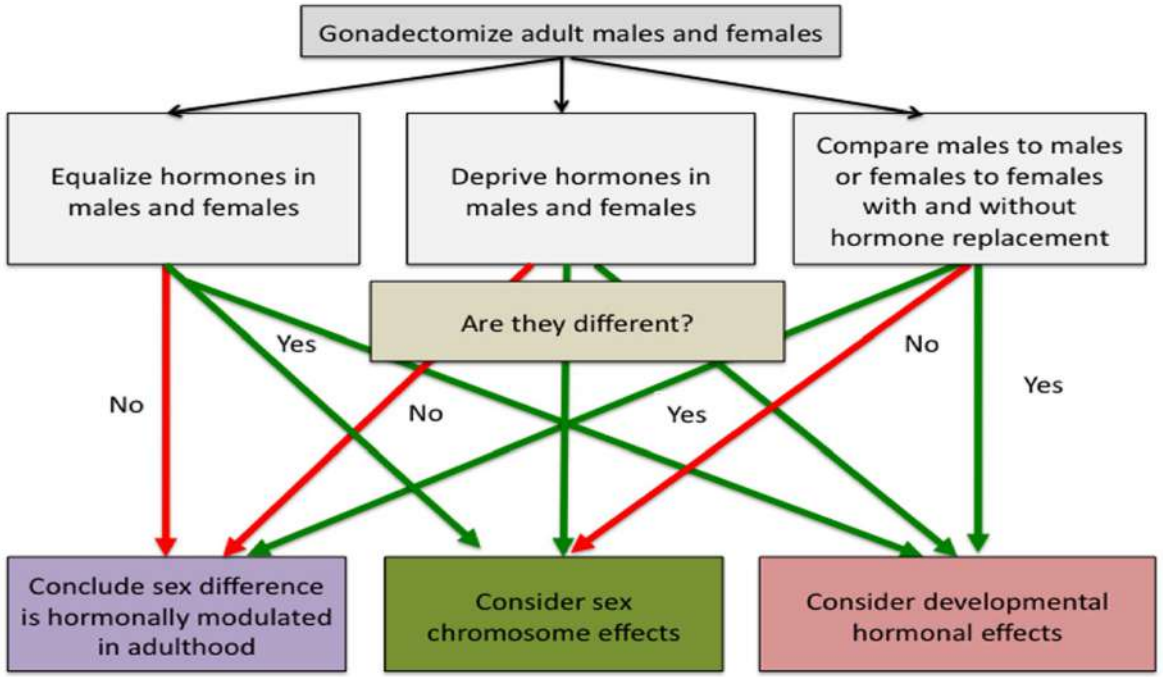
Current Opinion in Behavioral Sciences

Inclusion of females does not increase variability in rodent research studies

Annaliese K Beery[1,2]

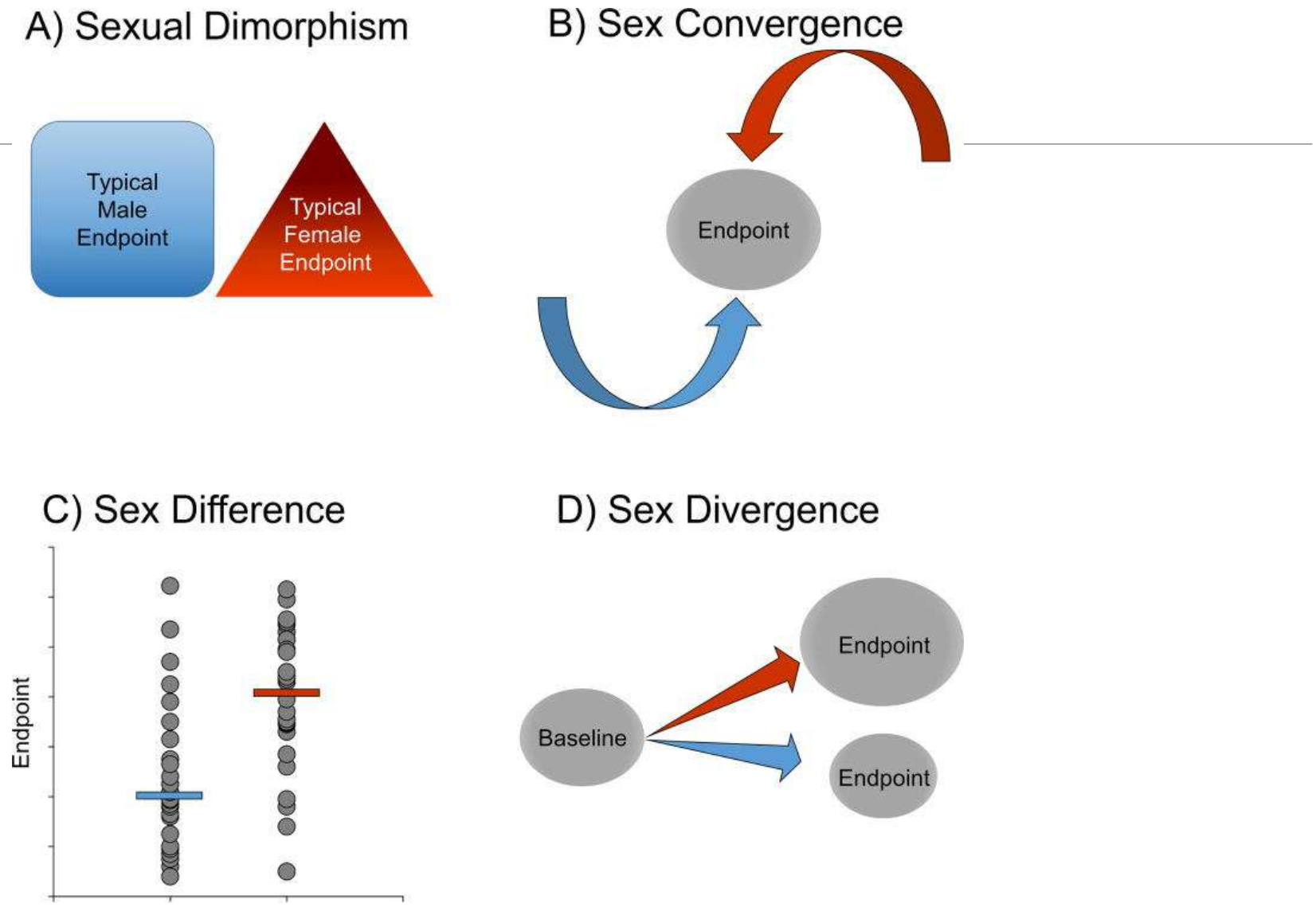


Approaching Sex Differences In Preclinical Research



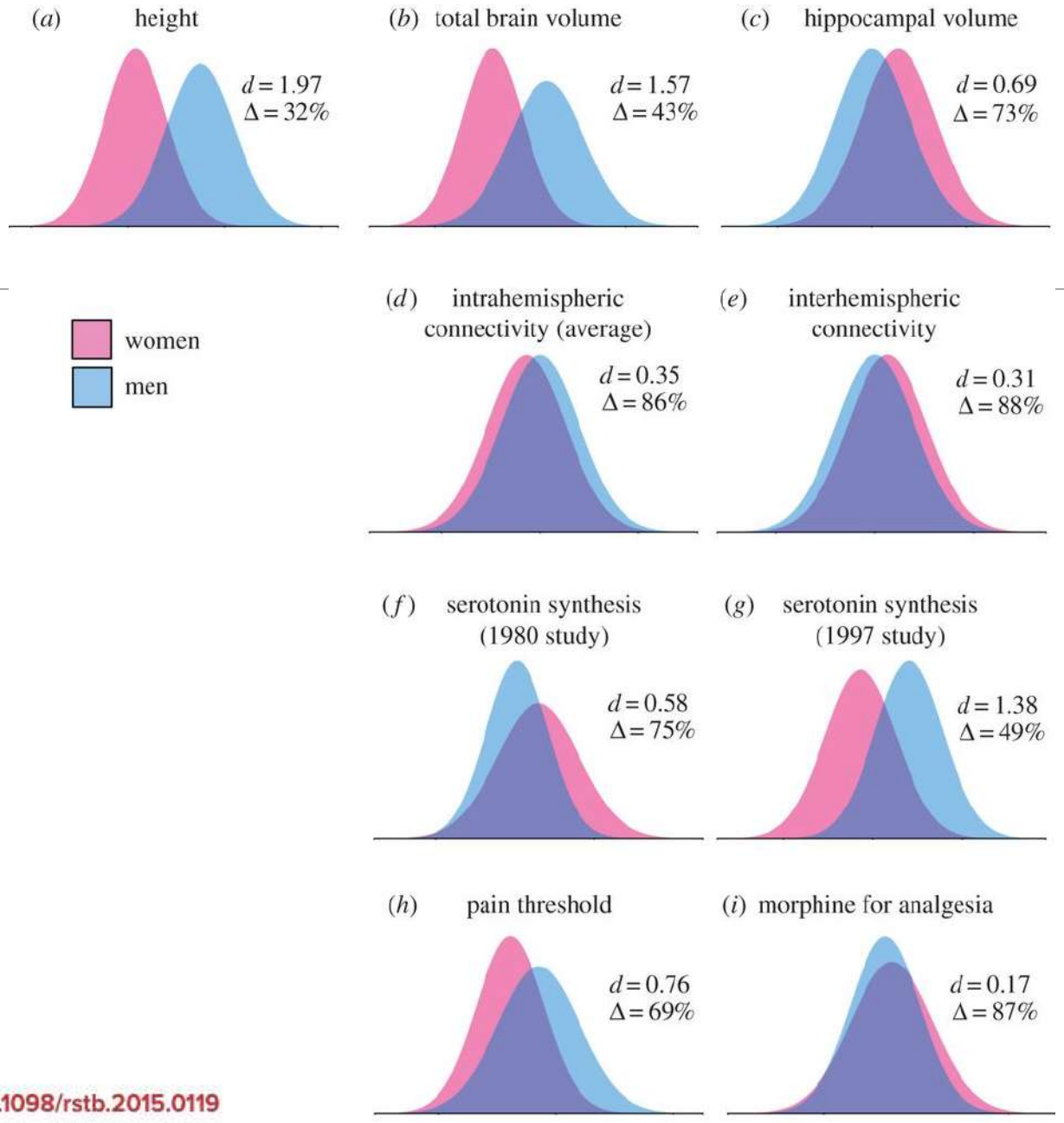
McCarthy et al, J Neurosci 2012

Types of sex differences



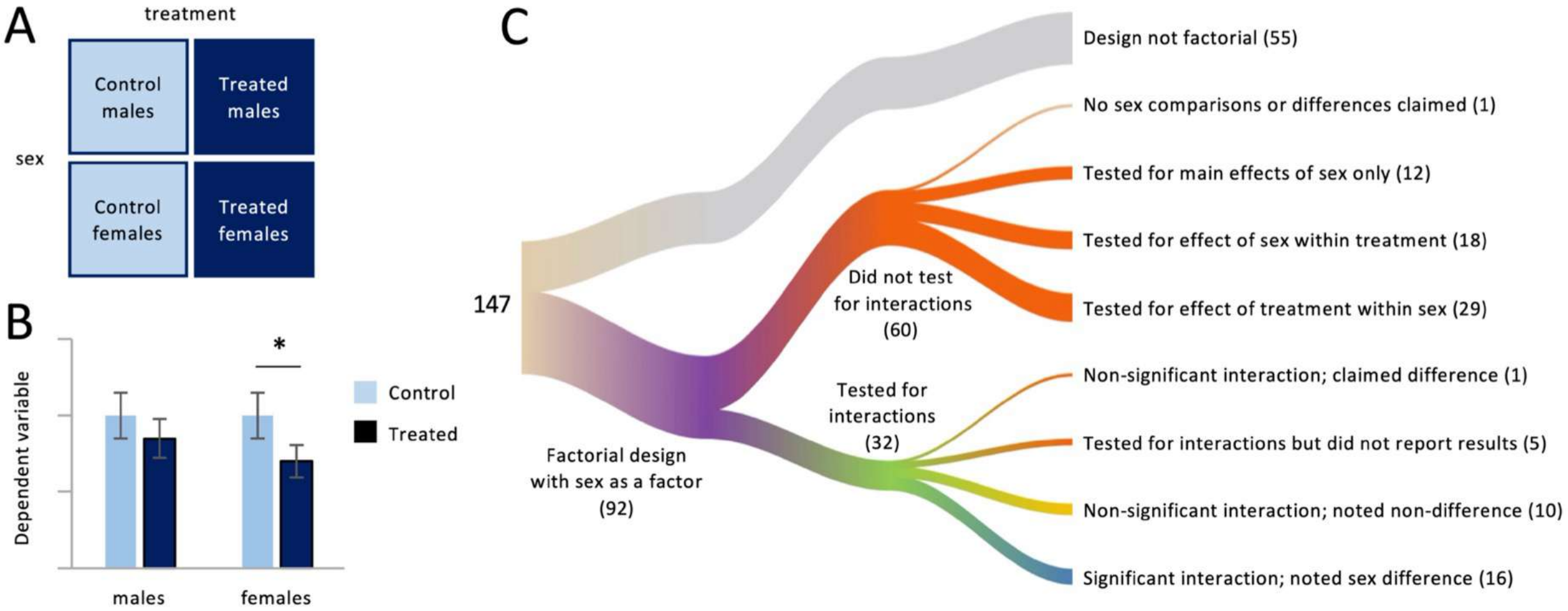
Bangasser and Wicks, 2016, J. of Neuro. Rsh.

Sex differences



Donna L. Maney

Published: 19 February 2016 | https://doi.org/10.1098/rstb.2015.0119



147 articles, published in 2019, that were determined by Woitowich et al., 2020, to have (1) included both males and females and (2) reported data by sex (disaggregated or with sex included in the statistical model). More than one-third of the studies were on humans (35%) and a similarly large proportion on rats or mice (31%).

Sex differences in models of depression and anxiety

Psychoneuroendocrinology 87 (2018) 93–107

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Sex differences in behavioral and neurochemical effects of gonadectomy and aromatase inhibition in rats

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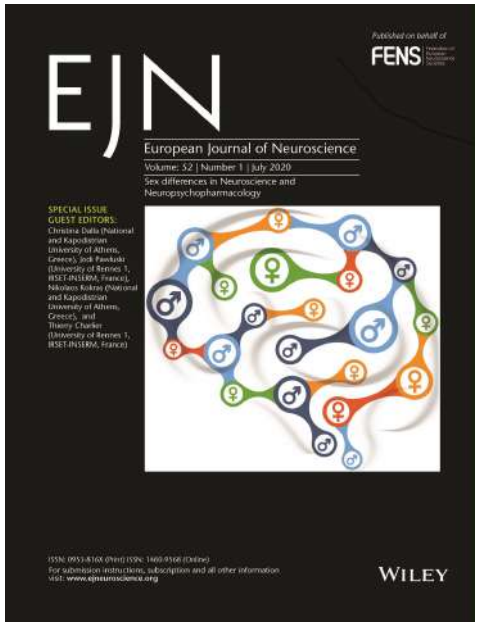

European Journal of Pharmacology 899 (2021) 173998

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Antidepressants' effects on testosterone and estrogens: What do we know?

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DOI: 10.1002/jnr.24686

MINIREVIEW

Do corticosterone levels predict female depressive-like behavior in rodents?

Nikolaos Kokras[1,2] | Stephanie Krokida[1] | Theoni Zoi Varoudaki[1] | Christina Dalla[1]

European Neuropsychopharmacology (2019) 29, 1–15

www.elsevier.com/locate/euroneuro

Neuroplasticity-related correlates of environmental enrichment combined with physical activity differ between the sexes

N. Kokras[a,b,1], I. Sotiropoulos[c,d,a,1], D. Besinis[a], E.L. Tzouveka[a], O.F.X. Almeida[e], N. Sousa[c,d], C. Dalla[a,*]

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DOI: 10.1111/ejn.14598

SPECIAL ISSUE ARTICLE

Escalating low-dose Δ^9-tetrahydrocannabinol exposure during adolescence induces differential behavioral and neurochemical effects in male and female adult rats

Nafsika Poulia[1] | Foteini Delis[1] | Charalampos Brakatselos[1] | Panagiotis Lekkas[1] | Nikolaos Kokras[2,3] | Christina Dalla[2] | Katerina Antoniou[1]

molecules

Article

Behavioral and Neurochemical Effects of Extra Virgin Olive Oil Total Phenolic Content and *Sideritis* Extract in Female Mice

Nikolaos Kokras [1,2], Eleni Poulogiannopoulou [1], Marinos G. Sotiropoulos [1,†], Rafaella Paravatou [1], Eleni Goudani [1], Maria Dimitriadou [1], Electra Papakonstantinou [1], George Doxastakis [3], Despina N. Perrea [4], George Hloupis [3], Apostolis Angelis [5], Aikaterini Argyropoulou [5], Anthony Tsarbopoulos [1,6], Alexios-Leandros Skaltsounis [5] and Christina Dalla [1,*]

Psychopharmacology
https://doi.org/10.1007/s00213-020-05545-5

ORIGINAL INVESTIGATION

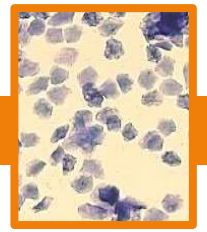
Psychoactive properties of BNN27, a novel neurosteroid derivate, in male and female rats

Nikolaos Kokras [1,2] · Chrysoula Dioli [1] · Rafaella Paravatou [1] · Marinos G. Sotiropoulos [1,3] · Foteini Delis [4] · Katerina Antoniou [4] · Theodora Calogeropoulou [5] · Ioannis Charalampopoulos [6,7] · Achilleas Gravanis [6,7] · Christina Dalla [1]

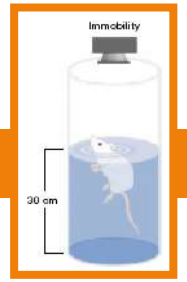
Is antidepressant response affected by estrous cycle?

Adult male & female Wistar rats

Vaginal Smears



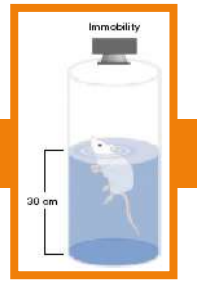
FST Pretest

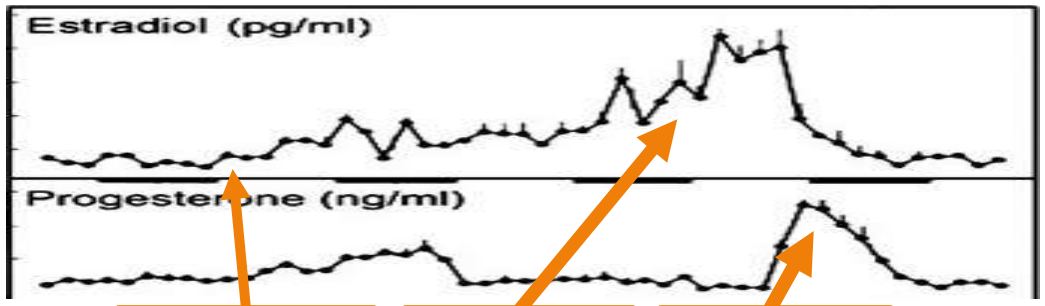


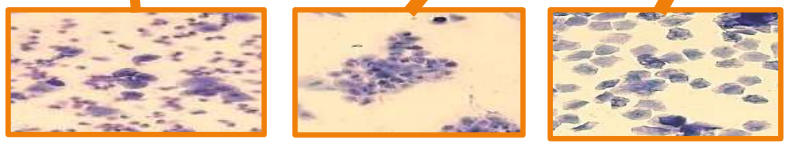
SSRI antidepressant Treatment (3 inj. Sertraline i.p.)

10mg/kg or 40 mg/kg or Vehicle

FST Test







Diestrus I & II | Pro-Estrous | Estrous

Behavioral manual scoring:

Immobility

Swimming

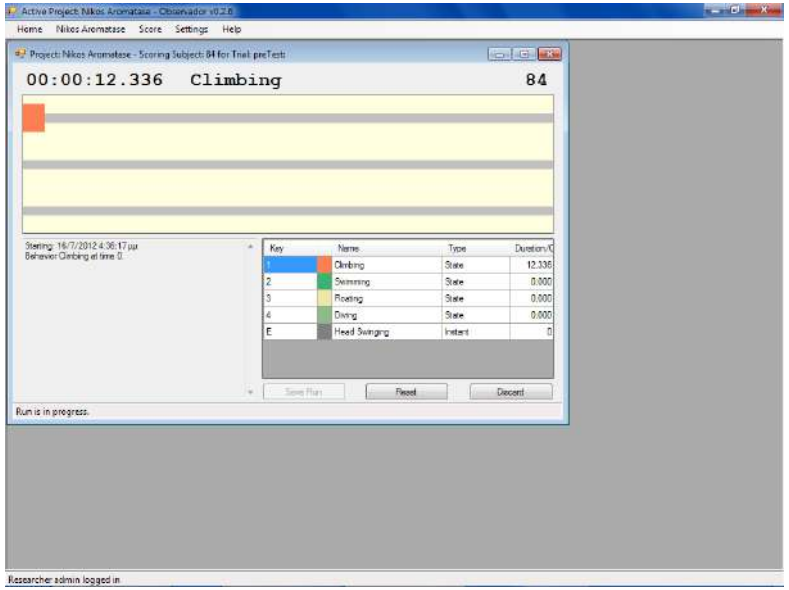
Climbing

Kinoscope:
an open-source program for behavioral scoring

For manual scoring and analysis

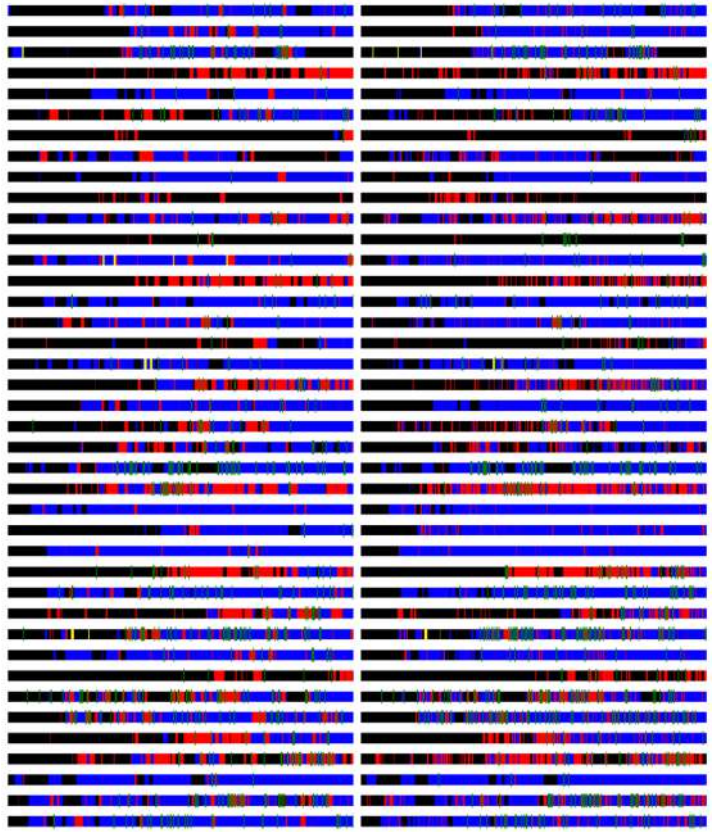
Open Source

Sourceforge.net/projects/kinoscope

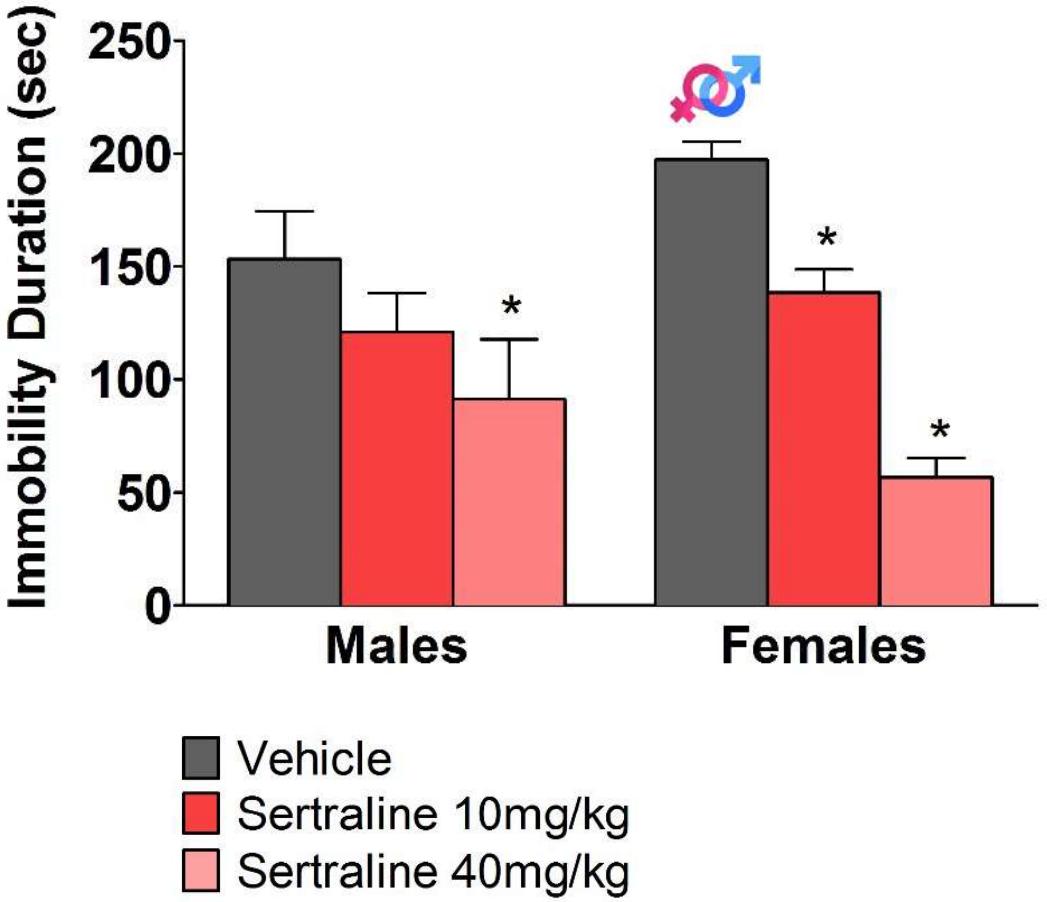


Behavioral Maps

Males

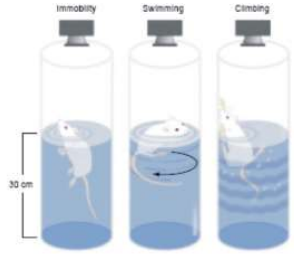


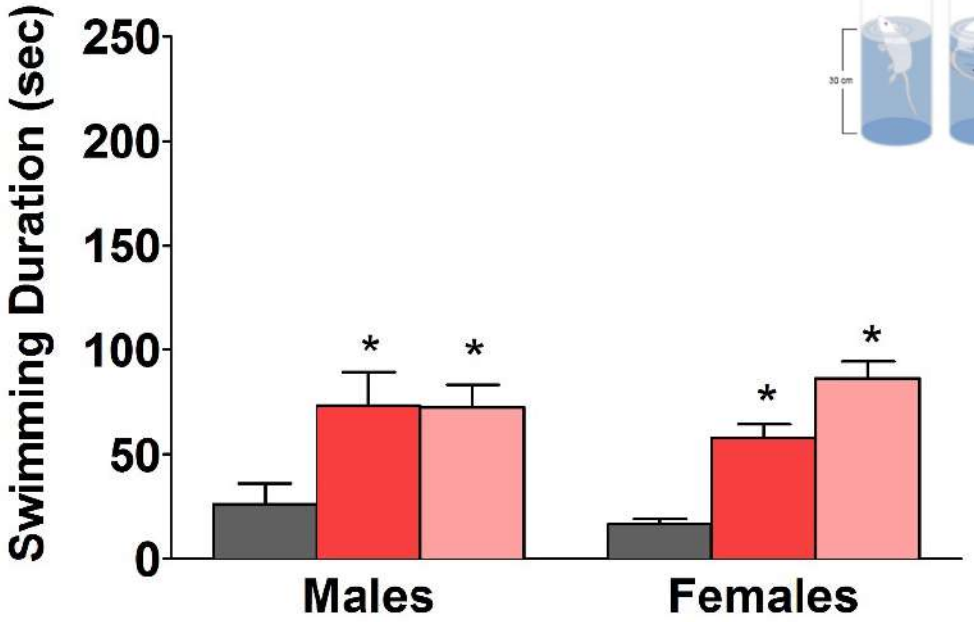
Females



Females show **more immobility** than males at baseline

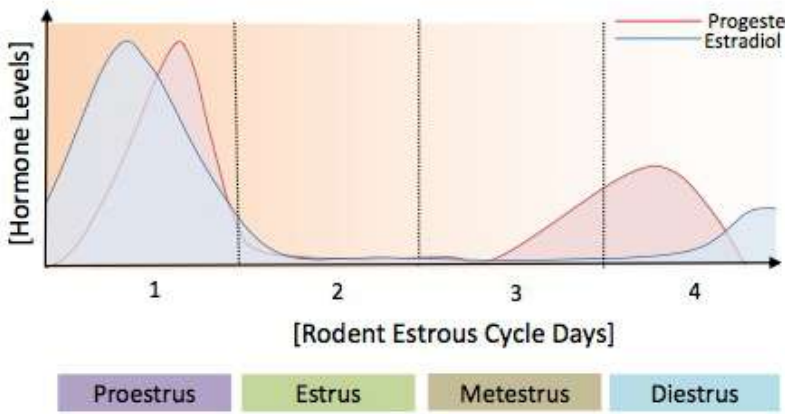
Females respond to a **lower** SSRI (sertraline) dose than males





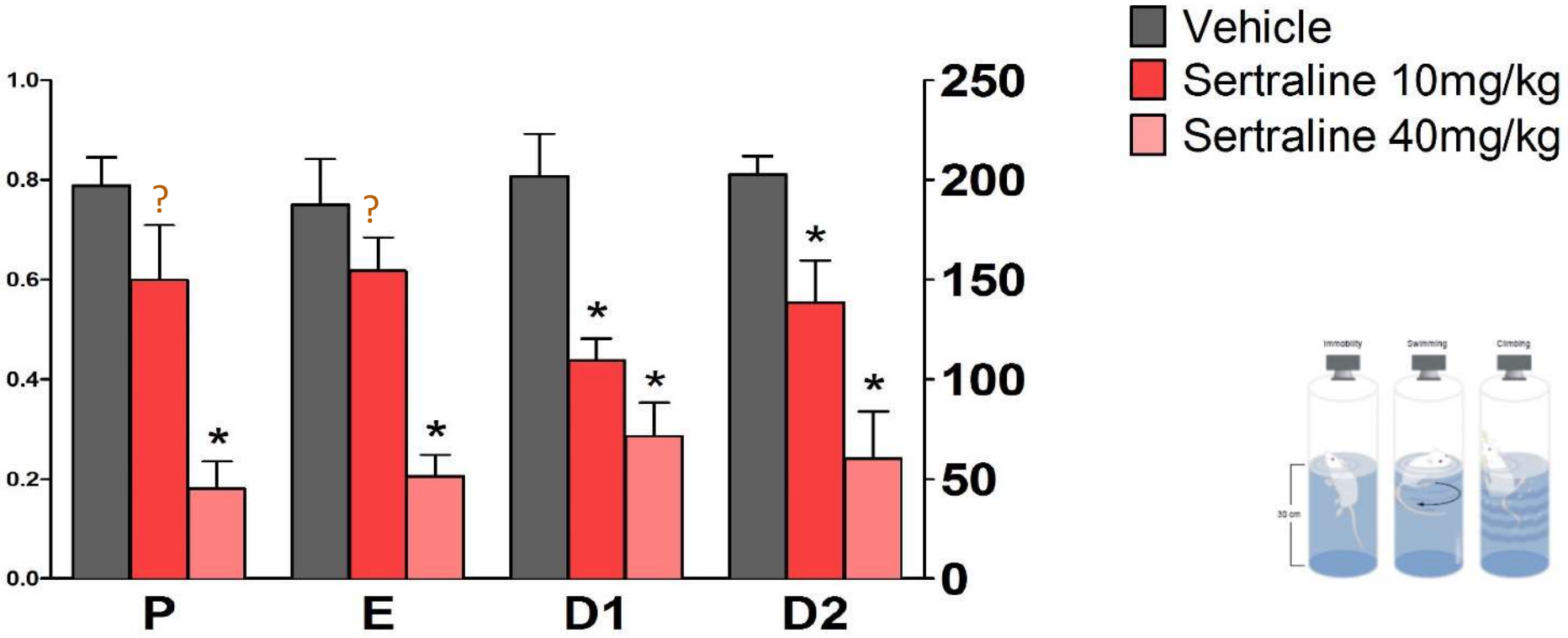
Swimming, which is indicative of serotonergic activity in the brain, is enhanced in both sexes by sertraline

Kokras N. …and Dalla C., Neuropharmacology, 2015



The antidepressant effect is less evident in proestrous and estrous phases of the female cycle

Immobility duration



Kokras N.... and Dalla C., Neuropharmacology, 2015

BJP British Journal of Pharmacology

Themed Section: Animal Models in Psychiatry Research

REVIEW

Sex differences in animal models of psychiatric disorders

N Kokras[1,2] and C Dalla[1]

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DOI:10.1111/bph.
www.brjpharma

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22 November 2013
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20 March 2014
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26 March 2014

- Sex Differences in Phenotype: Validation of models in both sexes
- Magnitude of antidepressant response as a function of baseline
- True sex differences in drug response, independent of baseline

Effects of Estrous Cycle

Pharmacology, Biochemistry and Behavior xxx (2016) xxx–xxx

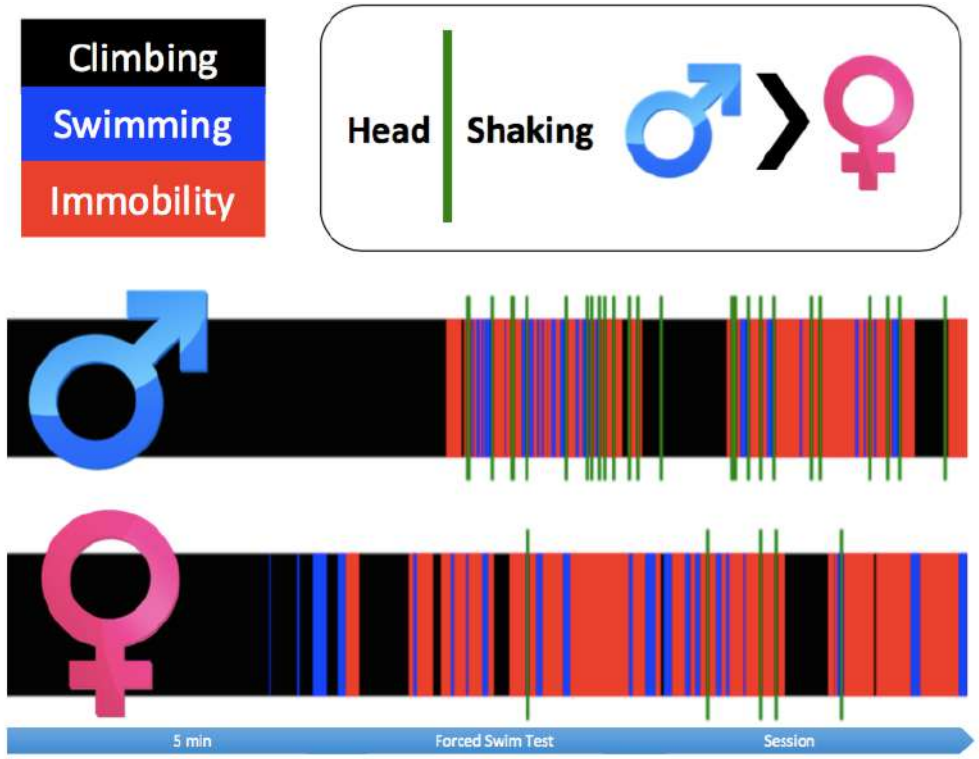
Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Head shaking in the forced swim test: A robust but unexplored sex difference

Nikolaos Kokras [a,b], Alexia Polissidis [a,c], Katerina Antoniou [d], Christina Dalla [a,*]

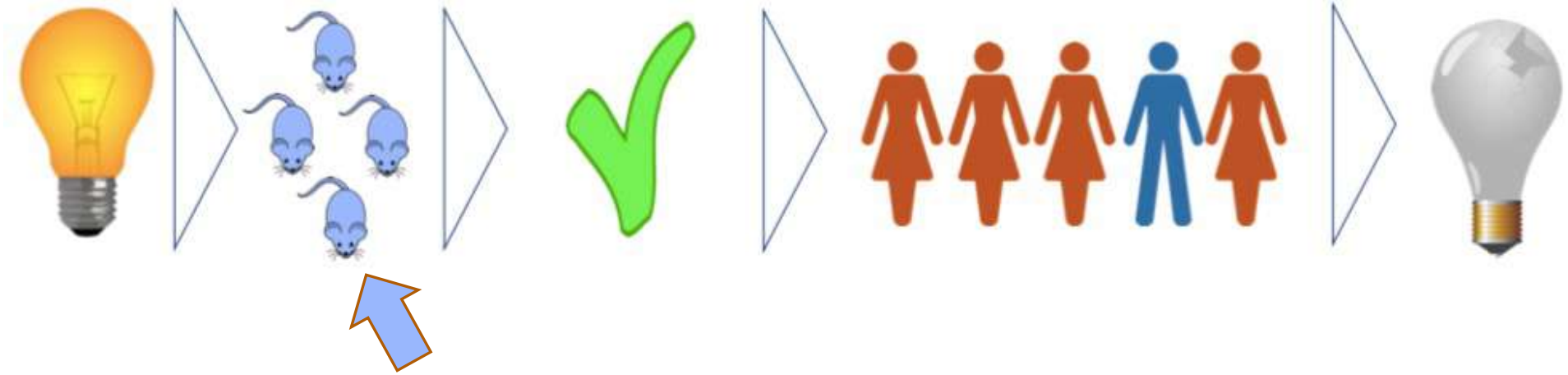


REVIEW ARTICLE THEMED ISSUE

Sex differences in the hypothalamic–pituitary–adrenal axis: An obstacle to antidepressant drug development?

Nikolaos Kokras[1,2] | Georgia E. Hodes[3] | Debra A. Bangasser[4] | Christina Dalla[1]

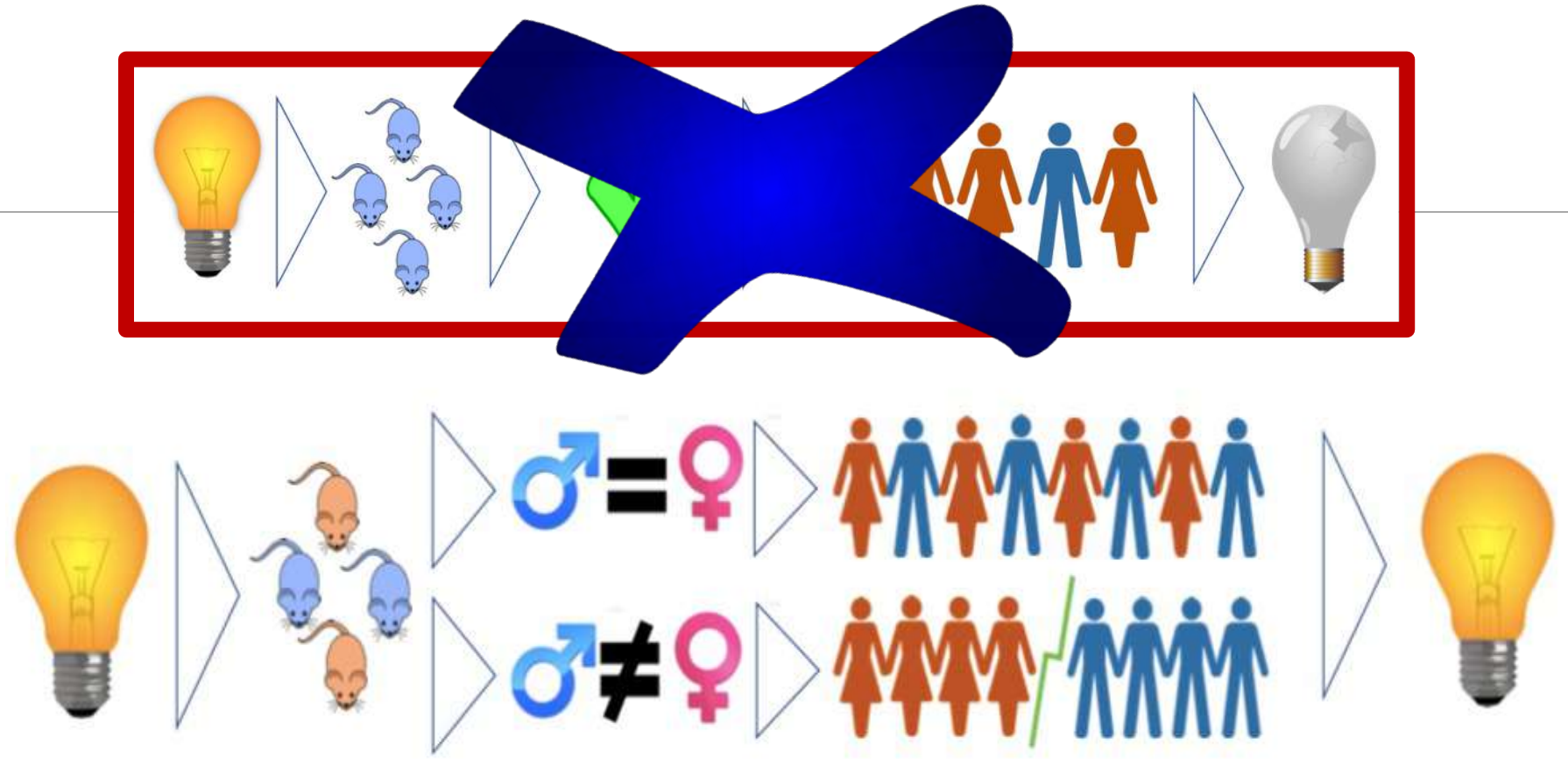
Preclinical Development of candidate antidepressants takes place using **male** only experimental animals



All, animal models of depression simulate or induce a **dysfunctional HPA** axis and drugs are tested in this altered HPA axis milieu

Compound	Preclinical Modelling	Clinical Development	HPA Axis Monitoring	Compared between Sex	RCT Successful
R121919	♂	♀ 55% 45% ♂	X	X	X
NBI-34041	♂	100% ♂	✓		✓
ONO-2333Ms	♂	♀ UN% UN% ♂	X	X	X
SSR125543	♂	♀ UN% UN% ♂	X	X	X
CP-316,311	♂	♀ 60% 40% ♂	X	X	X
Verucerfont	♂	♀ 100%	X		X
Pexacerfont	♂	♀ 100%	X		X
SSR149415	♂	♀ 65% 35% ♂	(✓)	X	X
ABT-436	♂	♀ 35% 65% ♂	(✓)	X	X

Kokras N., ..and Dalla C., British Journal of Pharmacology, 2019



Improving drug development programs & clinical trials

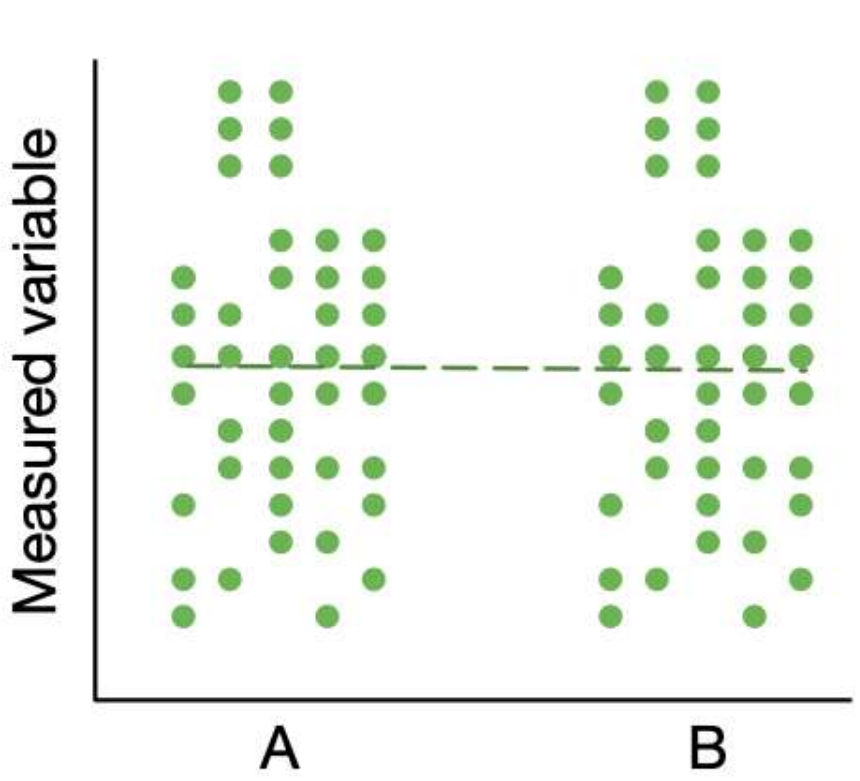
Commonly Applied Statistics Mask Sex Differences in search for the "true" intervention effect

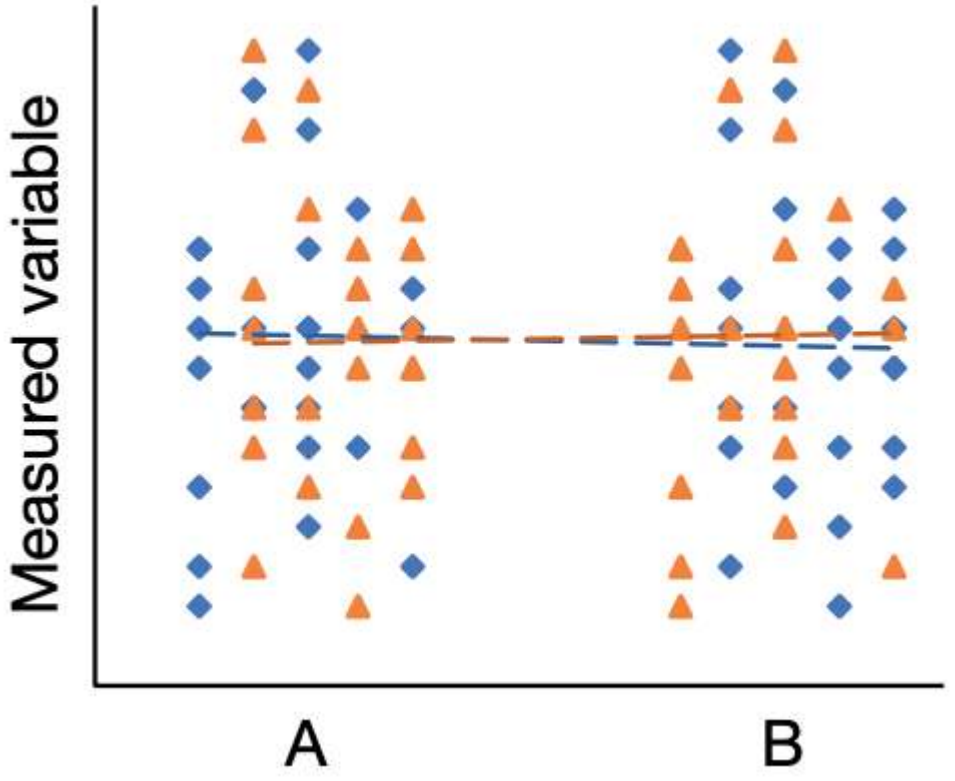
… adjusted for sex (age, etc)

… after controlling for sex (age, etc)

still searching for silver bullets …

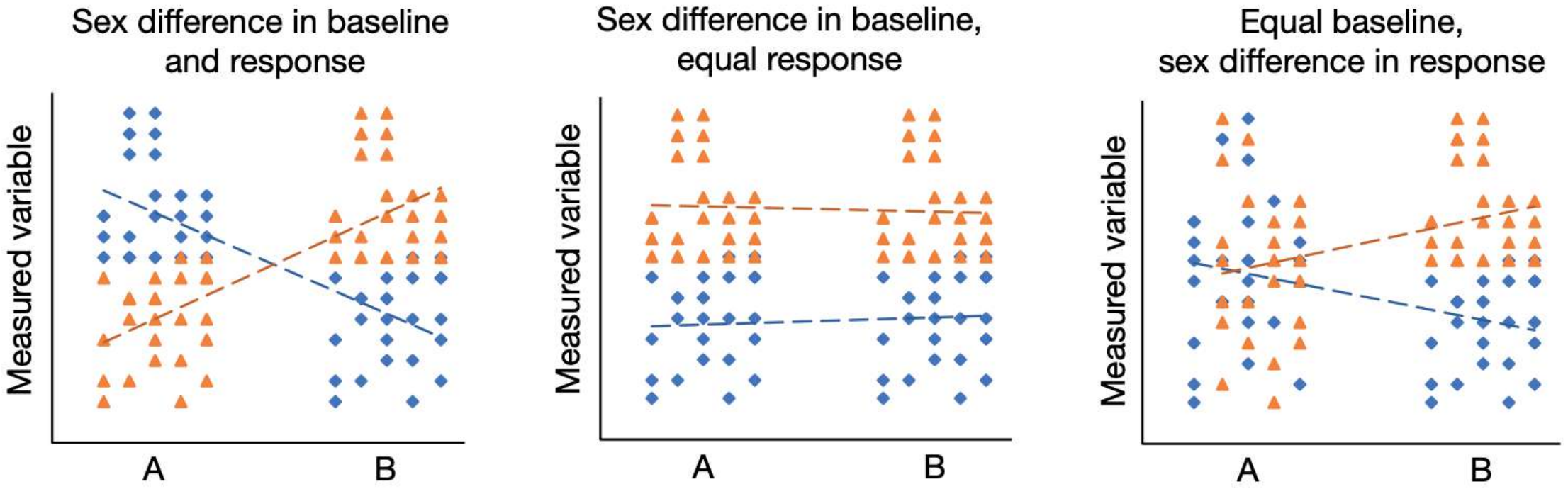
What should happen ideally, if there are no sex differences



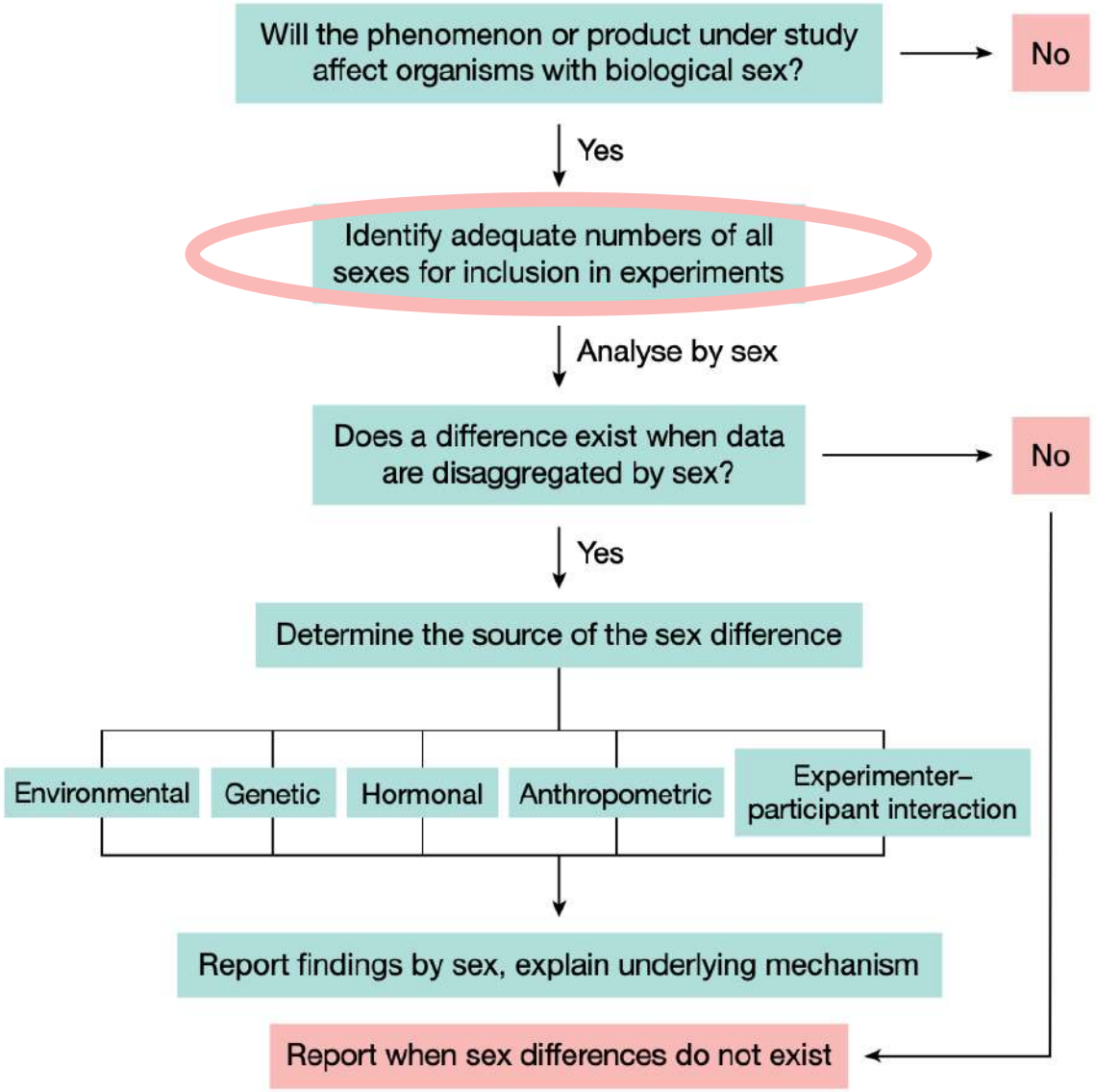


Tannenbaum et al, Nature 2019

What may be happening without our knowledge: possible scenarios



Tannenbaum et al, Nature 2019



Assessing potential sex differences: an algorithm

Biggest drawback is statistical power

- Assuming equal ratio of males:females, **some** comparisons have half the original power
- If one sex is over-represented, power may be less !
- Report minimum effect for 80% power (sensitivity power analysis)

Tannenbaum et al, Nature 2019

nature reviews
drug discovery

COMMENT

Implications of sex-related differences in central nervous system disorders for drug research and development

Florence Butlen-Ducuing[1] ✉, Ewa Balkowiec-Iskra[2], Christina Dalla[3], David A. Slattery[4], Maria Teresa Ferretti[5], Nikolaos Kokras[6], Pavel Balabanov[1], Corinne De Vries[7], Simona Mellino[5] and Antonella Santuccione Chadha[5]

Research on sex differences in central nervous system disorders has developed substantially in recent years. Here, we discuss selected examples and the implications for drug development.

Christina Dalla ***O****f the National and Kapodistrian University of Athens points out that many of these drugs were researched in male mice, then tested in women during clinical trials. "There was a huge mismatch between the sexes of the animals and the humans, and all these compounds failed," she adds.*

Dalla suggests that the model of depression studied in male animals may induce a dysregulation of the HPA axis that doesn't occur in females.

https://doi.org/10.1038/s41587-021-00844-4

Check for updates

news feature

NATURE BIOTECHNOLOGY | www.nature.com/naturebiotechnology

The missing sex

For most of its history, biomedical research and clinical testing has neglected over half of the world's population. Finally, researchers and funders are starting to recognize the importance of sex differences.

Caroline Seydel

Bangasser and Milad respectively showed how responses to stress and fear also vary between male and female mice.

«Dalla proposes that changes across the clinica process are needed. She outlines an approach that would involve studying both male and female animals in pre-clinical studies. If sex differences are identified, the clinical research stage should reflect this by separating participants by sex and studying drugs' effects on the groups independently. If no differences are seen, mixed-sex trial groups would be suitable.»

"Even if, as scientists, we hope we are very goo at what we are doing, still we might have some ideas or some theories that could influence our results or our experimental designs."

FENS | Federation of European Neuroscience Societies

Psychiatric Research Suffering From Legacy of Ignoring Sex Differences, Say Neuroscientists

ARTICLE Jul 11, 2020 | by Ruairi J Mackenzie, Science Writer for Technology Networks

Cohen Veterans Bioscience

How Preclinical Research Contributes to Clinical Research and Development: The Need for Improved Inclusion of Sex as a Biological Variable by Academic Researchers

Preclinical sex differences in depression and antidepressant response: Implications for clinical research

Nikolaos Kokras, Christina Dalla

Recommendations?

Study	Consider	Include	Create	Bring
Study sex differences in the neurobiology of neuropsychiatric diseases and their treatment. Make PK/PD data on both sexes available.	Consider sex-specific dosing of drugs in preclinical/clinical studies with the aim to reduce ADRs.	Include a gender-specific analysis in clinical trials, when needed. Take reproductive status and/or contraceptive use under consideration.	Create a strategy, policy, guideline about sex difference on a regulatory, funding, editorial level.	Bring awareness and educate researchers, academics, industry, clinicians etc.

Cohen Veterans
Bioscience

Study Design Toolbox and Reporting Considerations for Incorporating Sex as a Biological Variable: Part I

Women's Brain Project

a Swiss-based international non-profit organization focused on sex and gender determinants of brain and mental health as a gateway to precision medicine

Received: 30 January 2020 | Accepted: 6 February 2020
DOI: 10.1002/jnr.24602

COMMENTARY

Voices of women in neuroscience

Christina Dalla

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Email: cdalla@med.uoa.gr

ΕΘΝΙΚΟΝ & ΚΑΠΟΔΙΣΤΡΙΑΚΟΝ ΠΑΝΕΠΙΣΤΗΜΙΟΝ ΑΘΗΝΩΝ

NATIONAL & KAPODISTRIAN UNIVERSITY OF ATHENS

Cohen Veterans Bioscience

INTERNATIONAL BRAIN IBRO RESEARCH ORGANIZATION

MARIE CURIE FELLOWSHIPS

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- ✓ Pavlina Pavlidi MSc, PhD candidate
- ✓ Athina Kamitsou, Lida Serveta, Anastasia Rapti, Maria Sageorgi

NIH National Institutes of Health

ΕΣΠΑ 2007-2013

HSN

H.F.R.I. Hellenic Foundation for Research & Innovation

For Women in Science FONDATION L'ORÉAL

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- ✓ Prof. A. Gravanis and Dr. I. Charalabopoulos, Crete, Greece
- ✓ Prof. A. Tsarbopoulos and L. Skaltsounis, NKUA, Greece
- ✓ Prof. T. Charlier and Dr. J. Pawlunski, INSERM, France
- ✓ Prof. D. Bangasser, Temple University, Philadelphia, USA

ΙΔΡΥΜΑ ΚΡΑΤΙΚΩΝ ΥΠΟΤΡΟΦΙΩΝ ΙΚΥ

ΠΡΟΓΡΑΜΜΑ ΓΙΑ ΤΙΣ ΓΥΝΑΙΚΕΣ ΣΤΗΝ ΕΠΙΣΤΗΜΗ ΣΕ ΣΥΝΕΡΓΑΣΙΑ ΜΕ L'ORÉAL HELLAS

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