



Sex, Gender and Pain

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Sex Prevalence of Painful Disorders

(Berkley, *Behav. Brain Sci.*, 1997)

fibromyalgia: :

TMD: :

arthritis (RA): :

migraine w/a: :

CRPS: :

IBS: :

Female Prevalence

migraine headache with aura
chronic tension headache
post-dural puncture headache
hemicrania continua
cervicogenic headache
tic douloureux
temporomandibular joint disorder
occipital neuralgia
periapical periodontitis & abscess
atypical odontalgia
burning tongue
carotidynia
chronic paroxysmal hemicrania
temporal arteritis
carpal tunnel syndrome
Raynaud's disease
chilblains
causalgia
reflex sympathetic dystrophy
hemicrania continua
chronic venous insufficiency
fibromyalgia syndrome
esophagitis
reflux esophagitis with peptic ulcer
slipping rib syndrome
twelfth rib syndrome
gallbladder disease
post-cholecystectomy syndrome
irritable bowel syndrome
interstitial cystitis
acute intermittent porphyria
proctalgia fugax
chronic constipation
pyriformis syndrome
peroneal muscular atrophy
multiple sclerosis
rheumatoid arthritis
pain of psychological origin

Male Prevalence

migraine without aura
cluster headache
post traumatic headache
SUNCT syndrome
Raeder's paratrigeminal syndrome
Pancoast tumor
thromboangiitis obliterans
brachial plexus avulsion
pancreatic disease
duodenal ulcer
abdominal migraine
lateral femoral cutaneous neuropathy
post herpetic neuralgia
hemophilic arthropathy
ankylosing spondylitis

No Sex Prevalence

acute tension headache
cluster-tic syndrome
"jabs" and "jolts" syndrome
secondary trigeminal neuralgia
neuralgia of nervus intermedius
painful ophthalmoplegia
maxillary sinusitis
toothache due to dentinoenamel defects
toothache due to pulpitis
cracked tooth syndrome
dry socket
vagus nerve neuralgia
stylohyoid process syndrome
thoracic outlet syndrome
brachial plexus tumors
esophageal motility disorders
chronic gastric ulcer
Chron's disease
diverticular disease of colon
carcinoma of the colon
familial Mediterranean fever
hereditary coproporphyria
acute herpes zoster
burns

Age Dependent Sex Differences

Female Prevalence	Male Prevalence
gout (after age 60)	gout (before age 60)
osteoarthritis (after age 45)	osteoarthritis (before age 45)
livedo reticularis (after age 40)	coronary artery disease (before age 65)
	erythromelalgia (over age 50)

Basic Scientists Ignore Epidemiology



55-year old female human

vs.



8-week old male Sprague Dawley rat

Male Rodents are *Overwhelmingly* the Subjects of Basic Science Studies of Pain

Mogil & Chanda, *Pain*, 2005

Table 1

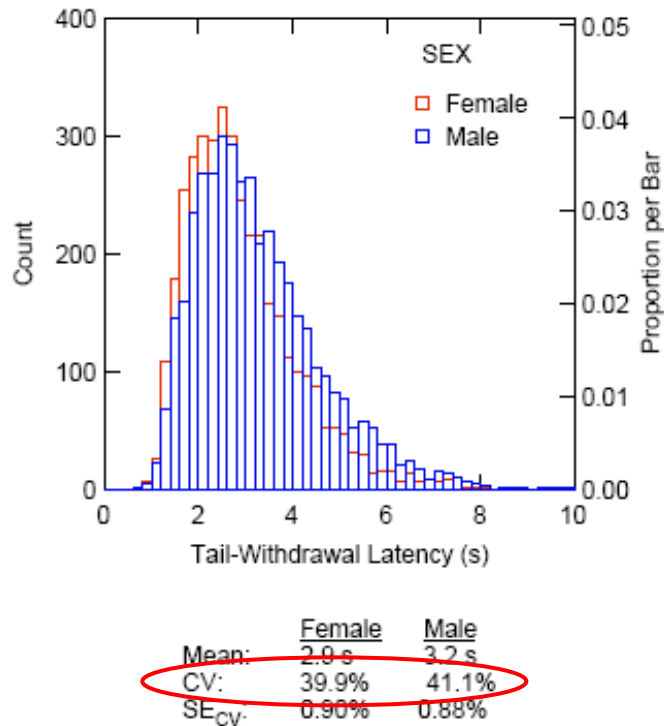
Year	# Studies ^a	♂ Only	♀ Only	♂ + ♀ No disc. ^b	♂ + ♀ No diff. ^c	♂ + ♀ Diff. ^d	N.r.
1996	45	36	5	2	1	0	1
1997	48	41	2	2	0	2	1
1998	52	36	9	4	1	1	1
1999	70	60	5	4	0	0	1
2000	68	56	5	4	0	2	1
2001	61	50	2	3	1	2	3
2002	64	51	4	0	2	2	5
2003	56	44	4	0	0	4	4
2004	46	35	4	5	1	1	0
2005 ^e	30	19	2	3	1	4	1
TOTAL	540	428 (79%)	42 (8%)	27 (5%)	7 (1%)	18 (3%)	18 (3%)

**“Sex differences are to be enjoyed,
not to be studied!”** *Dr. Przemyslaw Marek, 1992*

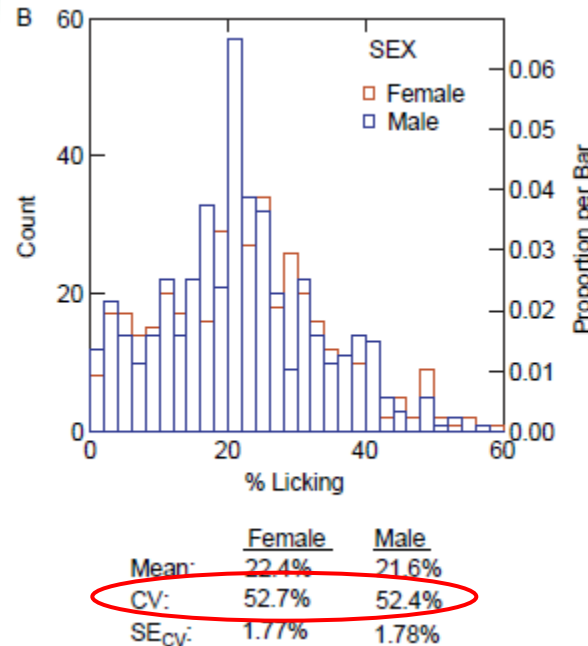
Q. Are Female Pain Data *Really* More Variable?

A. NO

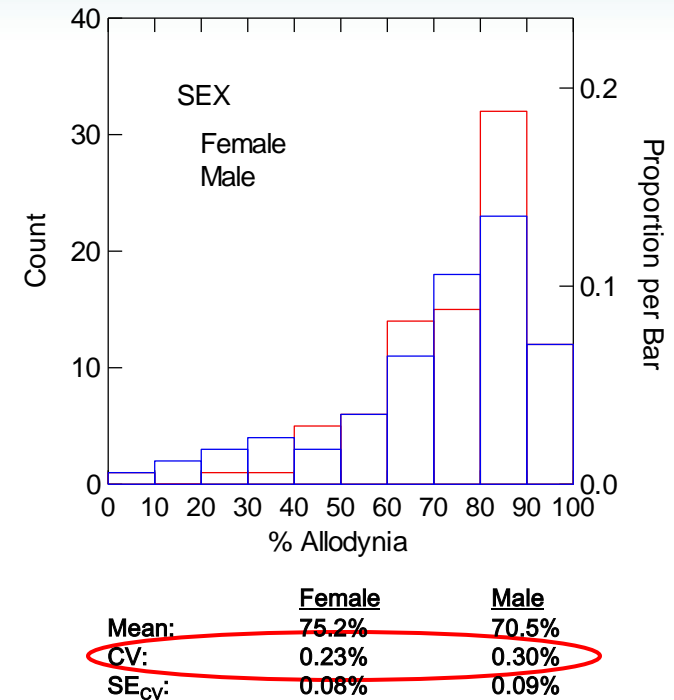
49°C Tail-Withdrawal Test



Formalin Test (Late Phase)



SNI Mechanical Allodynia

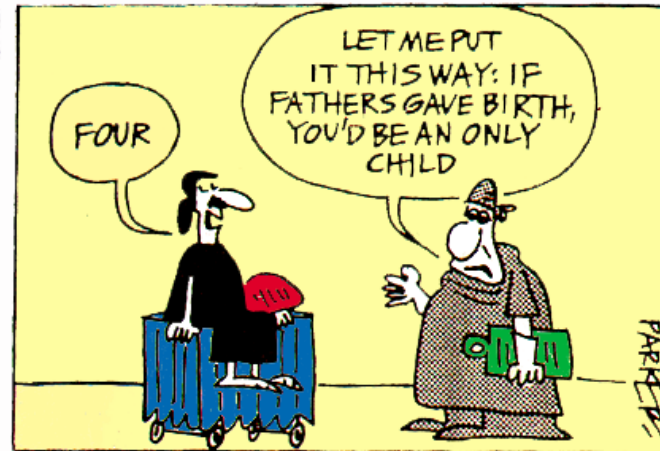
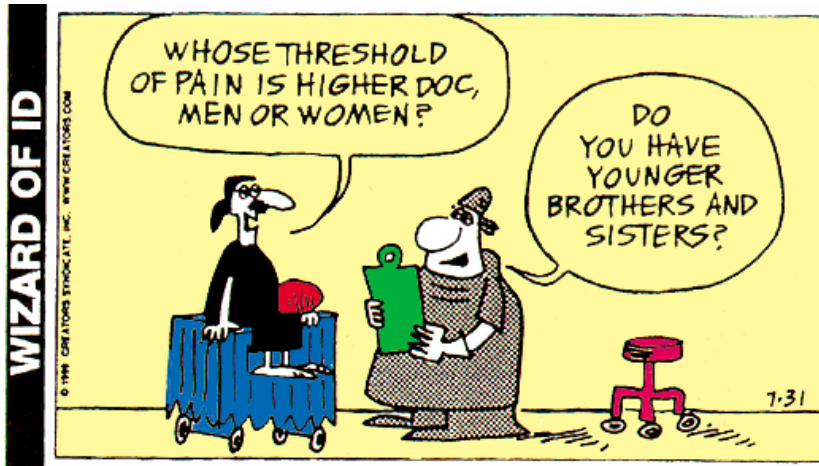


Mogil & Chanda, *Pain*, 2005 (and unpublished data)

Sex Differences in Pain Sensitivity?



VS.



OR



So Who's More Sensitive to Pain?

- **FEMALES:** when differences are reported, they are virtually always in the same direction
- **BUT,** it depends on the type of pain and the dependent measure (Riley III et al., 1998)
- **BUT,** “...deduction from known biological sex differences suggests that there are **powerful sex differences in the operation of pain mechanisms.**” (Berkley, 1997)



Males and Females Have Different Brains?!

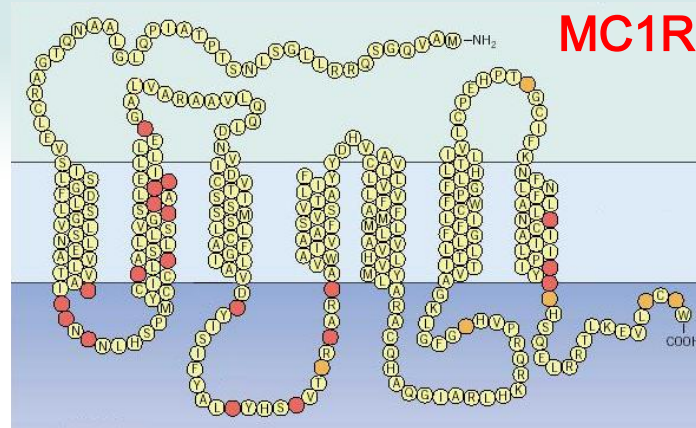


A radical hypothesis:

Males and females have *qualitatively* different (i.e., neurochemically and genetically distinct) pain processing mechanisms.

..... = μ -receptor - aspartate receptor
..... = melanocortin receptor

Female-Specific Involvement of Melanocortin-1 Receptors in κ -Opioid (Pentazocine) Analgesia in Humans



Study Design

- 24 men; 19 women
- 22 redheads; 21 non-redheads
- test all for *pentazocine* analgesia against pain
- all subjects had their *MC1R* gene sequenced

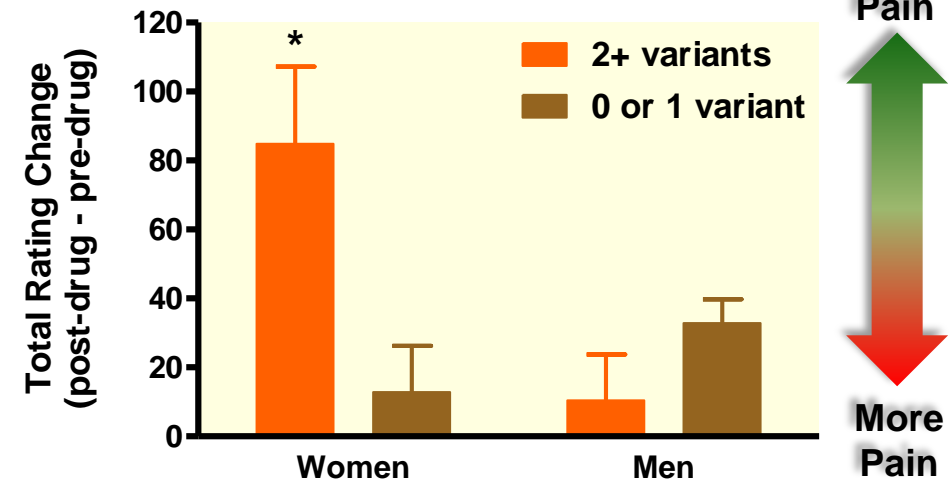
0-1 variants

2+ variants



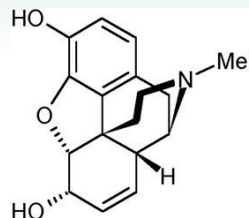
Mogil et al.,
Proc. Natl. Acad. Sci., USA, 2003

Pentazocine Analgesia



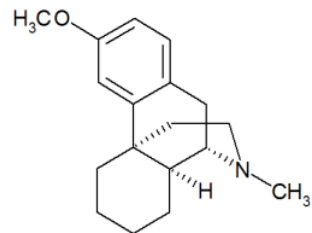
The Price of Ignoring Sex Differences: The Story of Morphidex[®]

Morphidex[®]



Morphine

+

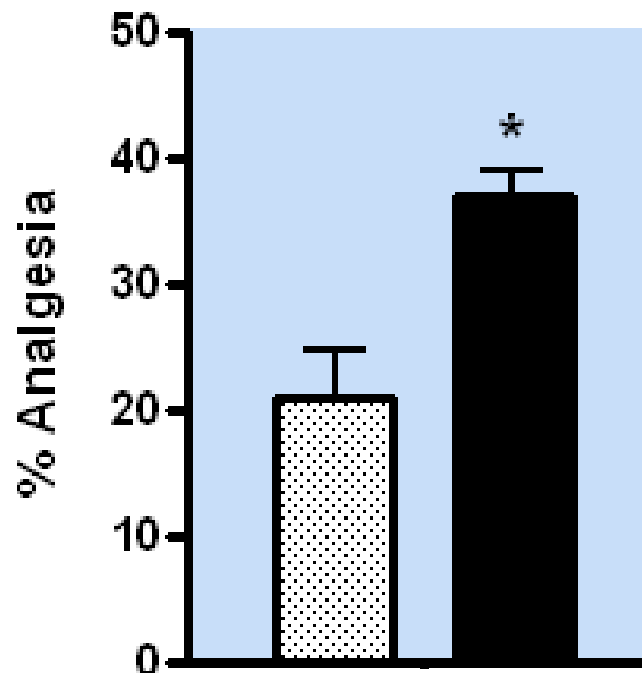


Dextromethorphan
(DXMP)

Less
Pain



More
Pain



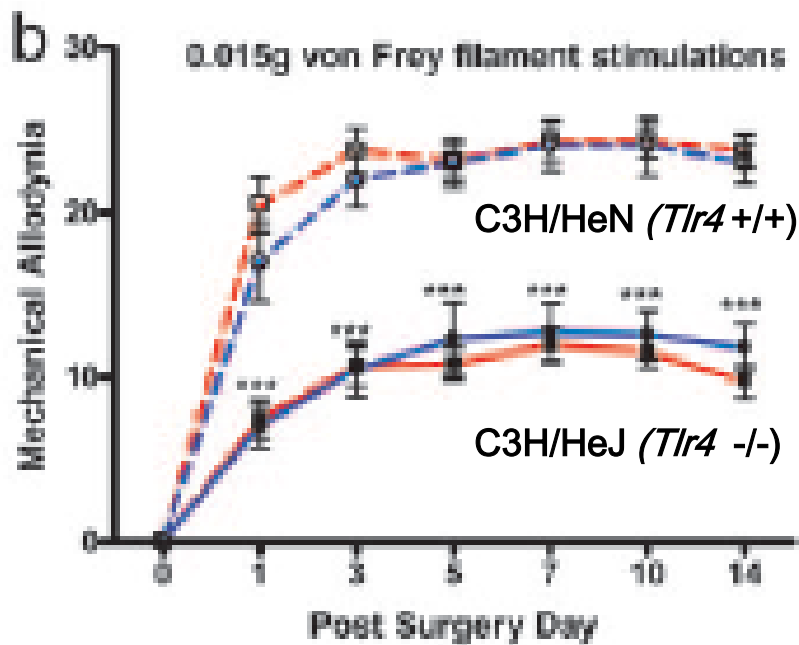
 Morphine Only
 Morphine + DXMP

Nemmani et al., *Pain*, 2004

Sex-Specific Effect of *Tlr4* (Toll-like receptor 4) Genetic Dysfunction on Neuropathic Mechanical Allodynia

PNAS The CNS role of Toll-like receptor 4 in innate neuroimmunity and painful neuropathy

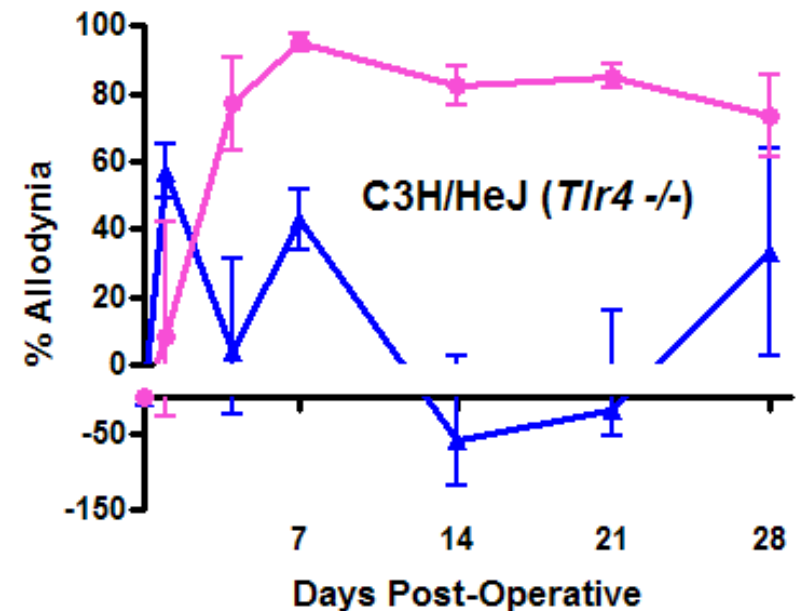
Florent Y. Tanga^{*,†}, Nancy Nutile-McMenemy^{*,‡}, and Joyce A. DeLeo^{*,†,§}



More Pain

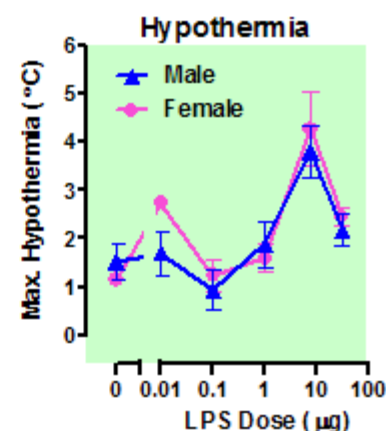
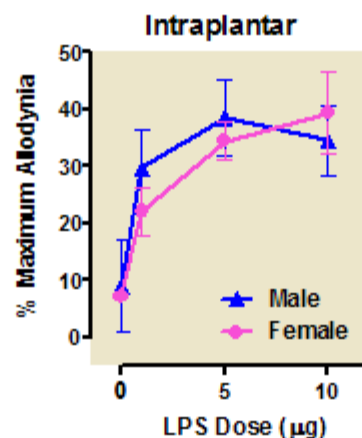
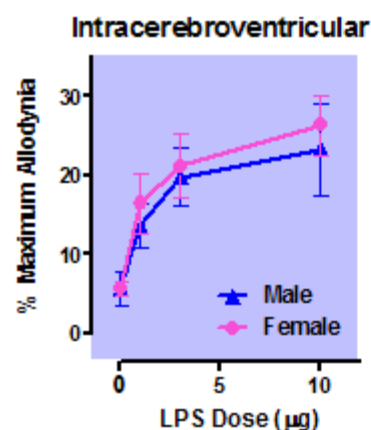
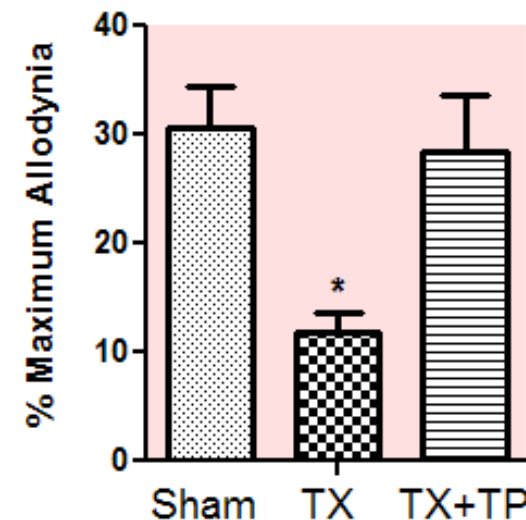
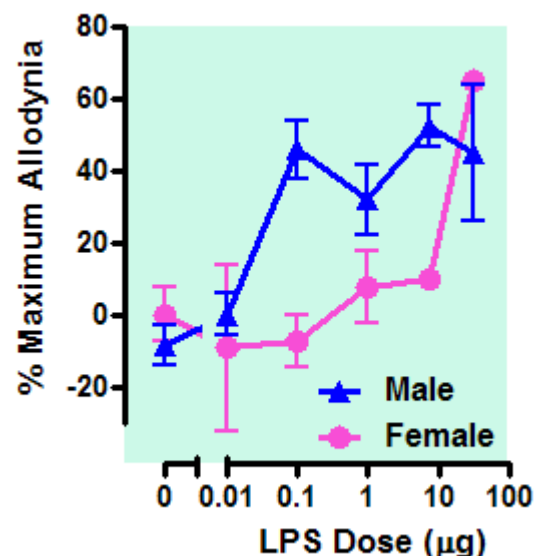
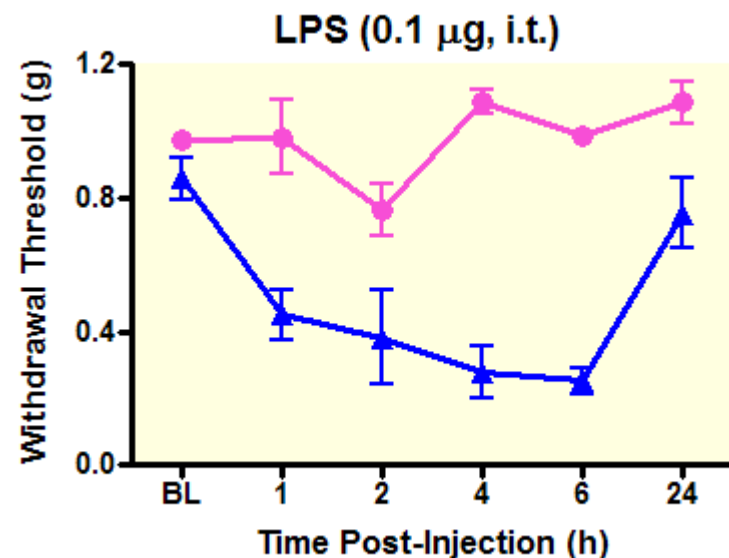


Less Pain



Sorge et al., unpublished

Male-Specific and Testosterone-Dependent Involvement of *Spinal* TLR4 in Chronic Pain



Sorge et al.,
unpublished

Thanks to...

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