SEX, GENDER, AND PAIN

Roger B. Fillingim, PhD
Editor

Progress
in Pain Research
and Management
VOLUME 17

INTERNATIONAL
ASSOCIATION
FOR THE
STUDY OF PAIN

IASP PRESS

Progress in Pain Research and Management
Volume 17

Sex, Gender, and Pain

Editor

Roger B. Fillingim, PhD

Departments of Psychology and Orthodontics,
University of Alabama, Birmingham, Alabama, USA

IASP PRESS® • SEATTLE

Library of Congress Cataloging-in-Publication Data

Sex, gender, and pain / editor, Roger B. Fillingim.
p. ; cm. -- (Progress in pain research and management ; v. 17)
Includes bibliographical references and index.
ISBN 0-931092-35-3 (hard cover : alk. paper)
1. Pain--Sex factors. I. Fillingim, Roger B., 1962- II. Series.
[DNLM: 1. Pain. 2. Sex Characteristics. 3. Sex Factors. WL 704 S518 2000]
RB127.S44 2000
616'.0472--dc21

00-033589

Published by:

IASP Press
International Association for the Study of Pain
909 NE 43rd St., Suite 306
Seattle, WA 98105 USA
Fax: 206-547-1703
www.halcyon.com/iasp
www.painbooks.org

Printed in the United States of America

Contributing Authors

Graciela S. Alarcón, MD, MPH *Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama, USA*

Anna Maria Aloisi, MD, PhD *Institute of Human Physiology, University of Siena, Siena, Italy*

Karen J. Berkley, PhD *Program in Neuroscience, Florida State University, Tallahassee, Florida, USA*

Laurence A. Bradley, PhD *Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama, USA*

Lin Chang, MD *CURE Digestive Diseases Research Center, Neuroenteric Disease Program, Department of Medicine, School of Medicine, University of California, Los Angeles, California, USA*

Roger B. Fillingim, PhD *Departments of Psychology and Orthodontics, University of Alabama at Birmingham, Birmingham, Alabama, USA; currently Department of Operative Dentistry, Public Health Services and Research, University of Florida, Gainesville, Florida, USA*

Robert W. Gear, DDS, PhD *Department of Oral and Maxillofacial Surgery, University of California, San Francisco, California, USA*

Maria Adele Giamberardino, MD *Pathophysiology of Pain Laboratory, Department of Medicine and Science of Aging, "G. D'Annunzio" University of Chieti, Chieti, Italy*

Alan R. Gintzler, PhD *Department of Biochemistry, Downstate Medical Center, Brooklyn, New York, USA*

Margaret M. Heitkemper, PhD, FAAN *Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle, Washington, USA*

Kenneth A. Holroyd, PhD *Department of Psychology, Ohio University, Athens, Ohio, USA*

Kevin S. Jones, MA *Department of Psychology, University of Western Ontario, London, Ontario, Canada*

Barry R. Komisaruk, PhD *Department of Psychology, Rutgers, The State University of New Jersey, Newark, New Jersey, USA*

Stefan Lautenbacher, PhD *Department of Psychiatry and Psychotherapy, University of Marburg, Marburg, Germany; and Department of Physiological Psychology, University of Bamberg, Bamberg, Germany*

Linda LeResche, ScD *Department of Oral Medicine, University of Washington, Seattle, Washington, USA*

Jon D. Levine, MD, PhD *Division of Neuroscience, NIH Pain Center, University of California, San Francisco, California, USA*

Gay L. Lipchik, PhD *Department of Psychology, Ohio University, Athens, Ohio, USA; currently Department of Physical Medicine and Rehabilitation, Saint Vincent Health Center, Erie, Pennsylvania, USA*

Nai-Jiang Liu, PhD *Department of Biochemistry, Downstate Medical Center, Brooklyn, New York, USA*

William Maixner, DDS, PhD *Dental Research Center, University of North Carolina, Chapel Hill, North Carolina, USA*

Emeran A. Mayer, MD *CURE Digestive Diseases Research Center, Neuroenteric Disease Program, Departments of Medicine and Physiology, School of Medicine, University of California, Los Angeles, California, USA*

Christine Miaskowski, RN, PhD, FAAN *Department of Physiological Nursing, University of California, San Francisco, California, USA*

Jeffrey S. Mogil, PhD *Department of Psychology and Program in Neuroscience, University of Illinois at Urbana-Champaign, Champaign, Illinois, USA*

Cynthia D. Myers, PhD *Department of Operative Dentistry, University of Florida, Gainesville, Florida, USA*

Bruce D. Naliboff, PhD *CURE Digestive Diseases Research Center, Neuroenteric Disease Program, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, California, USA; and Department of Psychophysiology Research, VA Medical Center, Los Angeles, California, USA*

Timothy J. Ness, MD, PhD *Department of Anesthesiology, University of Alabama at Birmingham, Birmingham, Alabama, USA*

Joseph L. Riley III, PhD *Departments of Clinical and Health Psychology and Operative Dentistry, University of Florida, Gainesville, Florida, USA*

Michael E. Robinson, PhD *Department of Clinical and Health Psychology, University of Florida, Gainesville, Florida, USA*

Gary B. Rollman, PhD *Department of Psychology, University of Western Ontario, London, Ontario, Canada*

Wendy F. Sternberg, PhD *Department of Psychology, Haverford College, Haverford, Pennsylvania, USA*

R. William Stones, MD *Department of Obstetrics and Gynaecology, University of Southampton, Princess Anne Hospital, Southampton, United Kingdom*

Melissa W. Wachterman, BS *Department of Psychology, Haverford College, Haverford, Pennsylvania, USA*

Beverly Whipple, PhD, RN, FAAN *College of Nursing, Rutgers, The State University of New Jersey, Newark, New Jersey, USA*

Foreword

This book is a very welcome and thorough account of relationships between sex, gender, and pain. During the past decade, this topic has become much better understood due to extensive laboratory and clinical research. While much remains to be explored, the various chapters of this volume address the main issues of the biological and psychological influences of sex and gender on the many facets of pain experience and behavior.

In the first chapter, Roger Fillingim creates a context for the book by introducing three important issues—the magnitude of sex differences in pain, the mechanisms underlying these differences, and their clinical relevance. The remaining chapters continue to address these issues.

This book brings together experimental and clinical knowledge regarding the complex influences of sex and gender on pain. The literature reviewed in this book is rich yet raises numerous questions. Clinicians will appreciate the detail and thoroughness with which practical clinical questions are explored. At the same time, both clinicians and experimentalists will develop a deeper understanding of the world of those who treat pain.

Two unfortunate assumptions are often made by those wishing to provide simple, unifying explanations for sex and gender differences in pain—first, that these differences primarily result from "first-order" biological mechanisms, and second, that they reflect psychological differences. This book shows that the answer is more complex for it demonstrates that biological and psychological mechanisms are interdependent. We see how the transmission of pain-related information at all levels of the nervous system is subject to numerous psychological and biological influences—even dorsal horn neurons are directly influenced by psychological context.

Many chapters begin to fill the missing gaps in knowledge concerning interactions between biological and psychological effects of sex and gender, and some guide us toward future research areas. For example, Linda LeResche points out that the prevalence ratio of women to men with temporomandibular pain is about 2:1 in the general community, yet the ratio of women to men seeking health care for this type of condition is between 5:1 and 9:1. Thus, although greater prevalence is a contributing factor to greater health

care utilization among women, it is not likely to be the exclusive factor; additional psychological and biological differences between men and women are likely to have critical influences. Chapters discussing experimental pain convincingly demonstrate sex and gender differences in subjects' responses and perceptions, and they reveal some implications of sex differences for development of persistent clinical pain conditions. For example, temporal summation of second pain ("wind-up") is, on average, of greater magnitude in women than in men. This difference has potential clinical interest because wind-up reflects the beginning stages of central sensitization, hence its mechanisms may support the hyperalgesia and allodynia of some persistent pain states. This consideration raises an important question. If women generally show greater magnitudes or rates of wind-up than men, could this sex difference explain the greater prevalence among women of pain conditions such as fibromyalgia, TMD, or irritable bowel syndrome? After all, these pain conditions are likely to be at least partly supported by mechanisms of central sensitization.

In reading these discussions of possible mechanisms underlying sex differences in pain, one cannot help being struck by the diversity of contributing factors, whether hormonal, psychological, neurophysiological, or neuropharmacological. The range of factors is almost overwhelming. Nevertheless, these multidimensional studies of sex and gender differences in pain produce an added and unexpected benefit by revealing the biological and psychological predisposing factors that produce common persistent pain conditions. As several chapters make clear, sex is only one of many interacting demographic factors that influence the magnitude and prevalence of different types of pain states.

In the last chapter Karen Berkley reflects on the important issues and questions raised in the previous chapters. She endorses a developmental lifespan perspective in which sex/gender is only one of several factors influencing the development of pain in individuals. This perspective emerges naturally from the varied topics presented and represents perhaps the book's most notable accomplishment.

Experienced scientists, clinicians, and students will find much to value within these pages. I am pleased to have this opportunity to introduce such an excellent book.

DONALD D. PRICE, PHD
Departments of Oral and Maxillofacial Surgery and Neuroscience
University of Florida

Preface

Pain is a complex and personal experience sculpted by a multitude of forces both internal and external to the organism. Over the past 30 years, recognition of the multidimensional nature of pain has fostered an increased interest in understanding individual differences that can influence nociceptive processing. Even more recently, appreciation has grown for the potential role of sex- and gender-related factors in determining an individual's experience of pain. Indeed, the uncompromised pursuit of the equality of the sexes that characterized previous decades has given way to a constructive discourse regarding potentially important differences between women and men. Dramatic advances in pain research, together with sweeping changes in cultural attitudes, have revolutionized the field of research on sex-related differences in pain responses. Substantial evidence now indicates that females and males differ greatly in their nociceptive processing, in their responses to analgesic manipulations, and in their experience of clinical pain. Indeed, a recent Gallup survey on pain in America found that women are more likely than men to experience daily pain (46% of women vs. 37% of men) and that women are 50% more likely than men to have missed work in the past year because of pain.

This book provides a single resource summarizing many of the most important findings regarding sex, gender, and pain. Its contributors are leading international experts in this field whose perspectives include basic neuroscience, human laboratory research, clinical investigation, and epidemiological studies. This book provides information on multiple sex-related factors that can influence pain—factors such as genetic, hormonal, and psychosocial influences.

Part I is devoted to a discussion of several basic processes that may contribute to sex-related influences on pain. Chapter 1 provides the biopsychosocial framework for sex differences in pain. In Chapter 2, Anna Maria Aloisi reviews the wide-ranging somatosensory effects of gonadal hormones in both the peripheral and central nervous systems. She discusses the effects of such hormones on non-nociceptive systems as well as their influence on nociceptive processing. In the following chapter, Jeffrey Mogil discusses genetic influences on nociceptive sensitivity and their potential interactions with sex. He emphasizes the need to examine qualitative

rather than simply quantitative sex differences in nociceptive processing. In Chapter 4, Michael Robinson and colleagues provide a very thorough review of the multiple psychosocial factors that may contribute to the sex-related differences in pain responses observed in human studies. This chapter discusses the importance of sex roles, social learning, and cognitive variables, and it describes sex differences in both clinical and experimental pain responses.

Part II focuses on the results of experimental research examining sex-related influences on pain. In Chapter 5, Wendy Sternberg and Melissa Wachterman review the complex nonhuman animal literature exploring sex differences and hormonal influences on nociceptive processing. This discussion covers not only the influence of sex and gonadal hormones on basal nociceptive responses, but also their effects on endogenous analgesic responses (e.g., stress-induced analgesia). Chapters 6 and 7 are devoted to two female-specific forms of analgesia. In Chapter 6, Alan Gintzler and Nai-Jiang Liu review Dr. Gintzler's pioneering exploration of how the hormonal events accompanying pregnancy alter nociceptive responses. The authors provide a logical analysis of research findings that have clarified the opioid and non-opioid neurochemistry underlying these effects. In Chapter 7, Barry Komisaruk and Beverly Whipple describe their impressive body of research demonstrating the analgesic effects of vaginocervical stimulation. The authors present both human and nonhuman animal data documenting these effects, and they discuss the neural mechanisms supporting this form of analgesia. In Chapter 8, Maria Adele Giamberardino discusses sex-related effects on visceral pain, which differs in important ways from the more typically studied pain arising in cutaneous and somatic structures. This comprehensive chapter reviews both the mechanisms underlying these effects and their clinical implications.

Gary Rollman and colleagues review human research on sex differences in experimental pain (Chapter 9). Rather than simply focusing on empirical findings, these authors provide an insightful discussion of multiple biopsychosocial mechanisms that may contribute to such differences. In Chapter 10, Tim Ness and I review the findings from prior research regarding the effects of the menstrual cycle and other hormonal events on pain responses in humans. This chapter discusses the clinical implications of these hormonal effects and analyzes their potential mechanisms. In Chap-

ter 11, Christine Miaskowski and colleagues discuss sex-related differences in responses to analgesic medications. The authors include a review of their very interesting recent work on opioids and also consider other human and nonhuman animal research in order to better characterize the role that sex plays in analgesic responses.

Part III of the book considers sex-related contributions to various clinical pain conditions. In Chapter 12, Linda LeResche provides an overview of epidemiological perspectives and data relevant to sex differences in pain. She examines sex differences in the prevalence of several different pain conditions and highlights changes in prevalence across the life cycle, which may have important mechanistic implications. Chapter 13, by Kenneth Holroyd and Gay Lipchik, reviews sex-based mechanisms influencing recurrent headache disorders. The authors discuss sex differences in headache epidemiology, hormonal influences on headache symptoms, and clinical implications of these sex-related differences. In Chapter 14, Laurence Bradley and Graciela Alarcón discuss fibromyalgia, highlighting the reasons for its far greater prevalence among females. The authors present a model of heightened pain sensitivity in this disorder and incorporate sex-related factors that may contribute to the abnormal pain processing that is frequently observed in patients. In Chapter 15, William Maixner and I review sex-related contributions in temporomandibular disorders. We propose various neurobiological and psychophysiological mechanisms that may help explain the increased occurrence of this painful condition in females relative to males. Chapter 16, by Bruce Naliboff and colleagues, presents an overview of sex and gender as important contributors to irritable bowel syndrome and discusses mechanisms underlying sex-related influences in this disorder, including neuroanatomical, neuroendocrine, and gonadal hormonal factors. Chapter 17, by R. William Stones, reviews pelvic pain syndromes, a group of female-specific pain conditions. Dr. Stones presents diagnostic and treatment considerations in several different disorders and places these syndromes in a sociocultural context.

In the final chapter, Karen Berkley, clearly a pioneer in this field, distills and synthesizes the information presented by the authors of the other chapters. She discusses the limitations of our current knowledge and highlights the need for further research in several important areas.

I hope this volume will heighten the awareness of basic and clinical scientists and providers of pain treatment as it alerts them to the potential importance of sex-related factors in the experience of pain. This book should encourage us to discuss what we all believe: *women and men really are different!* A better understanding of the differences between the sexes will ultimately enhance our ability to diagnose and treat pain disorders of all types.

ROGER B. FILLINGIM, PHD

Contents

Sex, Gender, and Pain, Progress in Pain Research and Management, Vol. 17, edited by R.B. Fillingim, IASP Press, Seattle, © 2000.

1

Sex, Gender and Pain: A Biopsychosocial Framework

Roger B. Fillingim

Departments of Psychology and Orthodontics, University of Alabama at Birmingham, Birmingham, Alabama, USA

The experience of being female or male depends on complex interactions among multiple endogenous and exogenous variables. These include obvious anatomical differences such as body size, genital organs, and muscle mass; differing levels and temporal patterns of gonadal hormones; psychosocial factors such as emotional experience and sex role expectancies; and multiple environmental and cultural influences. These and other variables are responsible for creating substantial differences between the sexes. However, investigators face the difficult task of determining when these differences are robust enough to overcome the tremendous variability *within* each sex and to merit scientific attention in and of themselves. The publication of this volume suggests that the topic of sex-related differences in pain has crossed that threshold. In this introductory chapter, I will outline recent events that have influenced research in this area, culminating in the publication of this book. I will then highlight several important issues regarding sex, gender, and pain, many of which will be addressed in detail in subsequent chapters.

RECENT DEVELOPMENTS

Important contributions to the literature on sex-related differences in the experience of pain have been made over many decades; however, I wish to focus on several recent events that provided important impetus and direction to this field. In pain research, as in all other areas of biomedical research, women have traditionally been eschewed as research subjects, partly because of the assumption that results derived from men were generalizable

to women. When this assumption proved invalid, the vagaries of controlling for the pesky female menstrual cycle (or rodent estrous cycle) were used as an excuse to exclude women (and female rodents). Several years ago, Karen Berkley (1992) addressed this issue in a brief yet thought-provoking article emphasizing the importance of sex-related issues in neuroscience research. Her survey of 100 articles in reputable neuroscience journals indicated that 45% of the articles failed to report the sex of their subjects. The author also noted that the estrous cycle and other naturally occurring hormonal events in the female rat represent "experimental opportunities" rather than obstacles. In conclusion, Berkley stated that "the differences between females and males, which we all know to be important, can and should be exploited in scientific research." Shortly thereafter, M.A. Ruda wrote an editorial in the journal *Pain*, in which she discussed the importance of studying the differences between women and men, a topic that had been out of favor given the emphasis in the 1980s on equality of the sexes. These two publications both reflected and promoted renewed interest in the issue of sex-related differences in pain.

In 1995, we (Fillingim and Maixner 1995) wrote a review article in *Pain Forum* summarizing the literature on sex differences in experimental pain and providing a model for conceptualizing the mechanisms whereby sex differences could emerge. At about the same time, Karen Berkley (1997) prepared a review article for *Behavioral and Brain Sciences,* which received extensive commentary from many prominent pain scientists. Anita Unruh (1996) also published a comprehensive review article in *Pain* on sex differences in clinical pain. These and other publications indicated increasing interest in the topic in the 1990s, culminating in two National Institutes of Health (NIH) initiatives. First, in 1997, NIH issued a request for applications entitled "Sex and Gender-Related Differences in Pain and Analgesic Responses," which was sponsored by multiple institutes including the Office for Research on Women's Health. Then, in April 1998, the NIH Pain Research Consortium hosted a scientific conference entitled "Gender and Pain: A Focus on How Pain Impacts Women Differently Than Men," organized by M.A. Ruda. This well-attended conference featured presentations by many prominent basic and clinical scientists and received considerable attention in the popular media. Another important development began in August 1996 at the 8th World Congress on Pain in Vancouver, where Will Stones and Karen Berkley organized a meeting of researchers interested in sex, gender, and pain. This meeting led to the establishment of an International Association for the Study of Pain (IASP) Special Interest Group (SIG) on Sex, Gender and Pain, which held its first formal meeting in 1999 at the 9th World Congress on Pain in Vienna.

The objectives of this SIG are (1) to encourage basic and clinical research on how sex and gender affect pain mechanisms and all realms of its management, (2) to provide a central information resource on these issues, and (3) to develop multidisciplinary discussion groups on subtopics of these issues.

This group continues to thrive, and many of the authors in this volume are members. In summary, the 1990s witnessed several influential publications in the scientific press, strong support from the NIH for research in this area, and the organization of an international special interest group related to sex, gender, and pain. These events laid the groundwork for the publication of this book.

SEX DIFFERENCES IN PAIN

Many important issues are related to sex, gender, and pain. There is little doubt that female and male organisms of many species differ in their responses to pain. However, these differences can be complex and variable, and their exact nature is not always clear. Three important issues related to sex, gender, and pain are addressed in the chapters that follow: (1) the magnitude of sex differences in pain, (2) the mechanisms underlying these differences, and (3) their clinical relevance

THE MAGNITUDE OF SEX DIFFERENCES IN PAIN

Some authors have suggested that sex differences are relatively small (Berkley 1997), while others have reported moderate effects (Riley et al. 1998), and we have previously proposed that sex differences in pain responses are robust (Fillingim and Maixner 1995). Interestingly, all three opinions may be correct. The magnitude and direction of sex differences can be influenced by the type of pain being studied (i.e., experimental, acute clinical, or chronic), by the population under investigation (clinical vs. community-based), and by the specific empirical questions addressed in the study. For example, sex differences in experimental pain perception are well documented, but the consistency and magnitude of the effects vary across pain induction techniques (Riley et al. 1998). Also, sex differences in the epidemiology of certain pain disorders have been demonstrated, while other pain conditions appear to be equally common in women and men (LeResche 1999; see Chapter 12, this volume). However, in clinical samples of chronic pain populations, sex differences in pain reports have been difficult to detect (see Chapter 4). Thus, attempts to draw a general conclusion regarding the magnitude of sex differences in pain would be inadequate. A much more

productive approach would emphasize better characterization of sex differences in specific settings and populations, with the ultimate goal of understanding the mechanisms and clinical importance of these effects.

MECHANISMS UNDERLYING SEX DIFFERENCES

We (Fillingim and Maixner 1995; Fillingim 2000; Fillingim and Ness 2000) and others (Unruh 1996; Berkley 1997) have proposed various explanations for the sex differences that have emerged in studies of both clinical and experimental pain. These explanations are often classified as either psychosocial or neurophysiological. Examples of the former include sex role expectancies (i.e., femininity vs. masculinity), cognitive/affective factors (e.g., anxiety, coping, self-efficacy), and social learning. Examples of the latter include gonadal hormones, genetic factors, blood pressure, and differences in endogenous pain inhibition. This distinction between psychosocial and neurophysiological mechanisms, while convenient, is artificial, because psychosocial factors inevitably produce their effects via neurophysiological mechanisms, and because neurophysiological influences also affect psychosocial processes. The evidence related to many of these mechanisms is thoroughly reviewed in several chapters of this volume. However, it is important to resist the temptation to decide which factor is the real culprit in producing sex-related differences in pain response. I prefer to adopt a biopsychosocial approach, which recognizes that the experience of pain is inevitably sculpted by complex and dynamic interactions among biological, psychological, and sociocultural factors (see Fig. 1). Thus, our task is not to decide

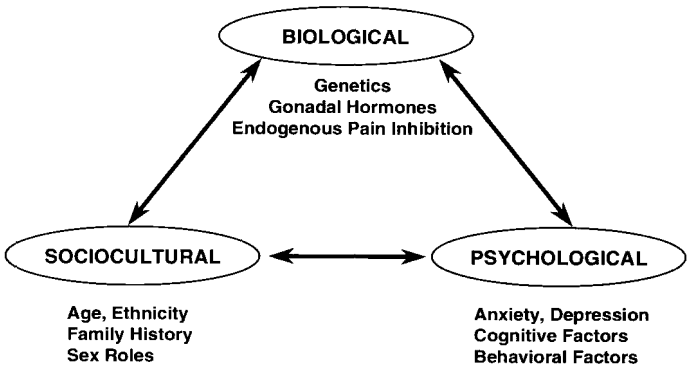

Fig. 1. Schematic diagram of the biopsychosocial model as it relates to sex differences in pain. Examples of biological, psychological, and sociocultural factors that may contribute to sex and gender effects on pain responses are included. The arrows indicate the important bidirectional interactions among the three sets of factors.