



Consensus Conference Report: The Study of Sex and Gender Differences in Pain and Analgesia

Gender Summit 3, North America
November 14, 2013

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Study

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Abstract

In September 2006, the International Association for the Study of Pain met to discuss "best practice" guidelines for the future? The resulting



UNIVERSITY OF MARYLAND DENTAL SCHOOL



THE PAINFUL TRUTH *A Conference on Gender and Pain Research*

September 27, 2006

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Sex, Gender & Pain

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Analgesia:

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Bjorklund ⁱ,
Murphy ^m,
X,

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(2) what are the "best
to address in the near
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A Brief History of Sex Differences in Pain Research

- Very little interest in this question until 1995-1997.
- Then, three influential reviews appeared:

BEHAVIORAL AND BRAIN SCIENCES (1997) **20**, 371–380

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Sex differences in pain

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Sex Differences in Clinical Pain

- Population based studies indicate increased frequency and severity of pain in women vs. men, overall (Unruh, 1996; LeReche, 2000).
- Women seek more pain-related health care than men (Unruh, 1996; Barsky, 2001).
- Women are more likely to use analgesics, even after controlling for differences in pain, other medical conditions, and economic factors (ratio = 1.39; Isacson & Bingefors, 2002).

Box 15-1 Painful Disorders With Documented Sex Differences in Prevalence and Reported Sex Ratios When Available

Craniofacial

Female Prevalence (Female:Male)

- Headache (general or specific): cervicogenic headache (history of neck injury), chronic tension headache, migraine with aura, post-dural puncture headache
- Atypical odontalgia (2:1)
- Burning mouth (tongue)
- Carotidynia
- Chronic paroxysmal hemicrania
- Occipital neuralgia
- Odontalgia (without pathology)
- Temporal arteritis
- Temporomandibular disorder (2-9:1)
- Trigeminal neuralgia (tic douloureux) (2:1)

Male Prevalence (Male:Female)

- Headache (specific): cluster headache, migraine without aura, post-traumatic
- Paratrigeminal syndrome (Raeder's syndrome) (>10:1)
- Trigeminal post-herpetic neuralgia

Limbs

Female Prevalence (Female:Male)

- Carpal tunnel syndrome (5:1)
- Chilblain
- Chronic venous insufficiency
- Peroneal muscular atrophy (Charcot-Marie-Tooth disease, sex-linked inheritance)
- Piriformis syndrome
- Raynaud's disease (5:1)
- Reflex sympathetic dystrophy
- Scleroderma (3:1)

Male Prevalence (Male:Female)

- Brachial plexus neuropathy
- Gout

- Hemophilic arthropathy (sex-linked inheritance)
- Intermittent claudication (lifestyle)
- Meralgia paresthetica (lateral cutaneous nerve neuropathy)
- Thromboangiitis obliterans (Buerger's disease) (>9:1)

Internal Organs

Female Prevalence (Female:Male)

- Chronic constipation
- Esophagitis
- Gallbladder disease (lifestyle)
- Interstitial cystitis
- Irritable bowel syndrome (2-5:1)
- Proctalgia fugax

Male Prevalence (Male:Female)

- Duodenal ulcer (<2:1)
- Pancoast's tumour (bronchogenic carcinoma, potential contributory causes, lifestyle)
- Pancreatic disease

General

Female Prevalence (Female:Male)

- Acute intermittent porphyria (sex-linked inheritance) (3:2)
- Fibromyalgia syndrome
- Lupus erythematosus (autoimmune)
- Multiple sclerosis (autoimmune)
- Postcholecystectomy pain
- Post-herpetic neuralgia
- Post-mastectomy pain
- Rheumatoid arthritis (autoimmune)

Common Chronic Pain Disorders that are More Prevalent in Women

	Prevalence	F:M Ratio
Migraine	12-17%	2-3:1
Tension-type headache	4-5%	2:1
Temporomandibular Disorder (TMD)	4-12%	1.5:1 8:1 (care seeking)
Irritable Bowel Syndrome (IBS)	4-10%	2:1
Rheumatoid Arthritis	1%	2.5:1
Osteoarthritis	12%	1.5 (≥ 45 y.o.)
Interstitial Cystitis	0.5%	9:1
Fibromyalgia	2-3%	6:1

Is There a Sex Difference in Human Experimental Pain Sensitivity?

Based on review of 161 published studies:

Results showing greater pain sensitivity in women: 56%

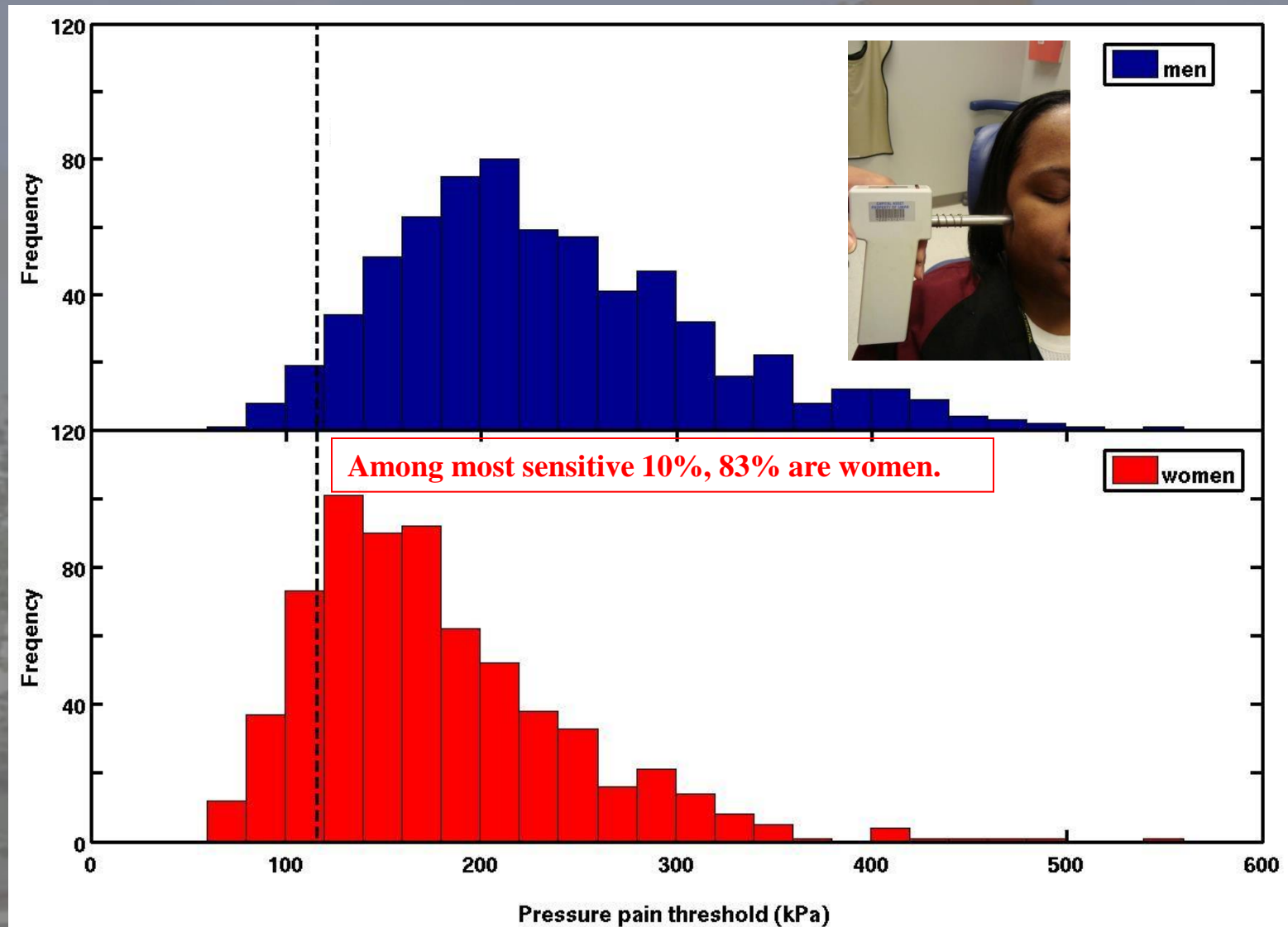
Results showing no sex differences in pain: 42%

Results showing greater pain sensitivity in men: 2%

Greenspan and Traub, "Gender Differences in Pain and Its Relief", *Textbook of Pain*, 2013.

Considerable overlap in pressure pain sensitivity

But the tail is important!



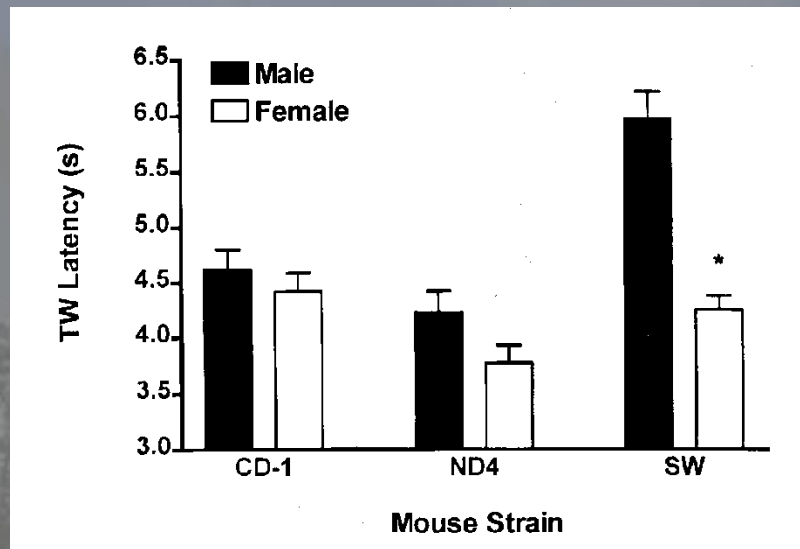
Factors That Contribute to Sex Differences in Both Experimental and Clinical Pain

- Genetic factors
- Gonadal hormones
- Immune/Inflammatory responses
- Nociceptive processing in the nervous system
- Mood and emotions
- History of trauma; physical abuse
- Stress and coping profiles
- Gender roles / Social learning

Sex differences in animal studies

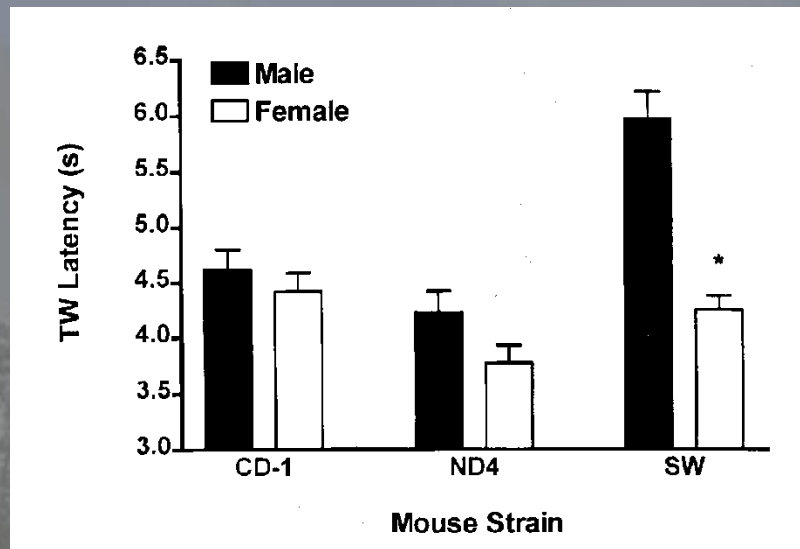
- Q: Do laboratory animals show sex differences in behavioral measures of pain reactivity similar to people?
- A: It depends...

Sex differences in acute pain model

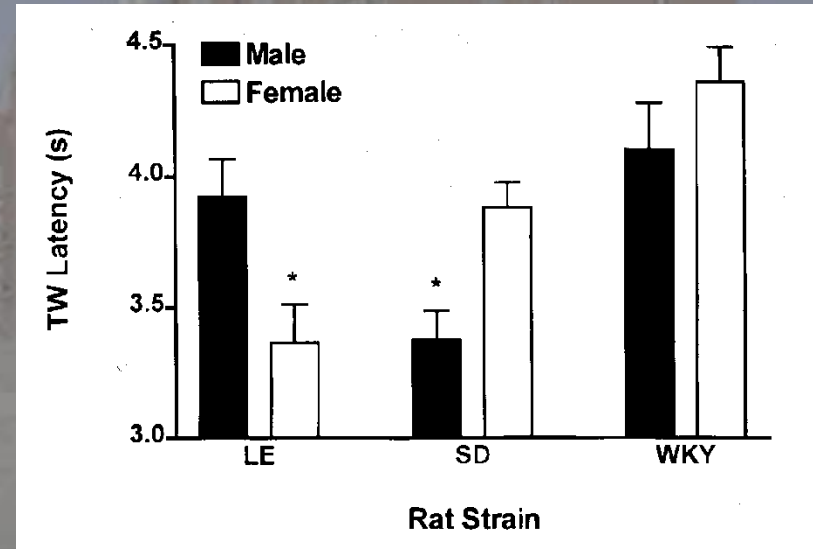


Significant sex differences only for Swiss Webster mice.

Sex differences in acute pain model



Significant differences only for Swiss Webster mice.



Significant differences for Long Evans and Sprague Dawley rats, but in opposite directions.

Also note: Results from other types of pain tests can be different!

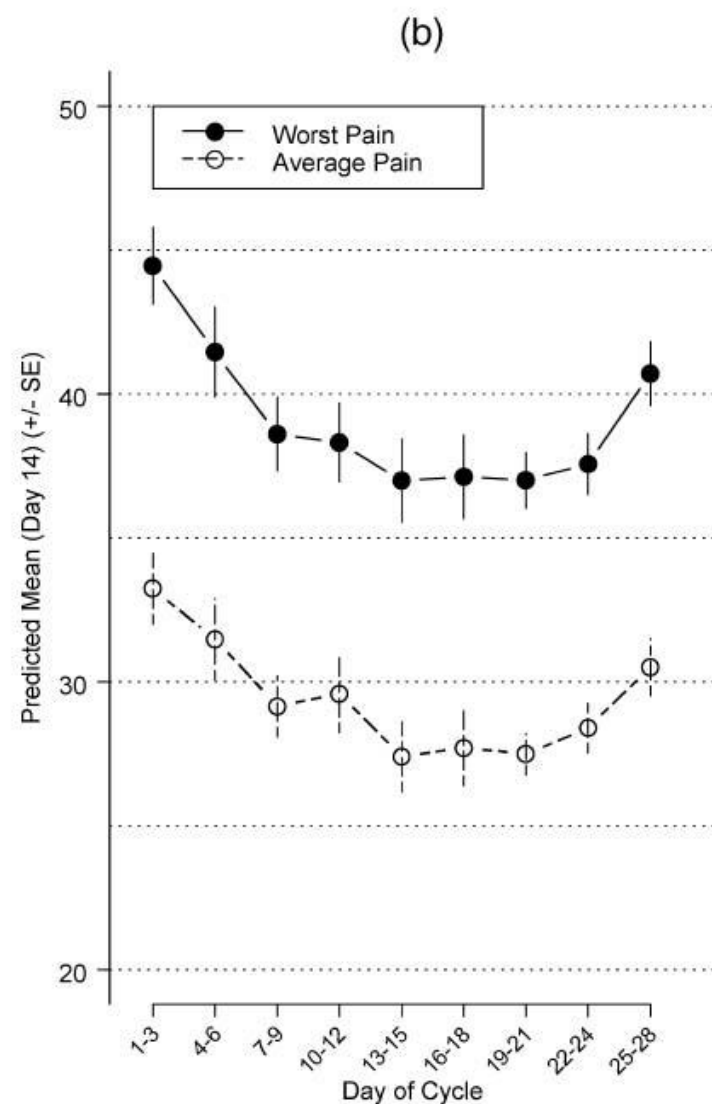
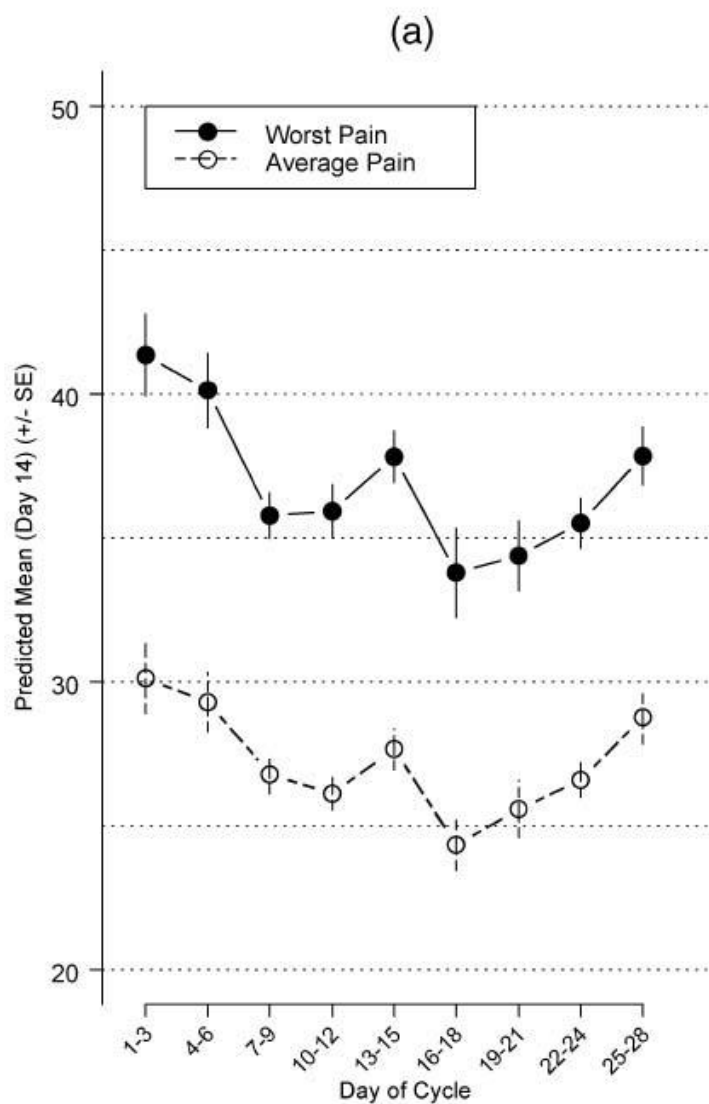
Table 1. Sex-specific genetic effects

Technique ^a	Gene ^b	Protein ^c	Trait	Sex Difference ^d	Reference		
Mutant	<u><i>Accn2</i></u>	ASIC3	Formalin test	M only	Unpublished data		
	<u><i>Esr1</i></u>	ERa	von Frey test	F only	Li et al. (2009)		
	<u><i>Esr2</i></u>	ERb	von Frey test	F only	Li et al. (2009)		
	<u><i>Kcnj6</i></u>	GIRK2	Tail-flick test	M only	Mitrovic et al. (2003)		
			Hot-plate test	M only	Mitrovic et al. (2003)		
			Clonidine analgesia (tail-flick)	M>F	Mitrovic et al. (2003)		
			Baclofen analgesia (hot-plate)	M>F	Blednov et al. (2003)		
			Ethanol analgesia (hot-plate)	M>F	Blednov et al. (2003)		
			<u><i>Oprd1</i></u>	DOR	Stress-induced analgesia (hot-plate)	F only	Contet et al. (2006)
			<u><i>Oprm1</i></u>	MOR	Stress-induced analgesia (hot-plate)	F only	Contet et al. (2006)
	Linkage	<u><i>Ptgs2</i></u>	COX-2	Cyclooxygenase analgesia (writhing)	F only ^e	Ballou et al. (2000)	
		<u><i>Tlr4</i></u>	TLR4	Neuropathic mechanical allodynia	M only	Mogil et al. (2010)	
		<u><i>Calca</i></u>	CGRP	Radiant heat paw-withdrawal test	M>F	Mogil et al. (2005)	
		<u><i>Mc1r</i></u>	MC1R	Kappa-opioid analgesia (tail-flick)	F only	Mogil et al. (2003)	
Stress-induced analgesia (hot-plate)				F only	Mogil et al. (1997b)		
Hot-plate test				M>F	Mogil et al. (1997a)		
Association		<u><i>P2rx7</i></u>	P2X7	Neuropathic mechanical allodynia	M>F	Unpublished data	
		<u><i>MC1R</i></u>	MC1R	Pentazocine analgesia	F only	Mogil et al. (2003)	
		<u><i>OPRD1</i></u>	DOR	Heat pain	M>F	Kim et al. (2004)	
		<u><i>OPRM1</i></u>	MOR	Pressure pain	M only	Fillingim et al. (2005)	
	Heat pain			M↑,F↓	Fillingim et al. (2005)		

What about the role of gonadal hormones in pain?

- Animal studies show distinct evidence of gonadal hormone effects upon pain responsiveness.
- Human studies show mixed results regarding hormonal influences on pain, as assessed by:
 - Fluctuations across the menstrual cycle
 - Effects of hormone replacement therapy

Oro-facial Pain Fluctuations Across the Menstrual Cycle



The Role of Psychological Biases

The Gender Role Expectations of Pain (GREP) questionnaire was developed by Michael Robinson and colleagues at Univ. of Florida to evaluate this psychological construct's influence upon experimental pain sensitivity.



Abstract

The primary purpose of this study was to investigate the influence of an individual's Gender Role Expectations of Pain (GREP) on experimental pain report. One hundred and forty-eight subjects (87 females and 61 males) underwent thermal testing and were asked to report pain threshold, pain tolerance, VAS ratings of pain intensity and unpleasantness, and a computerized visual analogue scales (VAS) rating of pain intensity during the procedure. Subjects completed the GREP questionnaire to assess sex-related stereotypic attributions of pain sensitivity, pain endurance, and willingness to report pain. Consistent with previous research, significant sex differences emerged for measures of pain threshold, pain tolerance, and pain unpleasantness. After statistically controlling for age, GREP scores were significant predictors of threshold, tolerance, and pain unpleasantness, accounting for an additional 7, 11, and 21% of the variance, respectively. Sex remained a significant predictor of pain tolerance in hierarchical regression analyses after controlling for GREP scores. Results provide support for two competing but not mutually exclusive hypotheses related to the sex differences in experimental pain. Both psychosocial factors and first-order, biological sex differences remain as viable explanations for differences in experimental pain report between the sexes. It appears that GREP do play a part in determining an individual's pain report and may be contributing to the sex differences in the laboratory setting. © 2002 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

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Going Forward: Why Study Sex/Gender Differences in Pain?

- The main goals of research on sex and gender differences in pain/analgesia are to:
 - 1) determine mechanisms that contribute to the generally greater prevalence of clinical pain in women vs. men;
 - 2) discover how sex-specific mechanisms of pain/analgesia can be exploited to improve pain management for both sexes; and
 - 3) determine differences in outcome when similar treatments (pharmacological, interventional, behavioral) are applied.

What is recommended for pain research?

- Include both sexes in any pain study.
 - Standard for human research studies (1994)
 - But, as for animal studies: “We surveyed the basic science of pain literature from 1996 to 2005 by considering papers using rats or mice as subjects in the flagship journal, *Pain*, and discovered that 79% of all published papers tested male subjects exclusively. In addition, 5% of papers tested both sexes but did not report any analyses of possible sex differences, and 3% did not report the sex of their subjects. There were no apparent trends toward increased use of female subjects in this decadal period.”

Mogil and Bailey, *Progress in Brain Research*, 2010.
Recounting data presented in Mogil and Chanda, *Pain*, 2006

What is recommended for pain research?

- Document as much of the conditions surrounding the experimental protocol as possible.
 - Many psychosocial and environmental factors influence results in pain studies, and some effects are likely to vary based on subject sex/gender and other situational variables.



Pain 112 (2004) 142–147

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The effects of experimenter characteristics on pain reports in women and men

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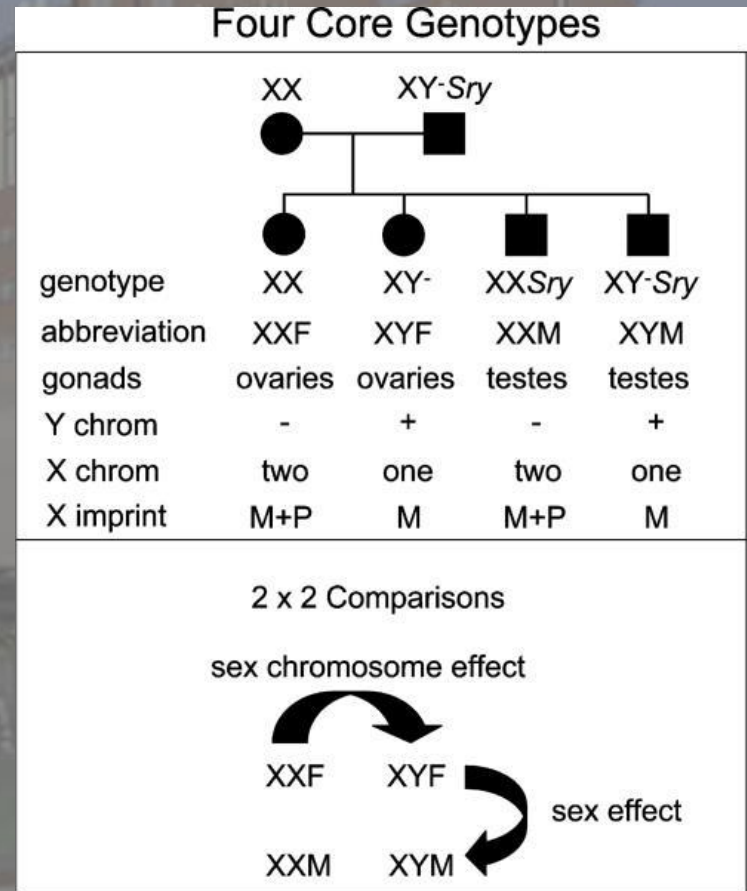
Current and Future Research Directions

- What are the hormonal vs. genetic (sex chromosome) contributions to sex differences in pain or analgesia?

Sex differences

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Gonadal hormone effects



Arnold and Chen, 2009,
Frontiers in Endocrinology

Current and Future Research Directions

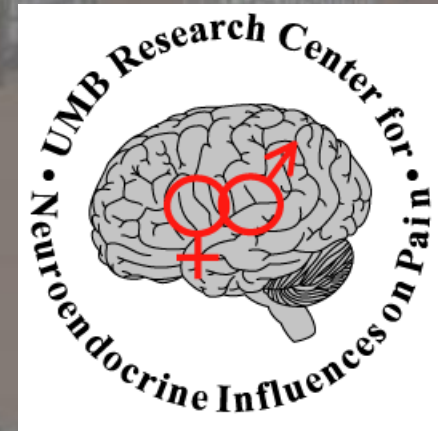
- How do psychological and experiential factors such as stress, mood, and conditioning (expectation) contribute to sex differences in pain/analgesia?
- How do sex differences in pain/analgesia change over the lifespan?
- Should diagnostic criteria for certain pain-related conditions differ by sex?

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Thank you for your attention!