Pain Begets Pain:
Modeling Chronic Overlapping Pain Conditions
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11th Annual Pain Consortium Symposium
Advances in Pain Research: Innovative Methods and Models
May 31-June 1, 2016
NIH, Bethesda, MD
**Chronic Overlapping Pain Conditions** comprise pain illnesses that exist in the absence of organic, systemic or metabolic disease that are likely to explain the symptoms. The currently recognized examples of COPCs include:

- Irritable bowel syndrome
- Temporomandibular disorder
- Chronic low back pain
- Chronic tension-type and migraine headache
- Endometriosis
- Fibromyalgia
- Myalgic encephalomyelitis/chronic fatigue syndrome
- Painful bladder syndrome/Interstitial cystitis
- Vulvodynia

It was previously thought these were individual conditions with distinct peripheral mechanisms at each affected body site. Current thinking has shifted, focusing on conditions sharing altered neural, immune and endocrine mechanisms and that dysregulation of “normal” CNS function is associated with pain hypersensitivity.

*(2015 White Paper on COPCs, Chronic Pain Research Alliance)*
• Most of these chronic pain conditions are more prevalent or exclusive in women;
• Many symptoms, including pain, are exacerbated by stress;
• Stress/depression/anxiety are comorbid with pain;
• If you have one condition, there is a high likelihood you have multiple conditions.

Table 2. Number of Medical Journal Articles Published on Various Combinations of COPCs Between January 2013 and December 2014

A total of 804 (482 non-duplicate) medical journal articles were published in this time period. Most common were publications on the relationship between ME/CFS and FM (128 articles), IBS and FM (74 articles), migraine and TMD (66 articles) and ME/CFS and IBS (58 articles).

<table>
<thead>
<tr>
<th>Condition</th>
<th>ENDO</th>
<th>FM</th>
<th>IBS</th>
<th>IC/PBS</th>
<th>Migraine</th>
<th>cTTH</th>
<th>Vulvodynia</th>
<th>cLBP</th>
<th>TMD</th>
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<td>ME/CFS</td>
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</table>

US prevalence (in millions) | F:M ratio
< 4 | ---
6.3 | 6:1
6 | 2:1
44 | 9:1
8 | 2-3:1
7 | 2:1
6 | ---
19.5 | 1.5:1, 8:1 (care seeking)

Note: ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome; ENDO: endometriosis; FM: fibromyalgia; IBS: irritable bowel syndrome; IC/PBS: interstitial cystitis/ painful bladder syndrome; cTTH: chronic tension type headache; cLBP: chronic low back pain; TMD: temporomandibular disorders

(2015 White Paper on COPCs, Chronic Pain Research Alliance)
Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain/visceral hypersensitivity is a defining characteristic.
- It affects 10-20% of adults worldwide.
- Female:male ratio: 2-3:1.
- Peak prevalence between 20-50 years old.

Temporomandibular disorders (TMD) comprise a subset of orofacial musculoskeletal disorders inducing pain and tenderness in the temporomandibular joint and muscles of mastication.
- It affects 10-15% of the population; 50% are muscle related.
- Female:male ratio: 2-3:1 in the community setting.
- Prevalence peaks during reproductive years.

Hi comorbidity: >60% of patients with TMD report symptoms consistent with IBS, highlighting the fact that chronic pain conditions tend to occur in clusters, complicating pain management.

This can be studied mechanistically in animals
A Clinically Relevant Model of Overlapping Pain Conditions in Animals

TMD

Orofacial Pain
CFA, CCI

stress

stress: forced swim

Stress: forced swim

IBS

de novo visceral hypersensitivity

80 mmHg CRD

VMR

baseline

6 days post stress
Stressing an animal *in pain* induces chronic visceral hypersensitivity.

**Figure:**
- **VMR (normalized to baseline):**
  - Days post FS: 0, 2, 6, 10, 18, 26, 34, 42
  - Graphs show the magnitude of VMR over time for different conditions:
    - E2+saline+FS
    - E2+cfa+FS
    - oil+cfa+FS

**Injury following stress is the same as stress alone:**
- Graphs show the magnitude of VMR over time for different conditions:
  - Stress
  - Stress then inflammation

**Mean AUC:**
- Days post FS: 0, 2, 6, 10, 18
- Bar graph showing mean AUC for different conditions.

*Traub et al., 2014*
Mechanosensitivity indicates referred pain in comorbid pain model

Back - referred pain

forepaw

Masseter Muscle--TMD

Threshold (% baseline)

Withdrawals (% baseline)

Days post FS

Days post CFA

E2+cfa+FS
E2+saline+FS
oil+cfa+FS
Stress in the presence of pain induces chronic visceral hypersensitivity.

Stress alone or injury following stress induces a transient visceral hypersensitivity.

The chronic visceral hypersensitivity is estrogen dependent.

There is a concomitant referred mechanical hyperalgesia, but not a whole body increase in mechanosensitivity.

This is a unique animal model of comorbid hypersensitivity that allows examination of mechanisms underlying comorbidity between TMD and IBS.
Features common to IBS and TMD

1. Greater prevalence in women

Visceral pain and orofacial pain are greater in female rats compared to males.

Medullary dorsal horn neurons:

- Tashiro et al., 2007
- Ji et al., 2012
2. The level of pain fluctuates during the menstrual cycle

GI and Orofacial pain fluctuates across the estrous cycle in rats, and is estrogen dependent.

Ji et al., 2008

Distention pressure (mmHg)

Traub and Ji, 2013

Wu et al., 2010
3. Clinically, hypersensitivity may be triggered or exacerbated by stress.

**Stress modulates the response to visceral pain and gonadal hormones modulate the response to stress.**

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**Graphs and Figures:**

- **Bars for Magnitude of VMR:**
  - Intact female and male
  - Control, intact, T, OVx, E2, GDx
  - Stress conditions

- **Graph for Days post stress:**
  - Intact female
  - Intact male
  - Stress conditions

- **Plots for Testosterone and Estradiol**
  - Control, intact, E2, GDx

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References:

Ji et al., 2015
Are Stress-induced pain and Comorbid pain the same?
### Differential gene expression at 1 week

<table>
<thead>
<tr>
<th>FDR</th>
<th>P-value</th>
<th>Read-count-perc.</th>
<th>LFC (UP)</th>
<th>LFC (DOWN)</th>
<th>Sample</th>
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<th>DOWN</th>
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**Note:**
- **FDR**: False Discovery Rate
- **P-value**: Probability value
- **Read-count-perc.**: Read-count percentile
- **LFC (UP)**: Logfold change (UP)
- **LFC (DOWN)**: Logfold change (DOWN)
- **Sample**: Sample description
Are Stress-induced pain and Comorbid pain the same?

**Diagram:**
- **Stress** → **CNS** → **PAIN**
- **HPA** → **Immune cells** → **CRF**
- **Astressin** → **Mast Cells** → **Colon**
- **Sensory Afferents** → **Enteric neurons**
- **Alteration in colonic function**

**Graphs:**
- **Stress + astressin**
  - % baseline VMR over weeks:
    - Sal + stress
    - Ast + stress

- **Comorbid + astressin**
  - % baseline VMR over weeks:
    - Sal + comorbid
    - Ast + comorbid
Blocking peripheral sensitization blocks comorbid hypersensitivity

Colonic mast cells

PAIN

STRESS

CNS

Sympathetic NS

Sensory Afferents

Altered colonic function

HPA

Immune cells

CRF

Afferents

Enteric neurons

Mast Cells

Colon

VMR (%baseline)

Days post FS

baseline 2 10 18 26

DSCG

saline

% degranulated mast cells

naive CFA+FS

**

*
Sex difference in comorbid visceral hypersensitivity

Magnitude of VMR

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<th>Baseline</th>
<th>1w</th>
<th>2w</th>
<th>3w</th>
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<td>Female##</td>
<td></td>
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Comorbid pain

EF50 (g)

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<tr>
<th>After Forced Swim</th>
<th>Baseline</th>
<th>CCI 10/day</th>
<th>1 day</th>
<th>3 day</th>
<th>5 day</th>
<th>7 day</th>
<th>9 day</th>
<th>11 day</th>
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<tr>
<td>CCI n=6 Male</td>
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</table>

After Forced Swim

| CCI+ SWIM n=6 Female|          |            | **    | **    | **    | **    |        |        |
| CCI n=6 Female     |          |            |       |       |       |       |        |        |
Referred pain is centrally mediated.

![Graph showing the number of withdrawals vs. force (g) with three conditions: baseline, CFA+FS, and post lidocaine. The graph includes error bars for each condition.](image1)

**Cumulative withdrawals histogram**

- Baseline: 10
- CFA + FS: 20
- Lido + CFA FS: 15

**Magnitude VMR**

- Baseline: 40 mmHg CRD
- Post lidocaine: 80 mmHg CRD

**Legend:**

- Green triangle: post lidocaine
- Red square: CFA + FS
- Black circle: baseline
Pain and stress activate descending facilitation through spinal 5-HT3R

Pain

Stress

???

RVM

Spinal cord

Depletion of 5-HT in the RVM by shRNA

Intrathecal 5-HT3 receptor antagonist

Depletion of 5-HT in the RVM by shRNA

Force (g)

# withdrawals

1 3 5 6 7 10 15 23 61 111 201
Retrograde tracing reveals Dorsomedial Hypothalamic → RVM neurons

Fluorogold in the RVM

Retrogradely labeled neurons in the hypothalamus
Stress activates RVM projection neurons in the dorsomedial hypothalamus
Lidocaine in hypothalamic DMN attenuates comorbid hypersensitivity
Stress
Transient phase

Orofacial pain
Inflammation, nerve injury

Comorbid
Visceral
Hypersensitivity

Chronic phase

Stress

Amygdala
Hippocampus
Prefrontal cortex

Hypothalamus

RVM
5-HT

HPA axis
Sympathetic Nervous System

CRF
Mast cells
Colon

Descending facilitation via 5-HT3 receptor

Spinal Cord
Central Sensitization

Peripheral sensitization
Thanks to:

**UMB School of Dentistry**
- Yaping Ji
- Dong-Yuan Cao
- Jane Karpowicz
- Sangeeta Pandya
- Dean Dessem
- David Seminowicz
- Catherine Hubbard
- Joyce Teixeira da Silva
- Feng Wei
- Jiale Yang
- Robert Ernst
- Alison Scott
- Ohannes Melemedjian

**UMB School of Nursing**
- Susan Dorsey
- Cameron Lassiter

**Supported by:**

NIH:
- NIDCR
- NINDS
- NINR

Pilot study from the University of Maryland Organized Research Center on Persistent Pain
Estrogen-dependent visceral hypersensitivity following stress in rats: an fMRI study

Hubbard et al., In Press
Animal models can be used to examine several aspects of nociceptive processing.

The visceromotor response (VMR) and referred mechanical hypersensitivity to measure visceral pain

Drugs (i.t., s.c.)

Amplifier records EMG

Computer

Von Frey filaments to measure mechanical nociceptive threshold

Referred pain

Colorectal Distender Controller

Solenoid

Reservoir

N2

VMR

Distention pressure (mmHg)

Magnitude VMR

% escape responses

Withdrawal threshold (% baseline)

CFA/saline

Days post CFA

Traub et al., 2014

Baseline

Inflamed

***

0

20

40

60

80

20

40

60

80

0

20

40

60

80

0

20

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60

80

0

20

40

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60

80
E2 increases and T decreases stress-induced changes in spinal BDNF

BDNF in female LS

- Cholesterol
- Testosterone

BDNF in male LS

- M oil
- M E2

Spinal TrkB blockade attenuates stress-induced hypersensitivity in females

% baseline VMR

- FS
- TrkB-Fc+FS

* indicates statistical significance.