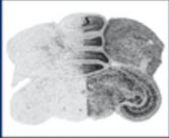


sex DIFFERENCES IN THE BRAIN
from GENES to BEHAVIOR



edited by JILL B. BECKER
KAREN J. BERKLEY
NORI GEARY
ELIZABETH HAMPSON
JAMES P. HERMAN
ELIZABETH A. YOUNG

Sex Differences in the Brain

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Edited by

Jill B. Becker, Karen J. Berkley, Nori Geary,
Elizabeth Hampson, James P. Herman, and Elizabeth A. Young

OXFORD
UNIVERSITY PRESS

2008

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Oxford University Press, Inc., publishes works that further
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Oxford New York
Auckland Cape Town Dar es Salaam Hong Kong Karachi
Kuala Lumpur Madrid Melbourne Mexico City Nairobi
New Delhi Shanghai Taipei Toronto

With offices in
Argentina Austria Brazil Chile Czech Republic France Greece
Guatemala Hungary Italy Japan Poland Portugal Singapore
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Published by Oxford University Press, Inc.
198 Madison Avenue, New York, New York 10016
www.oup.com

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Library of Congress Cataloging-in-Publication Data
Sex differences in the brain : from genes to behavior /
edited by Jill Becker . . . [et al.].
p. cm. Includes bibliographical references.
ISBN 978-0-19-531158-7
1. Sex differences.
2. Sex differences (Psychology)
3. Brain—Sex differences.
4. Human behavior—Physiological aspects.
I. Becker, Jill B.
[DNLM: 1. Brain—physiology.
2. Behavior—physiology.
3. Central Nervous System Diseases—physiopathology.
4. Mental Disorders—physiopathology.
5. Mental Processes—physiology.
6. Sex Factors. WL 300 S5185 2008]
QP81.5.S484 2008 612.8'2—dc22 2007021143

1 3 5 7 9 8 6 4 2

Printed in the United States of America
on acid-free paper

This book is dedicated to Florence P. Haseltine, Ph.D., M.D., founder of the Society for Women's Health Research. Her unstoppable energy and commitment in support of sex differences research is inspirational to us all.
Florence—thank you for leading the way.

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Foreword

MENTAL DISORDERS ARE BRAIN DISORDERS: WHY SEX MATTERS

There seems to be no end to the debate over sex differences in the brain. When people finally agree that differences exist, there is an even more intense debate over what these differences mean. Do more neurons mean more computing power? Do more connections mean more communication between neurons? Do structural differences correlate with functional differences?

In fact, there are clear, reproducible mean differences in many neuroanatomical variables when groups of male and female brains are compared. But understanding these differences runs directly into a central quandary in neuroscience: How do we link form and function? We are now able to define form at the molecular level by identifying individual cells by their RNA transcripts. In addition, we are able to detect function in individual neurons by measuring physiological signatures of identified cells. Similarly,

we have been able to image physiological changes in brain systems associated with behavior and cognition. However, we have not been able to build the bridge from individual cells to brain systems in a way that allows a seamless understanding that spans from molecules to behavior.

This is one of the ways in which the study of sex differences can make a difference: by understanding how chromosomal sex confers genomic differences, how gonadal hormones and their transcription factor receptors lead to developmental changes in brain systems, and how systems in the brain become associated with differences in cognition and behavior. The study of sex differences is a unique opportunity to elucidate the entire trajectory from genes to behavior, or, as more frequently stated in the clinical realm, from genotype to phenotype.

Why is this important? Aside from answering fundamental questions for neuroscience, the study of sex differences is important for public health. According to the World Health Organization, mental

disorders are the leading source of disability in Americans between the ages of 15 and 44. We now understand mental disorders as brain disorders, but we do not understand how brain circuits become abnormal. Part of finding this answer will reside in being able to identify the risk factors for disease and, more importantly, defining the mechanisms by which these factors confer risk.

Among the various risk factors for mental disorders, gender is preeminent. Relative to males, females are at least three times as likely to have anorexia nervosa, twice as likely to have depression, and one fourth as likely to have autism. For schizophrenia and obsessive-compulsive disorder, with roughly equivalent prevalence in males and females, the onset is earlier in males. Moreover, there are gender differences in the clinical features: females with major depressive disorder are more likely to express sadness whereas males present with irritability.

We do not understand the mechanisms for any of these gender differences, but patterns of gonadal hormone action are major candidates. We know that many mental disorders emerge with hormonal transitions at puberty, parturition, and menopause. We

also know that the brain is a target organ for gonadal hormones. As we define the mechanisms by which these hormones alter brain function at the molecular, cellular, and systems levels, we should begin to define how gender and hormonal transitions increase risk for mental disorders.

This book results from the visionary leadership of the Society for Women's Health Research and specifically the staff who have sponsored the Isis Fund Network on Sex, Gender, Drugs, and the Brain. By exploring a range of sex differences from genes to behavior, the chapters herein review the latest insights into how sex and gender matter. The findings promise to alter our approach to mental disorders, leading initially to a better understanding of pathophysiology and ultimately to better treatments. Of course sex differences exist, but what really matters for public health is how these differences lead to vulnerability for some individuals and resilience for others.

Thomas R. Insel, MD
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Preface

Differences in the brain between males and females have been observed in behavioral traits, in the anatomy of the brain, and in the physiological responses of the nervous system to outside stimuli and internal perturbation. The brain is sensitive to the effects of gonadal hormones, beginning in fetal development and continuing throughout the lifespan, and there is mounting evidence that some sex differences may result from differences in gene expression that are independent of the effect of gonadal hormones. In humans, these differences are reflected in the differential impact of neurological and mental illness on men and women, including conditions as diverse as multiple sclerosis, major depression, dementia, and chronic pain disorders. This book brings together an international group of experts on sex differences in the brain, writing about critical methodological issues in sex differences research as well as the most recent developments in this rapidly moving field. It is the culmination of the work of many individuals, and has its origins in

a meeting at the Cosmos Club in Washington, DC, in 1990.

At that meeting, a group of researchers, clinicians, and activists began work that led to the founding of the Society for Women's Health Research (SWHR) to "advance the health of women through research." This group identified the paucity of women participants in medical research studies as a major barrier to such advancement. By 1993, SWHR had brought about changes in grant guidelines at the US National Institutes of Health, and in guidelines for new drug applications at the US Food and Drug Administration. Researchers are now required to include women in research studies unless there is an adequate scientific reason for doing a study in a single sex. By 1995, scientists on SWHR's Board of Directors had a clear vision of the outcome of the inclusion of women (and female animals) as research subjects: the discovery and elucidation of biological sex differences that have a significant impact on health and disease. The Society turned that vision into a proposal for a study by

the Institute of Medicine (IOM) that would address the questions, “Does sex matter?” “When does sex matter?” “How does sex matter?” Once the IOM accepted the report proposal, Society staff raised more than \$650,000 in public and private funds to cover the costs of producing a report.

The Institute of Medicine (IOM) published this landmark report in 2001. The book was a product of the IOM Committee on Understanding Sex and Gender Differences, entitled *Exploring the Biological Contributions to Human Health: Does Sex Matter?* (Wizemann & Pardue, 2001). The Committee concluded that sex is a significant and often ignored biological variable, and that understanding sex differences is crucial for improving human health. They found that much of what was known about sex differences came from descriptive findings, and that hypothesis-driven research to study the mechanisms and origins of sex differences is now needed. They identified several barriers to progress in research on sex differences, including the need for more accurate use of the terms “sex” and “gender,” and the need for better tools and resources for the study and analysis of sex differences.

Another barrier identified by the IOM committee was the inherently interdisciplinary nature of research on sex differences, the lack of funding for this type of research, and the lack of funding for collaborative opportunities for sex differences research. The report noted that progress in sex-based biology would require “synergy . . . between and among basic scientists, epidemiologists, social scientists, and clinical researchers.” In addition, integration of findings at different levels of biological organization (genes, cells, tissues, organs, whole animals) and better “bench-to-bedside” translational research is needed.

In the six years that it took to raise the funding for and produce the IOM report, SWHR developed and launched a strategic plan for developing interest and capacity in sex differences research among basic and clinical scientists. In addition to the traditional role of SWHR as an advocacy group working with the US Congress and federal agencies, SWHR worked to expand its direct outreach to the scientific community. The Society identified two ways in which it could work to encourage research on sex differences: by providing a venue for researchers to present and discuss their work in this area, and by providing financial support for research.

From 2000–2005 SWHR produced the annual Conference on Sex and Gene Expression (SAGE), a

small interdisciplinary meeting that explored all aspects of biological sex differences. The SAGE Conferences brought together researchers working at all levels of biological organization, in animal models from *C. elegans* to primates, and in various physiological systems and clinical disciplines. The SAGE Conferences were designed to allow ample time for informal discussion among the participants, and surveys of attendees found that a significant number of new collaborations and new lines of research were begun at these meetings.

In 1998 SWHR established the Isis Fund for Sex Differences Research, named for the Egyptian Goddess who was the founder of the art of medicine. The Society consulted with staff from the MacArthur Foundation, which had a program of highly successful interdisciplinary research networks to address issues in mental health. Using the MacArthur Networks as a model, funded by unrestricted grant of \$1 million over four years from Ortho-McNeil Pharmaceuticals, Society staff assembled a core group of five scientists and posed to them the question “How are sex and gender differences important in the development and testing of neuropharmaceuticals?” At their first meeting in 2002, the network quickly renamed itself the Isis Fund Network on Sex, Gender, Drugs, and the Brain, and established this mission: To develop collaborations for exploratory and hypothesis-driven research on sex differences in nervous system function, and to translate the results of this research into new and/or improved therapies for advancing human health. In addition to the original goal of network members collaborating on pilot projects, the Network established the following goals in support of that mission: to promote research and education in the area of sex/gender differences in brain health and disease, and to educate and advocate among research funders, scientists, reviewers, regulators and the public. They identified three ways to accomplish those goals: through Network publications, by organizing symposia at large scientific meetings, and by seeking funding for new investigator training grants for sex differences research.

By the third meeting of the Network, which had expanded to eight members, a discussion of potential network projects brought out the need for a guideline to “best practices” for research on sex differences. The network members were concerned that the greatest barrier to the study of sex differences (or to simply including females in an experiment) was difficulty of

dealing with the ovarian cycle (estrous and menstrual cycles). Many investigators are reluctant to include females in their experiments because they are uncertain how best to account for the female cycle, or how to determine the role of hormones when they observe an effect of the estrous cycle. The Network decided to create a document that described the strategies, methods, and procedures used in sex differences research. The product that resulted was a 24-page review that was published in *Endocrinology* (Becker et al., 2005). Although the review addressed these methodologic issues in the context of central nervous system function, the basic information was widely applicable to research on sex and gender differences in other systems.

Soon after the review appeared in *Endocrinology*, the Network (which by then had 11 members) discovered that the article was only a beginning. Many researchers who read the article appreciated its value, while at the same time mentioning that there was a much wider need for this kind of information. The Network agreed that the next step was to produce an edited volume that would expand on the material presented in the review, and would include chapters on basic and clinical sex differences research in neuroscience. This book is the result of that decision.

The Society for Women's Health Research, and specifically the staff who have had a direct role in the development of the Isis Fund Network on Sex, Gender, Drugs, and the Brain,* are proud of our role in funding and supporting the work of this Network, and of the other Networks supported by the Isis Fund for Sex Differences Research: the Network on Sex Differences in Metabolism, supported by an unrestricted grant from Aventis Pharmaceuticals (now sanofi-aventis); and the Network on Sex Differences in the Musculoskeletal System, supported by an unrestricted donation from Zimmer, Inc.

The Isis Fund Networks have significantly advanced innovative interdisciplinary research on sex

differences and, at the same time, have helped launch sex differences as a new field of biomedical research. Network members have organized and participated in symposia on sex differences at meetings of the Society for Neuroscience, the International Society for Psychoneuroendocrinology, and the Congress of the International Union of Physiological Societies. Network members served as guest editors for a special issue of the *American Journal of Physiology* on sex differences in pain and inflammation and a special issue of *Brain Research* featuring papers presented at a joint meeting of the Conference on Sex and Gene Expression and the Workshop on Steroid Hormones and Brain Function held in 2006.

Network members have also been instrumental in founding the Organization for the Study of Sex Differences (OSSD). The OSSD is a new scholarly scientific society for which the Society for Women's Health Research is providing fiscal sponsorship and staff support. The OSSD was founded so that the mission of the Network on Sex, Gender, Drugs, and the Brain, "to promote research and education in the area of sex/gender differences in brain health and disease, and to educate and advocate among research funders, scientists, reviewers, regulators, and the public for the study of sex differences," will continue long after the Network no longer meets.

It is our hope that this volume will prove informative and inspiring, that it will engender curiosity about the role of sex as a factor in the development and function of physiological systems, and that it will fuel the growth of a field of research that is crucial to advancing our knowledge of human biology, and our understanding of human health and disease.

Sherry A. Marts, PhD
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Introduction

In August 2001, the Institute of Medicine (IOM) published a report called “Exploring the Biological Contributions to Human Health: Does Sex Matter?” The IOM concluded that sex is a variable of significant importance for understanding health and disease, and for understanding human physiology more generally. The IOM report was a wake-up call to basic and clinical researchers in many disciplines. In response, the past few years have witnessed a marked growth in research on the effects of sex, as well as signs of greater awareness among professionals that scientifically and clinically important sex differences can and do exist—in susceptibility, symptom expression, response to drugs, immune responses, and many other domains. Sex-based biology has come into its own!

In this volume, we focus on the neurosciences—a set of disciplines where research on sex differences has a lengthy history. In the 1970s, pioneering studies identified sex differences in brain morphology at both the cellular and macroscopic levels, with some structural differences visible even to the naked eye

(Raisman & Field, 1971, 1973; Greenough et al., 1977; Gorski et al., 1978). Outside the laboratory, neuropsychologists studying the effects of brain tumors and strokes in neurological patients noted sex differences in some of the cognitive effects of localized lesions, especially in the language domain (Kimura, 1983; Kimura & Harshman, 1984), an observation that suggested the functional organization of the brain might not be entirely the same in men and women. Now we know that even the basic neurochemistry of the brain can differ according to sex, due to developmental events and the effects of steroid hormones on neuronal and glial activity (e.g., Bazzett & Becker, 1994; Andersen et al., 1997; Auger, 2003; Walker et al., 2006). This book carries on the tradition of highlighting sex differences and illustrates the rich and varied work that is going on in the neuroscience of sex and gender today.

With this volume, we offer food for thought to both novices and experts in the field of sex differences. We open with an overview of the evolution of sex

differences (Chapter 1), and the biology of sexual differentiation of the brain (Chapter 2), emphasizing how cutting-edge ideas and discoveries are revolutionizing our concepts of what makes a male or female brain. Some expert readers might be surprised to discover a renewed emphasis on the direct actions of X and Y chromosome genes in bringing about sex differences. The endocrine model, however, is still ascendant, as many of the chapters reflect. Chapters 3 and 4 are both methodological chapters that discuss research methods and strategies for the intelligent study of sex differences. After all, discovering a sex difference is only the first step—identifying the genetic or hormonal pathways by which the sex difference is established, and understanding its significance in the context of an organism's ecology and larger behavioral context are the ultimate goals of the basic neuroscientist. The new science of pharmacogenomics is a promising tool to consider when studying central nervous system disorders, and here, too, sex differences are being discovered as discussed, in Chapter 5.

Several of the chapters in this book were written by basic scientists who study the brain and its outward product behavior, but many of these topics have exciting implications for the clinic. These include chapters on such fundamental topics as a thorough review of steroid hormone receptors and their role in sexual behavior (Chapter 7), sex differences in social bonding and affiliative behavior (Chapter 8), sex differences in the neural organization of movement (Chapter 9), as well as sex differences in motivation (Chapter 10) and sex differences in energy metabolism and eating behavior (Chapter 13). These chapters discuss information important for the understanding of the neural basis of addiction and other disorders related to the function of motivational systems.

In this volume we also discuss topics of importance for understanding the recovery from brain injury, as discussed in sex differences in neuroplasticity (Chapter 11). Three chapters deal with sex differences in cognitive function, either in rodents (Chapter 12) or in humans and other primates (Chapters 15 and 16). This has been an especially active arena for sex differences research over the past 20 years, and these chapters represent timely reviews on the topic. Newer areas of research discussed include sex differences in children's play and affiliation with same-sex and opposite-sex peers (Chapter 14).

Other chapters present sex differences in the neurobiology of disease, and illustrate how the rec-

ognition of sex differences has enlightened our understanding of a wide range of medical conditions. Chapters 17 and 18 offer insights into sex differences in infections and the activity of the immune system. Chapter 19 describes the important area of sex differences in pain, a difference with wide applicability in the medical sciences. Sex differences are a prominent feature of a number of psychiatric disorders, including major depression, and mood and anxiety-related disorders. These differences are described in Chapters 20 and 21, along with Chapter 6, where sex differences in the responsiveness to stress and in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis are discussed. As illustrated in these chapters, dysregulation of the HPA axis is a feature of many psychiatric conditions.

The book concludes with two chapters on aging and degenerative diseases of the nervous system (Chapters 22 and 23), including Alzheimer's (which shows a female predominance) and Parkinson's disease (which shows a male predominance). Understanding sex differences in aging, especially brain aging, will be an important practical issue over the next decades.

Does sex matter? To respond to the question posed by the IOM: of course sex matters! It matters to biology and medicine at every level of organization and function, from gene to behavior. The realization that there are real and identifiable differences between the sexes that can potentially have a major impact in physiology and medicine, and the potential significant applications of sex differences research, are now driving the agenda. We must have a clear understanding of the important role of sex if we are to optimize medical treatments, effectively target rehabilitation methods, and devise the most effective preventative strategies in the two sexes. Yes, sex does matter, and it matters to basic and clinical scientists in ways we can't even foresee—studying how phenomena in the brain might differ according to sex can help to illuminate the basic mechanisms and physiology that are the essential research targets of every neuroscientist.

No introduction is complete without thanking those who helped us. We thank Viviana Simon and her staff at the Society for Women's Health Research for all their assistance and support throughout the project. Without Viviana's valuable time and wonderful positive attitude, we could not have accomplished this in the short time we had. We also thank

Sherry Marts and Phyllis Greenberger, from the Society for Women's Health Research for their inspiration to create the Isis Fund Networks and for their constant efforts on behalf of sex differences research. We would not have come together without them, and we have benefited in many ways, both scientifically and personally, from our association with the Society and from our warm relationships with Sherry and Phyllis. Finally, we dedicate this book to Florence P. Hazeltine, founder of the Society for Women's Health Research, whose unstoppable energy on behalf of sex differences research is an inspiration to us all.

We hope you enjoy the book.

On behalf of the Isis Fund Network on Sex,
Gender, Drugs, and the Brain
Jill B. Becker, Karen J. Berkley, Nori Geary,
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July 2007

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