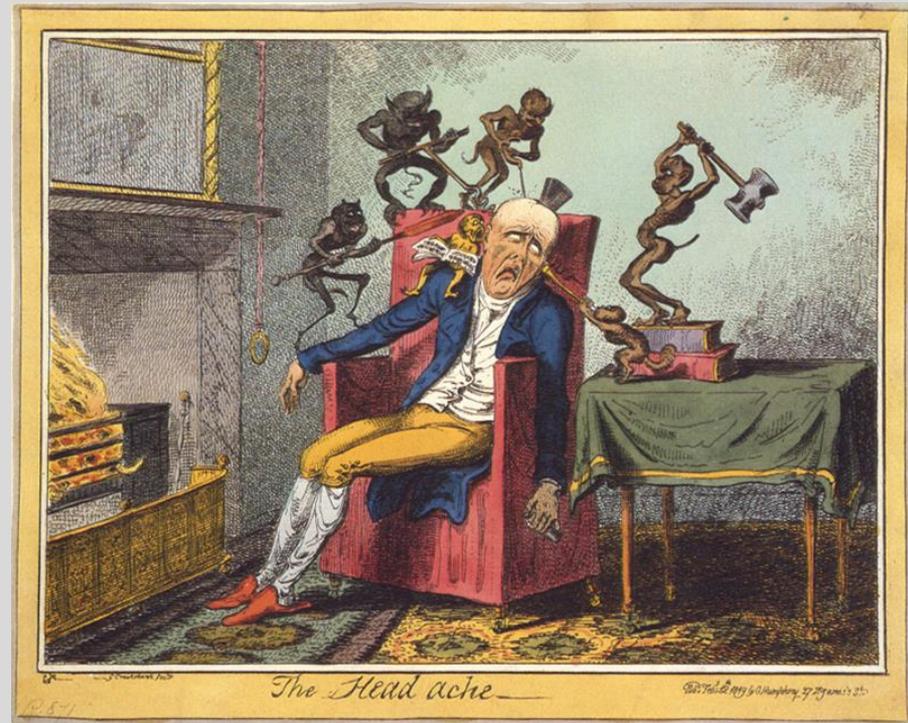


Pain Begets Pain: Modeling Chronic Overlapping Pain Conditions

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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).

	ENDO	FM	IBS	IC/PBS	Migraine	cTTH	Vulvodynia	cLBP	TMD	US prevalence (in millions)	F:M ratio
ME/CFS	9	128	58	23	15	2	6	3	6	< 4	
ENDO		13	16	18	8	1	10	8	2	6.3	---
FM			74	32	41	3	15	38	25	6	6:1
IBS				33	39	1	9	6	9	44	2:1
IC/PBS					7	0	10	1	4	8	9:1
Migraine						--	0	23	66	7	2-3:1
cTTH							0	5	20	7	2:1
Vulvodynia								1	4	6	---
cLBP									12	19.5	
TMD										35	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

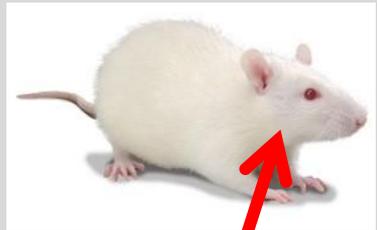
TMD



stress



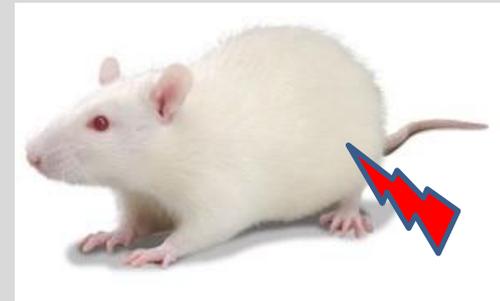
IBS



Orofacial Pain
CFA, CCI



Stress: forced swim



de novo visceral hypersensitivity

baseline



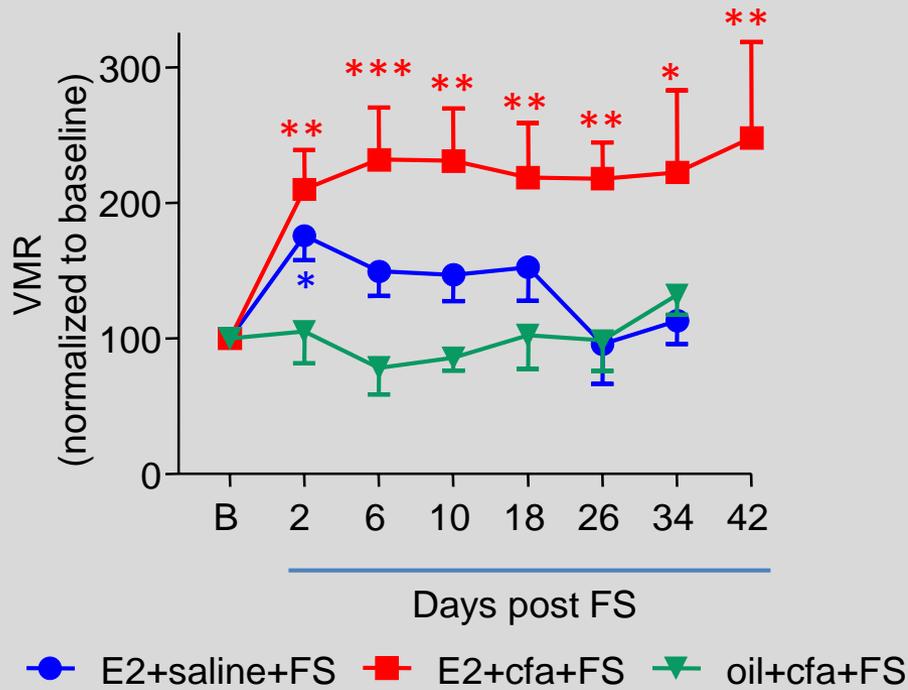
6 days
post stress



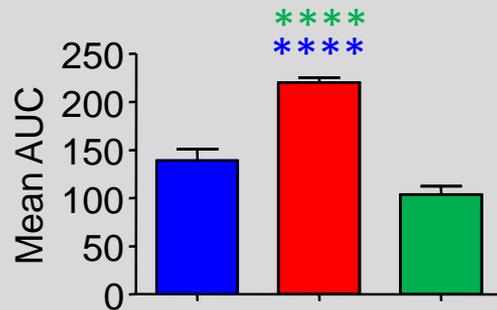
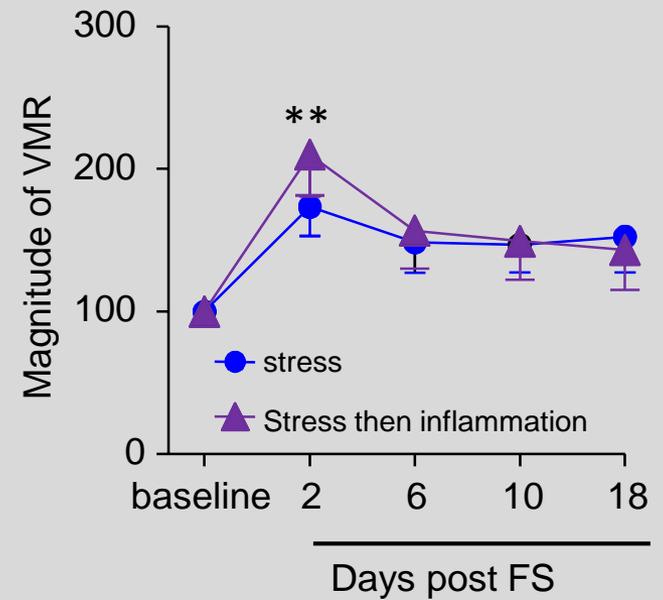
VMR

80 mmHg CRD

Stressing an animal *in pain* induces chronic visceral hypersensitivity

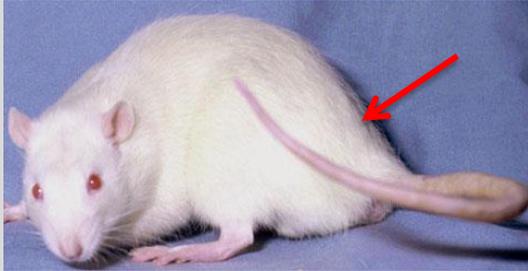


Injury following stress is the same as stress alone

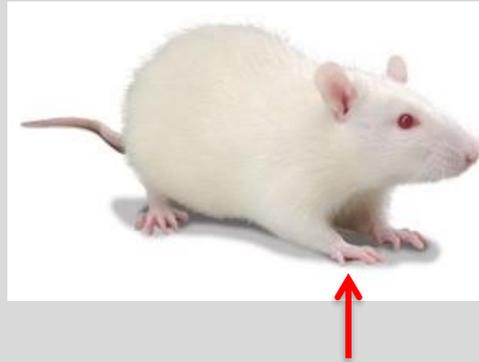


Mechanosensitivity indicates referred pain in comorbid pain model

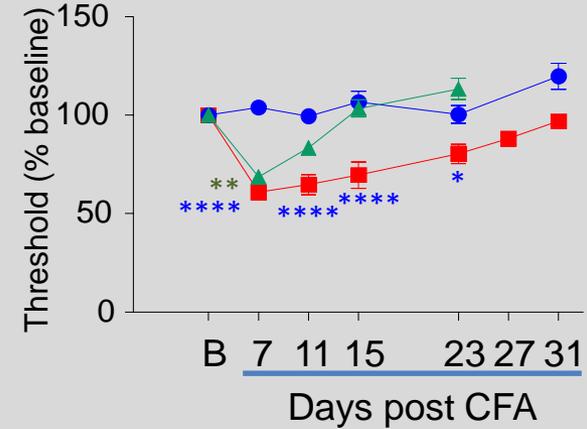
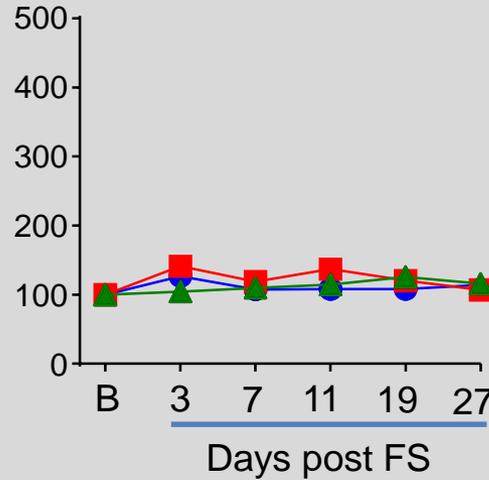
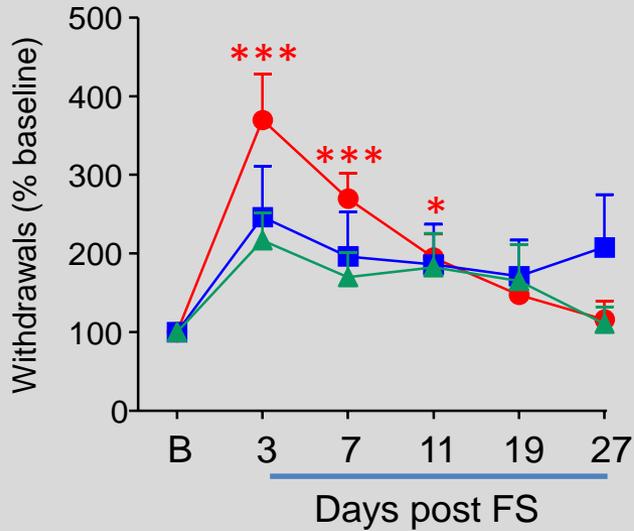
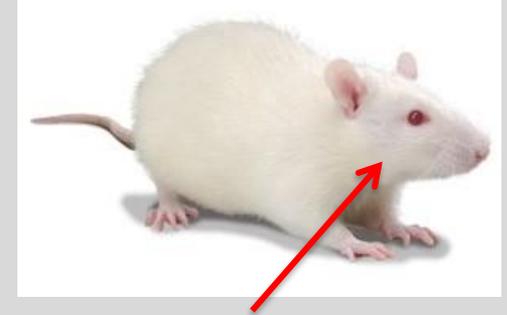
Back- referred pain



forepaw



Masseter Muscle--TMD



● 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.

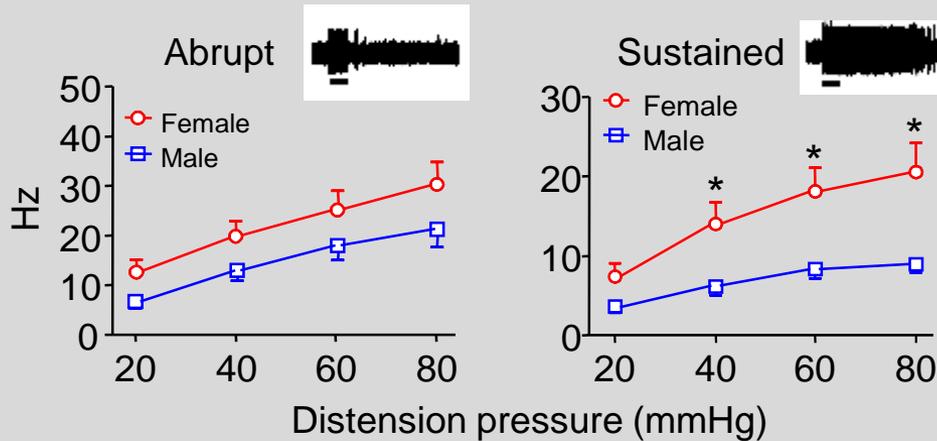
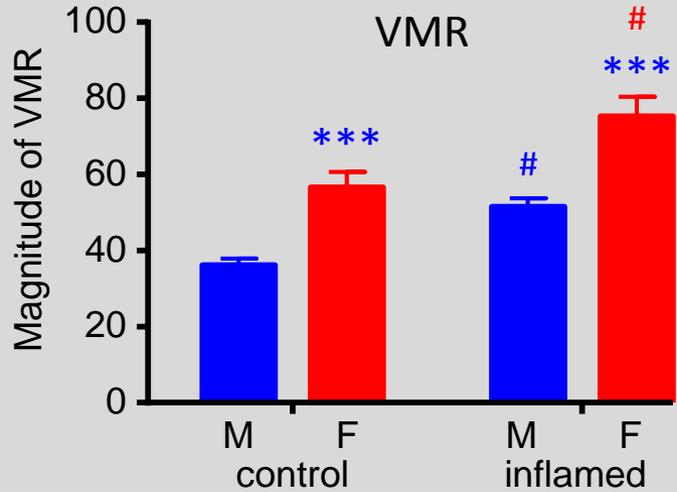
There is a concomitant referred mechanical hyperalgesia, but not a whole body increase in mechanosensitivity.

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

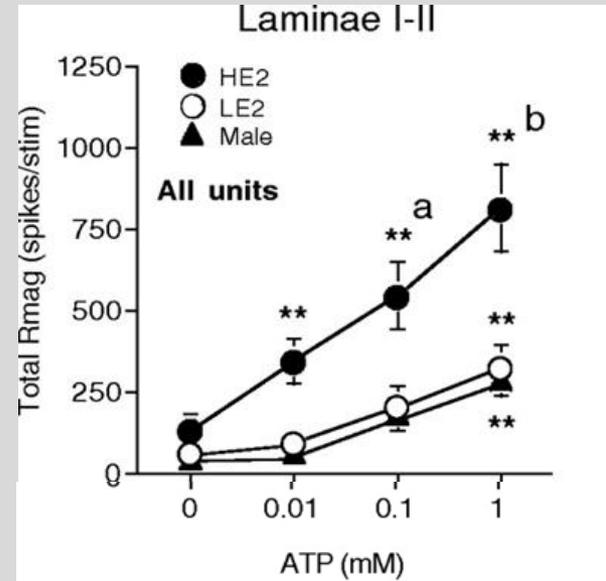
Features common to IBS and TMD

1. Greater prevalence in women

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



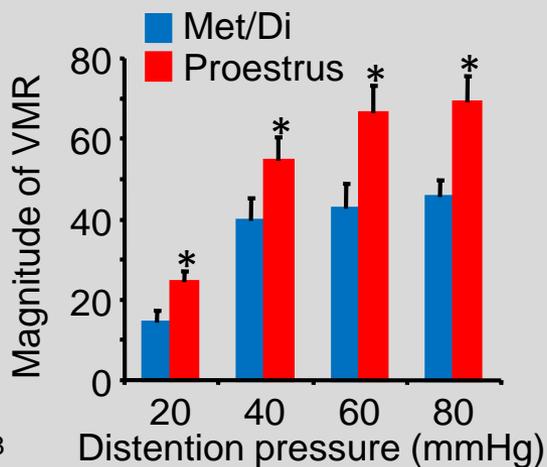
Medullary dorsal horn neurons:



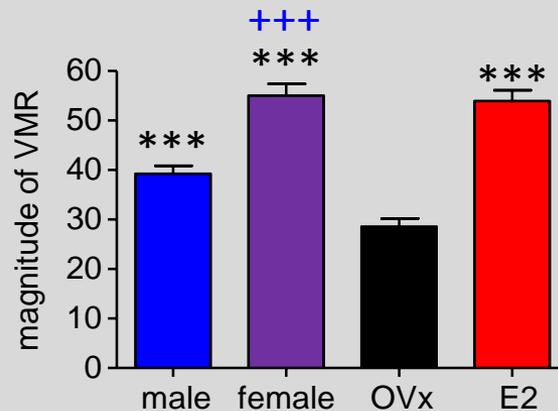
Tashiro et al., 2007

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

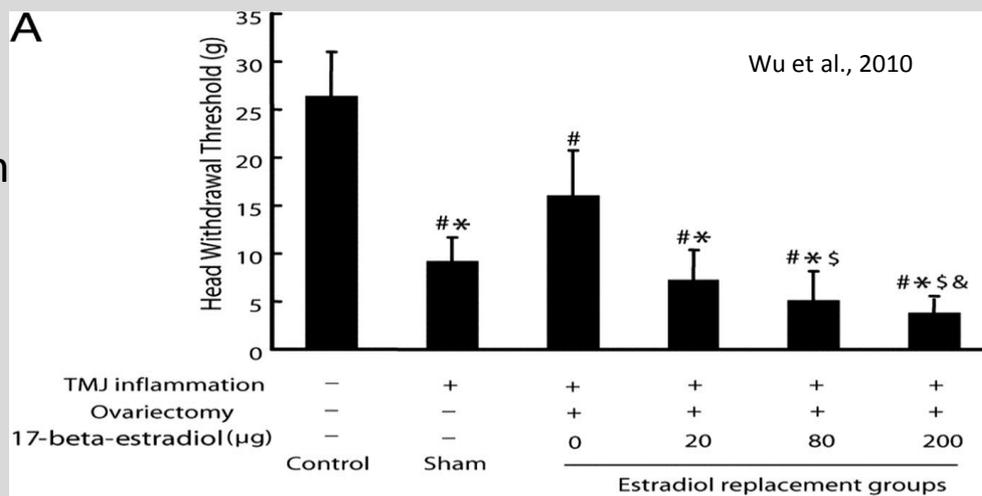


Ji et al., 2008



Traub and Ji, 2013

TMJ inflamm

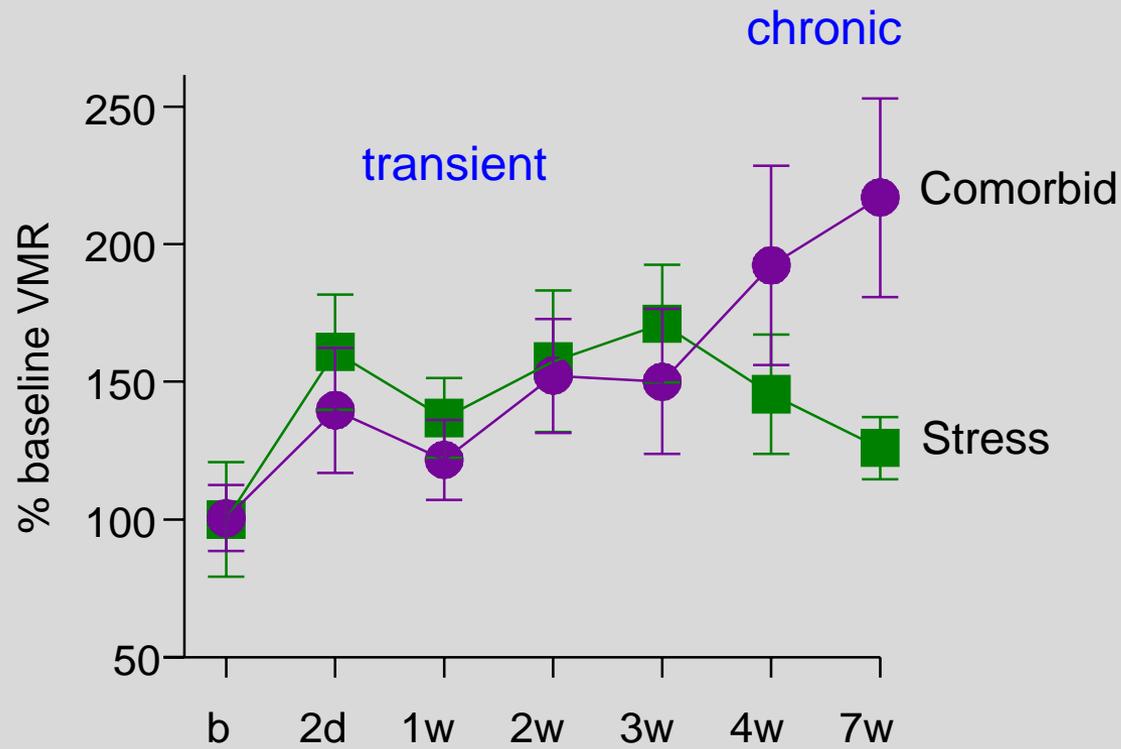


3. Clinically, hypersensitivity may be triggered or exacerbated by stress

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

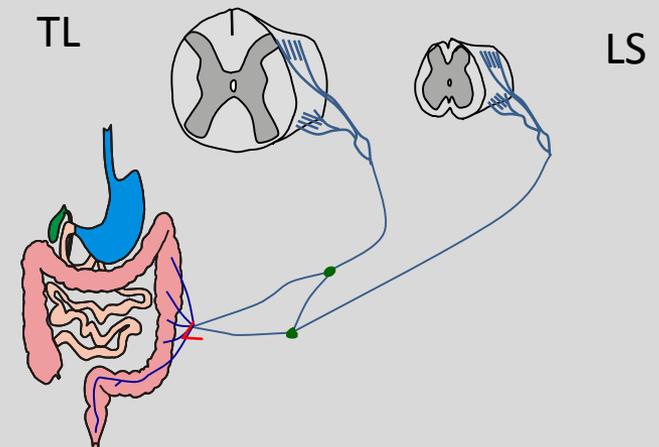
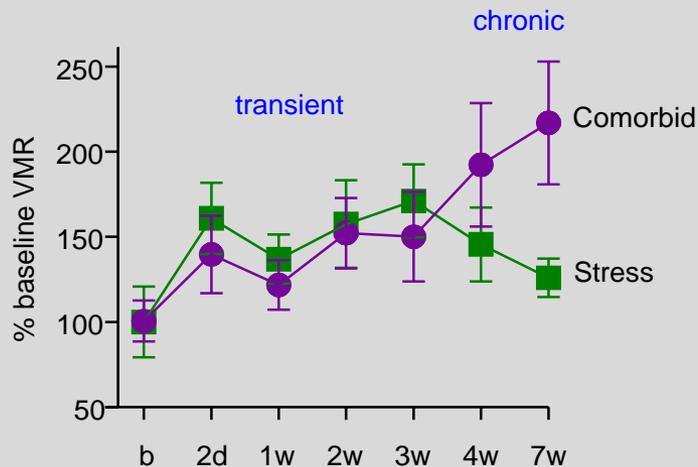


Are Stress-induced pain and Comorbid pain the same?

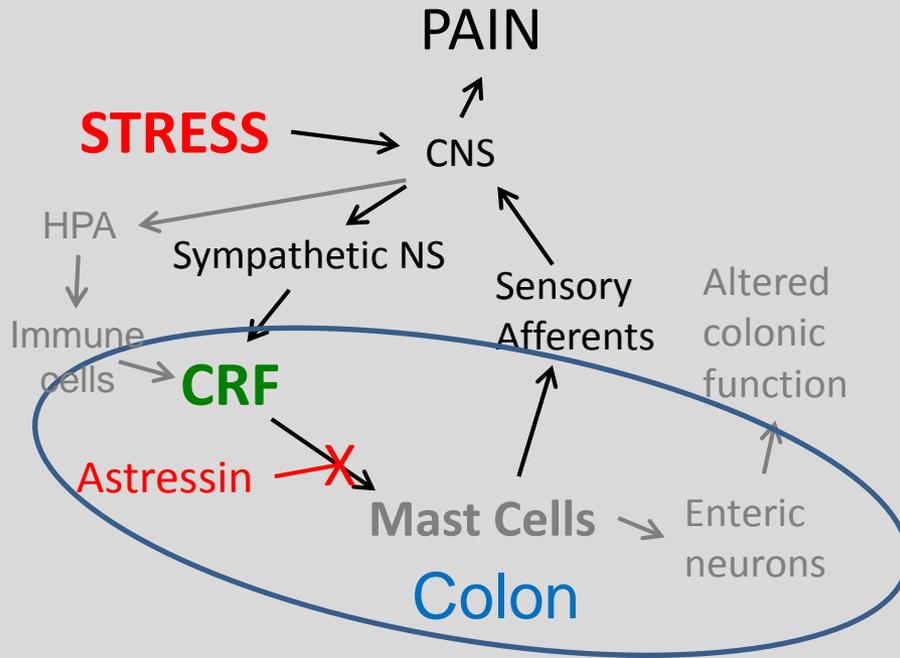


Differential gene expression at 1 week

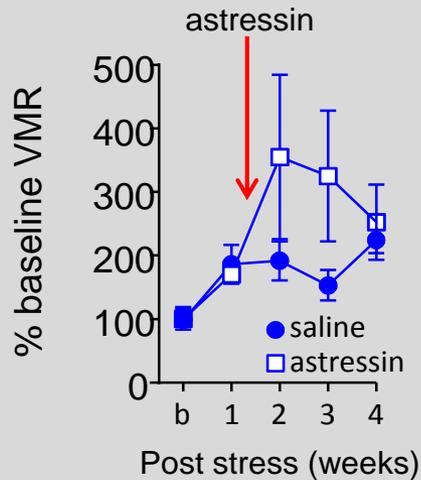
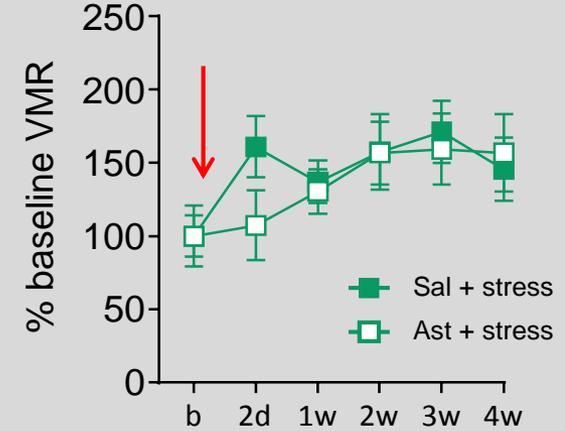
FDR	P-value	Read-count-percentile	LFC (UP)	LFC (DOWN)	Sample	UP	DOWN	Total
0.05	NA	0.1 (RC=0.46)	1	-1	LS_comorbid_vs_LS_naive_FDR	92	9	101
NA	0.05	0.1 (RC=0.46)	1	-1	LS_comorbid_vs_LS_naive_pvalue	189	54	243
0.05	NA	0.1 (RC=0.44)	1	-1	LS_comorbid_vs_LS_stress_FDR	117	8	125
NA	0.05	0.1 (RC=0.44)	1	-1	LS_comorbid_vs_LS_stress_pvalue	228	48	276
0.05	NA	0.1 (RC=0.46)	1	-1	LS_stress_vs_LS_naive_FDR	6	11	17
NA	0.05	0.1 (RC=0.46)	1	-1	LS_stress_vs_LS_naive_pvalue	58	78	136
0.05	NA	0.1 (RC=0.50)	1	-1	TL_comorbid_vs_TL_naive_FDR	64	272	336
NA	0.05	0.1 (RC=0.50)	1	-1	TL_comorbid_vs_TL_naive_pvalue	126	498	624
0.05	NA	0.1 (RC=0.54)	1	-1	TL_comorbid_vs_TL_stress_FDR	50	7	57
NA	0.05	0.1 (RC=0.54)	1	-1	TL_comorbid_vs_TL_stress_pvalue	134	59	193
0.05	NA	0.1 (RC=0.52)	1	-1	TL_stress_vs_TL_naive_FDR	14	169	183
NA	0.05	0.1 (RC=0.52)	1	-1	TL_stress_vs_TL_naive_pvalue	41	407	448



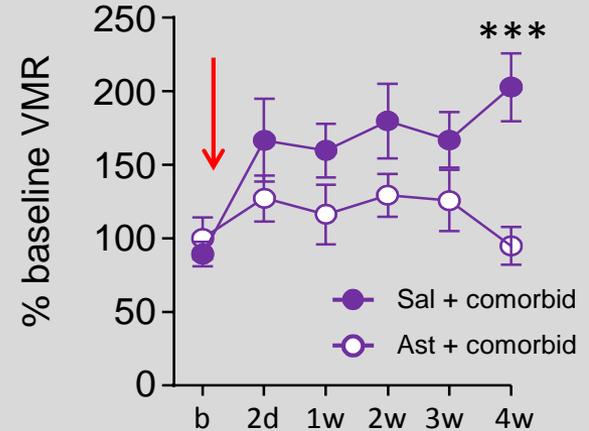
Are Stress-induced pain and Comorbid pain the same?



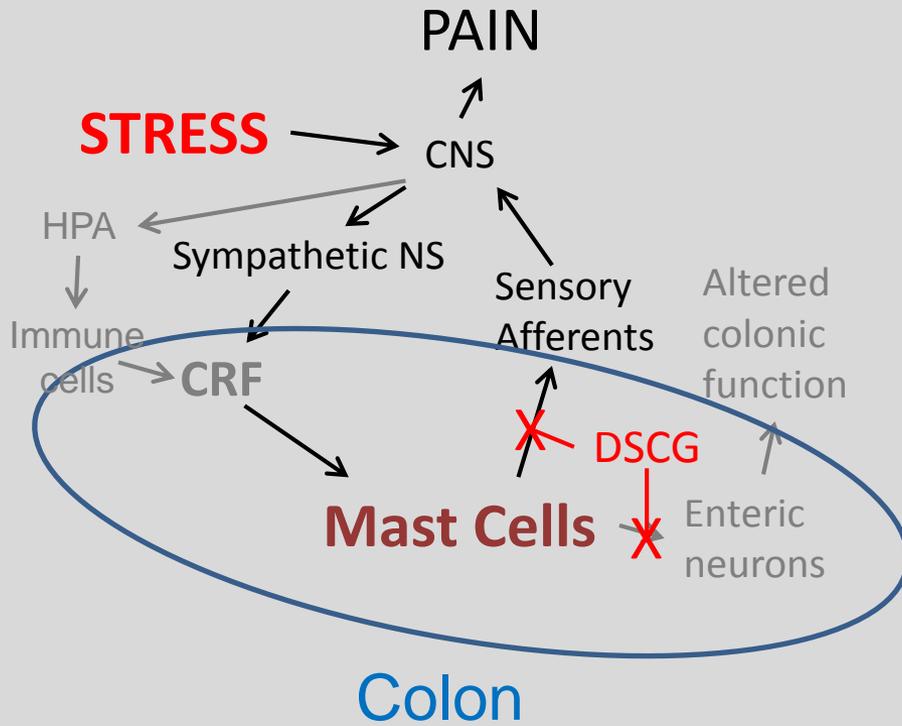
Stress + astressin



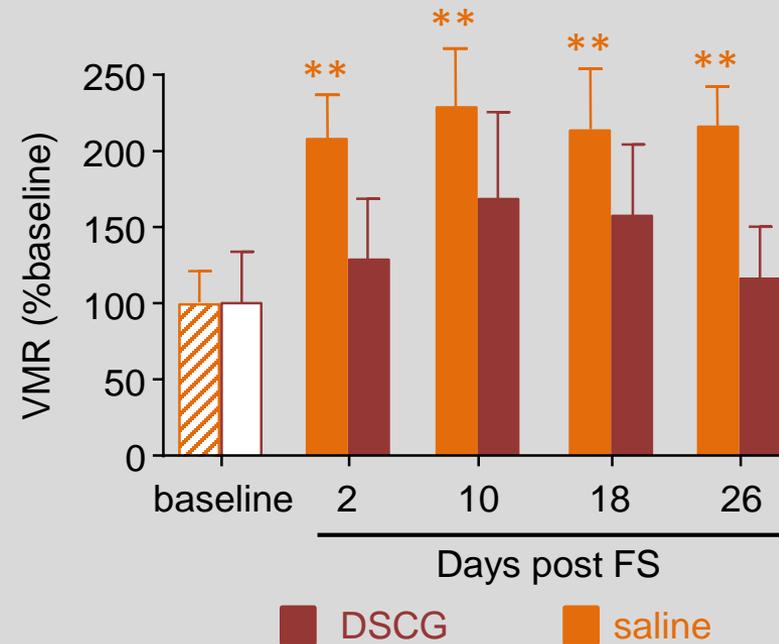
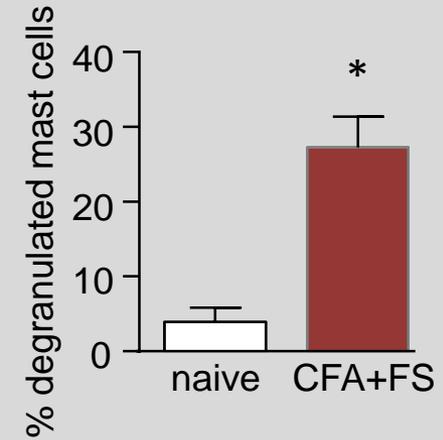
Comorbid + astressin



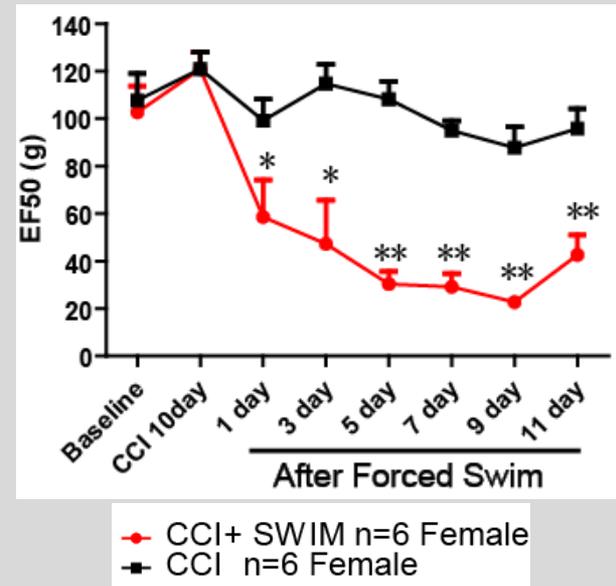
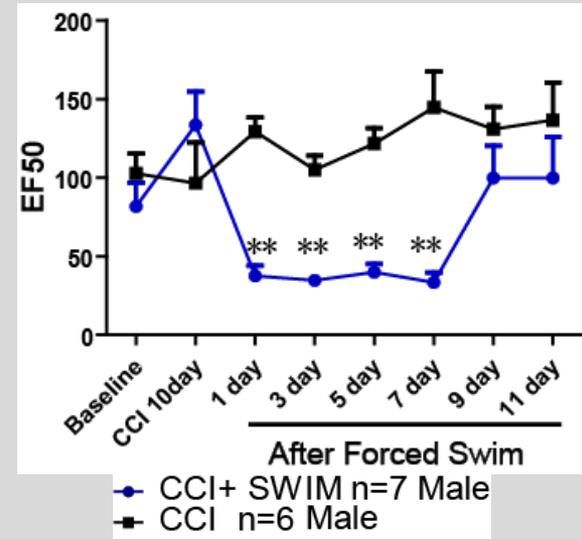
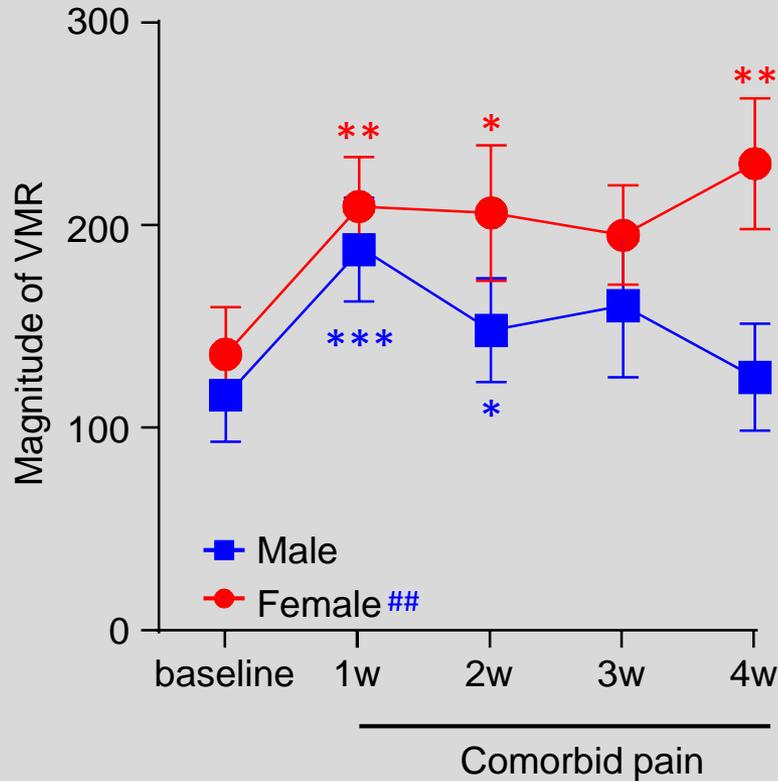
Blocking peripheral sensitization blocks comorbid hypersensitivity



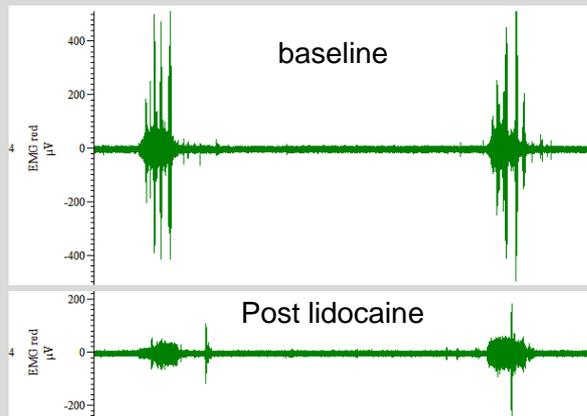
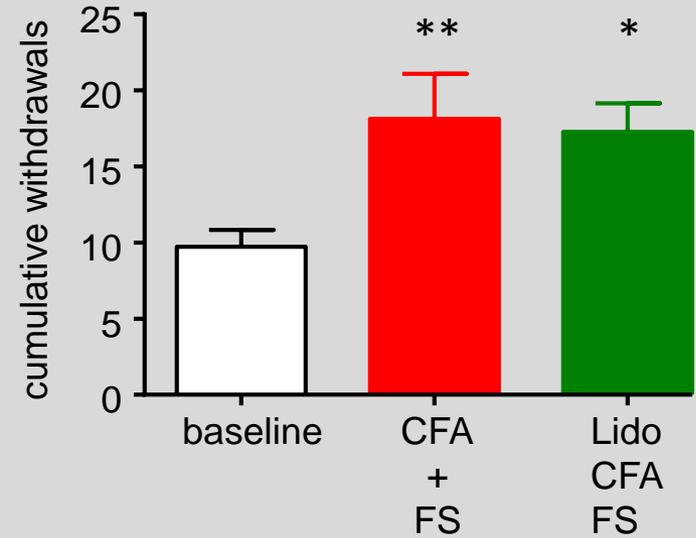
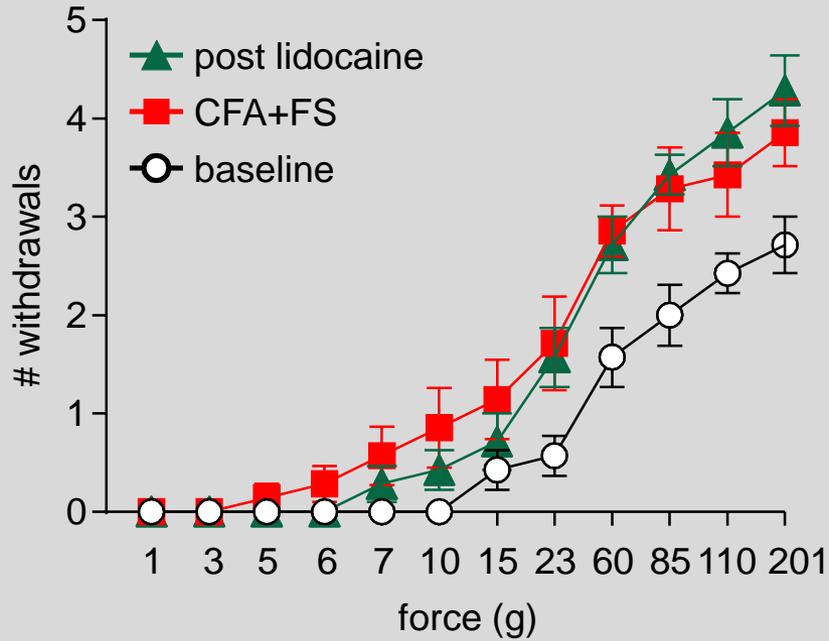
Colonic mast cells



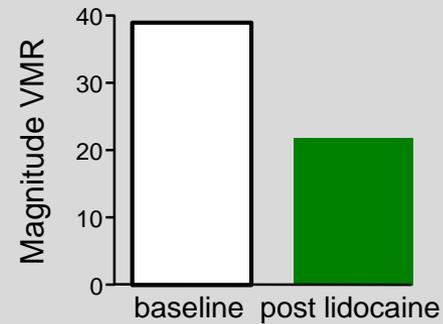
Sex difference in comorbid visceral hypersensitivity



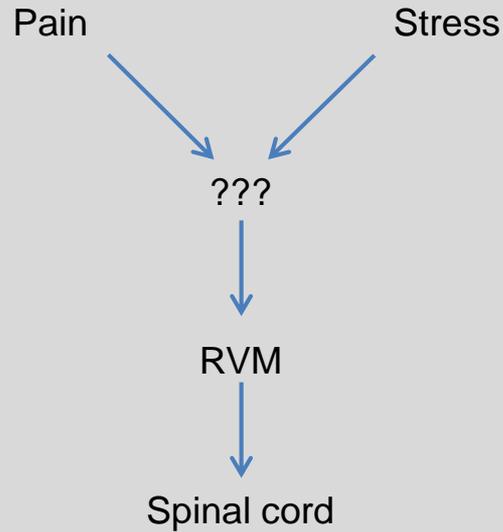
Referred pain is centrally mediated



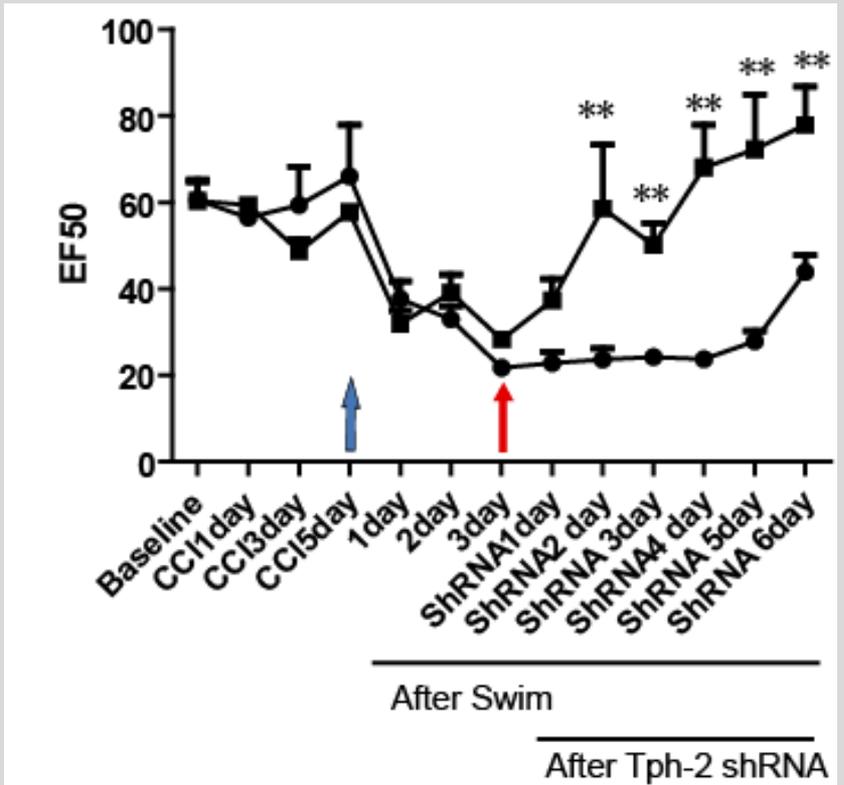
80 mmHg CRD



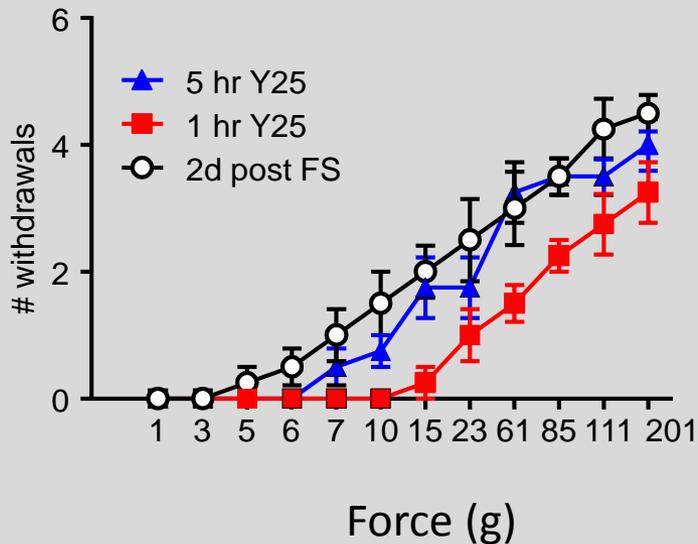
Pain and stress activate descending facilitation through spinal 5-HT₃R



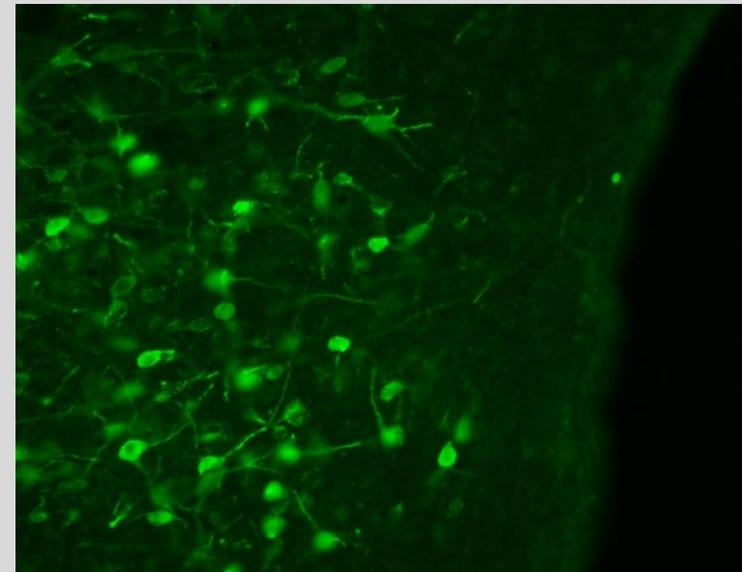
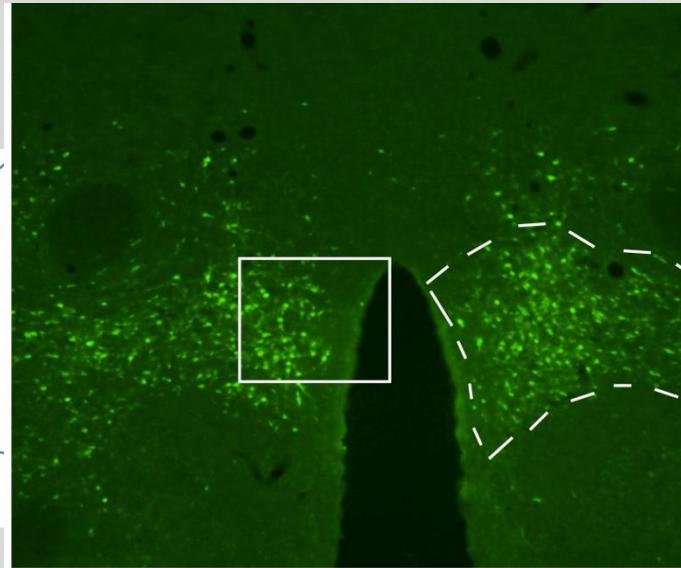
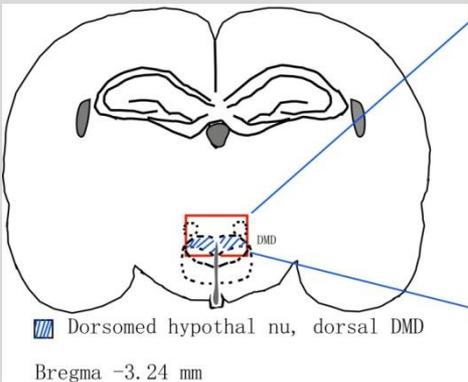
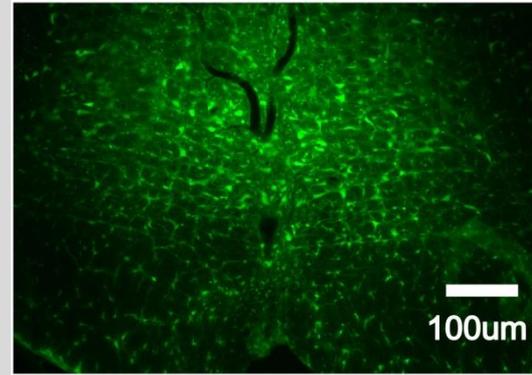
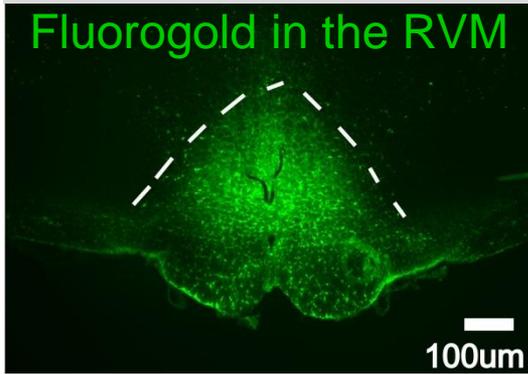
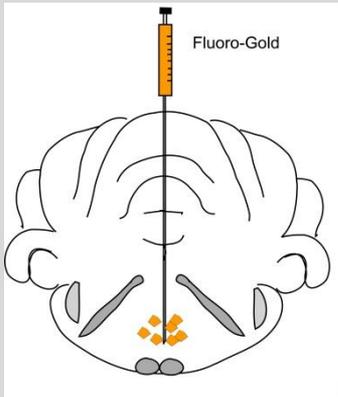
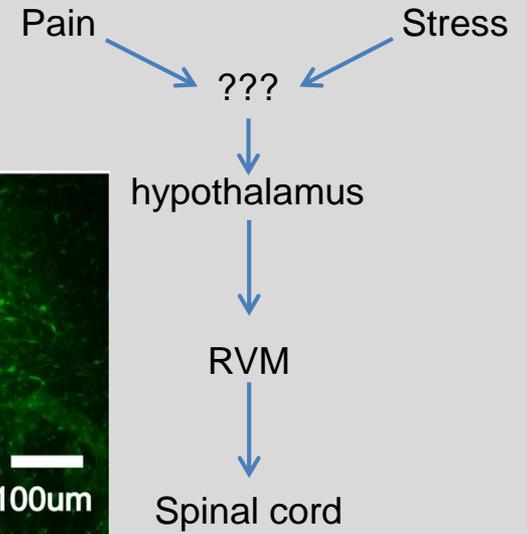
Depletion of 5-HT in the RVM by shRNA



Intrathecal 5-HT₃ receptor antagonist

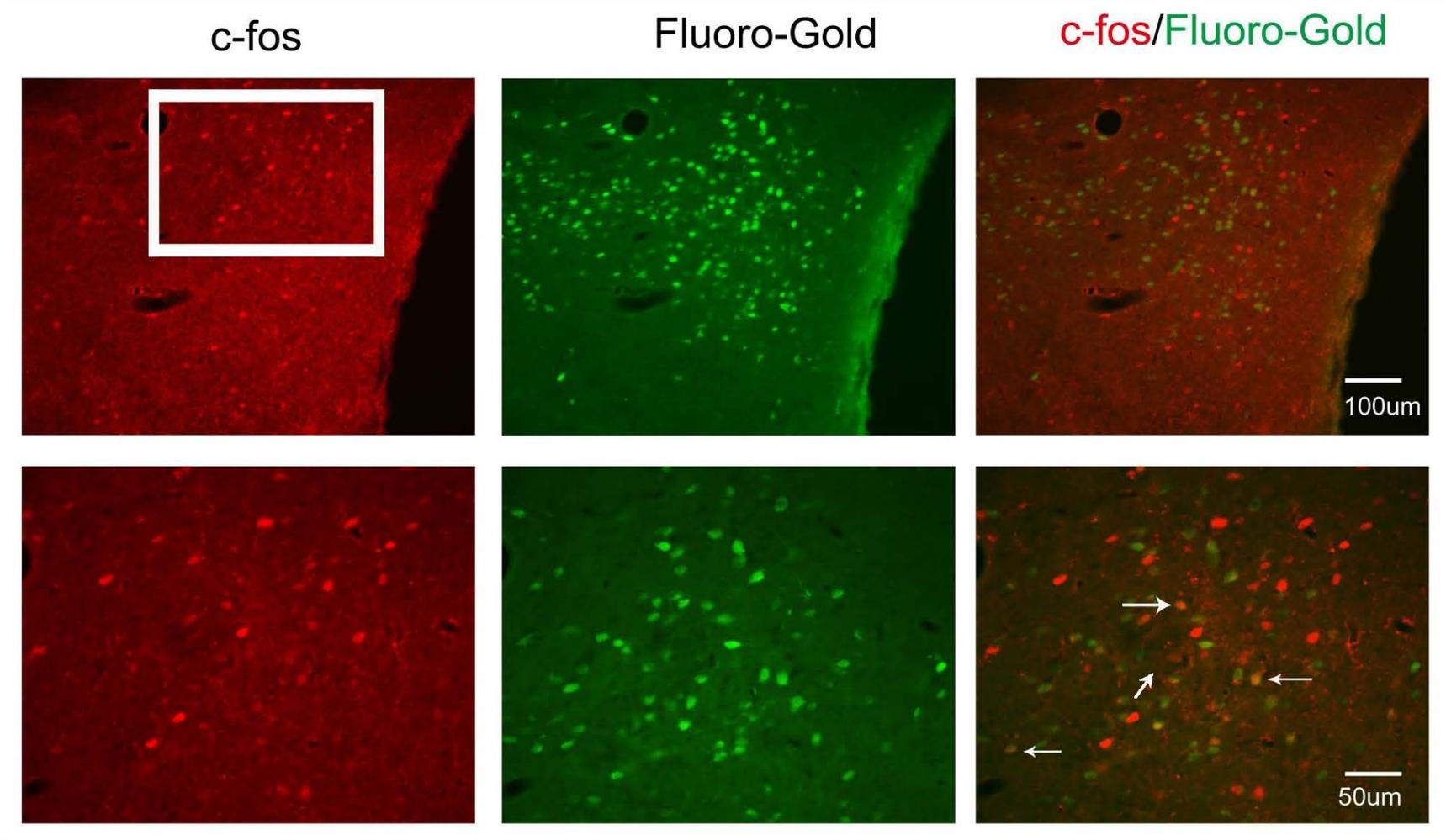


Retrograde tracing reveals Dorsomedial Hypothalamic → RVM neurons

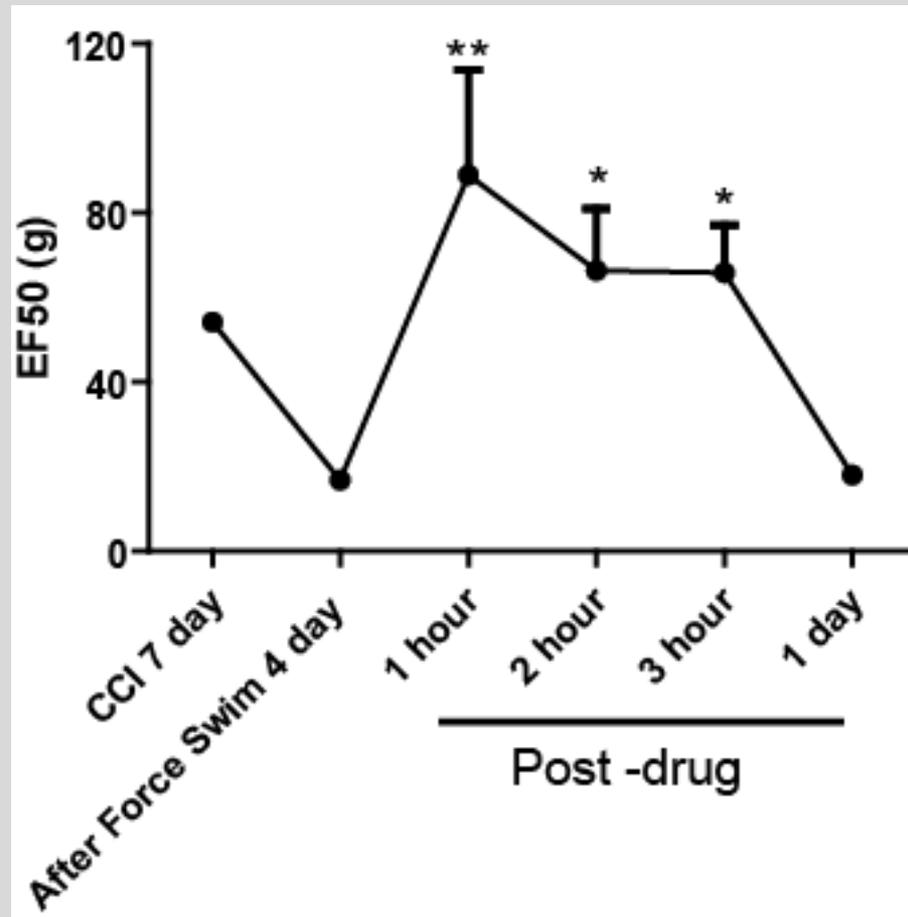


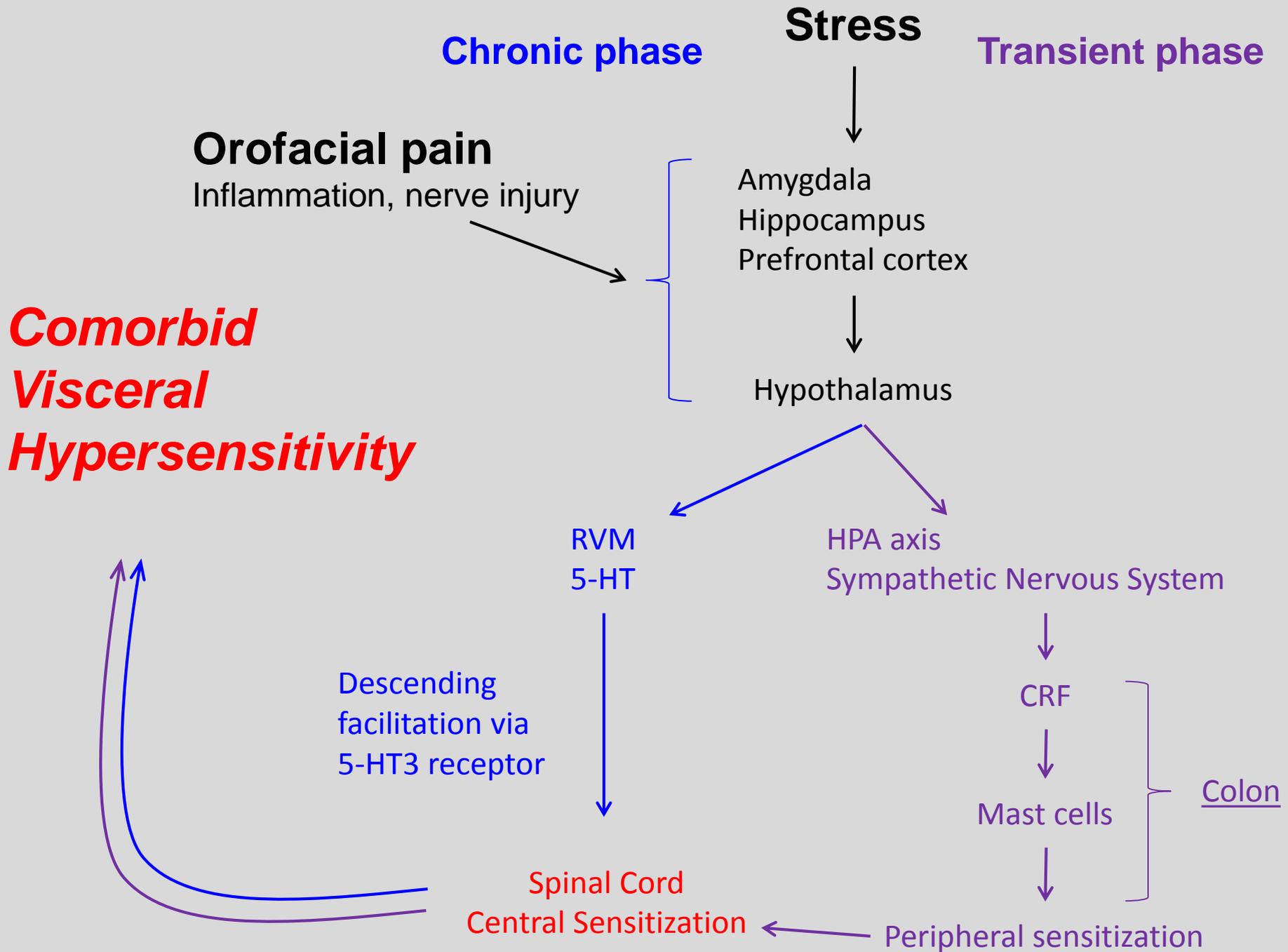
Retrogradely labeled neurons in the hypothalamus

Stress activates RVM projection neurons in the dorsomedial hypothalamus



Lidocaine in hypothalamic DMN attenuates comorbid hypersensitivity





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

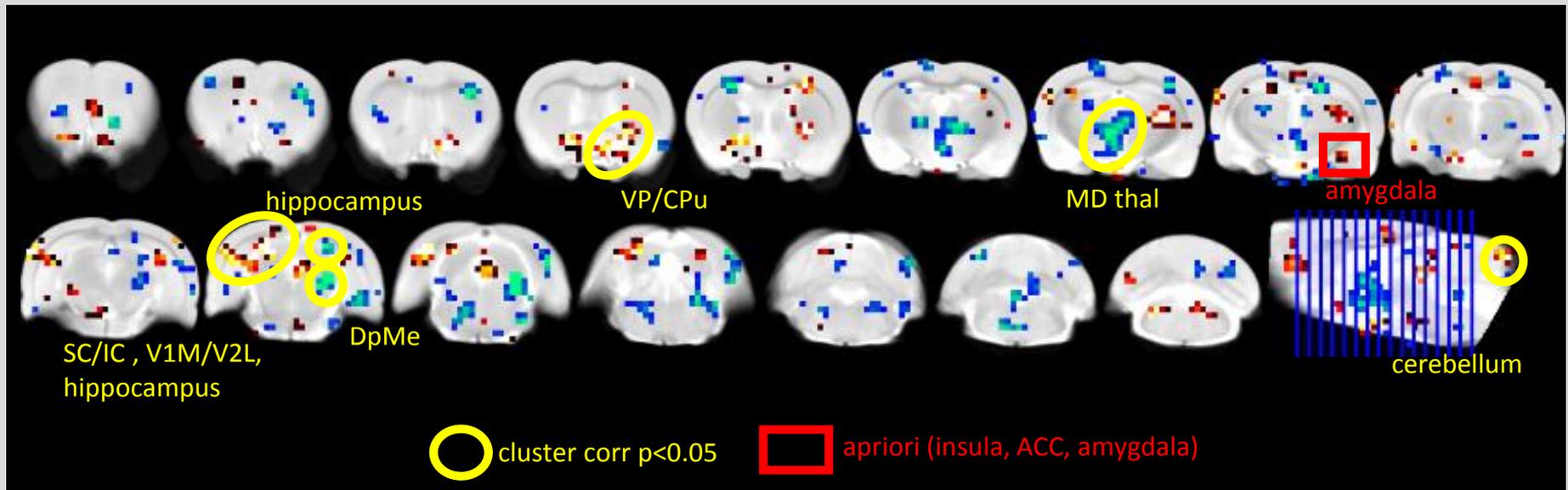
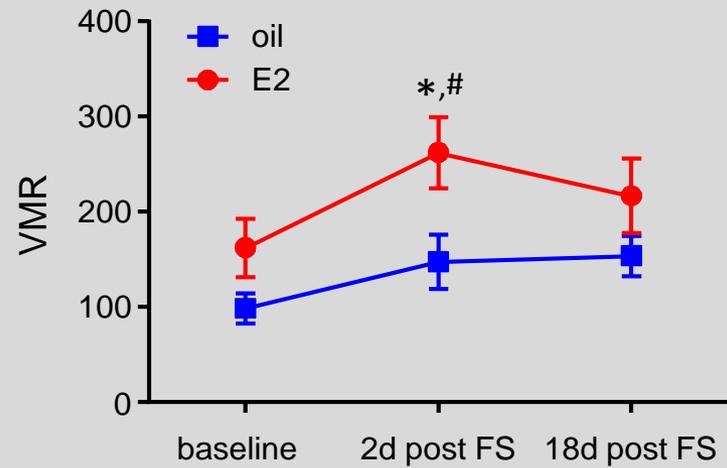
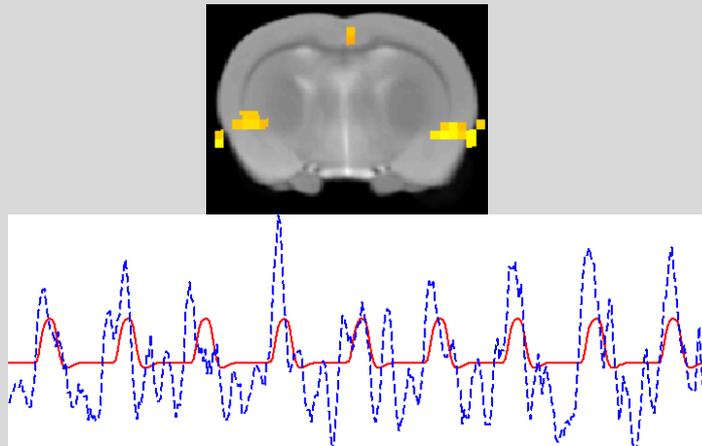
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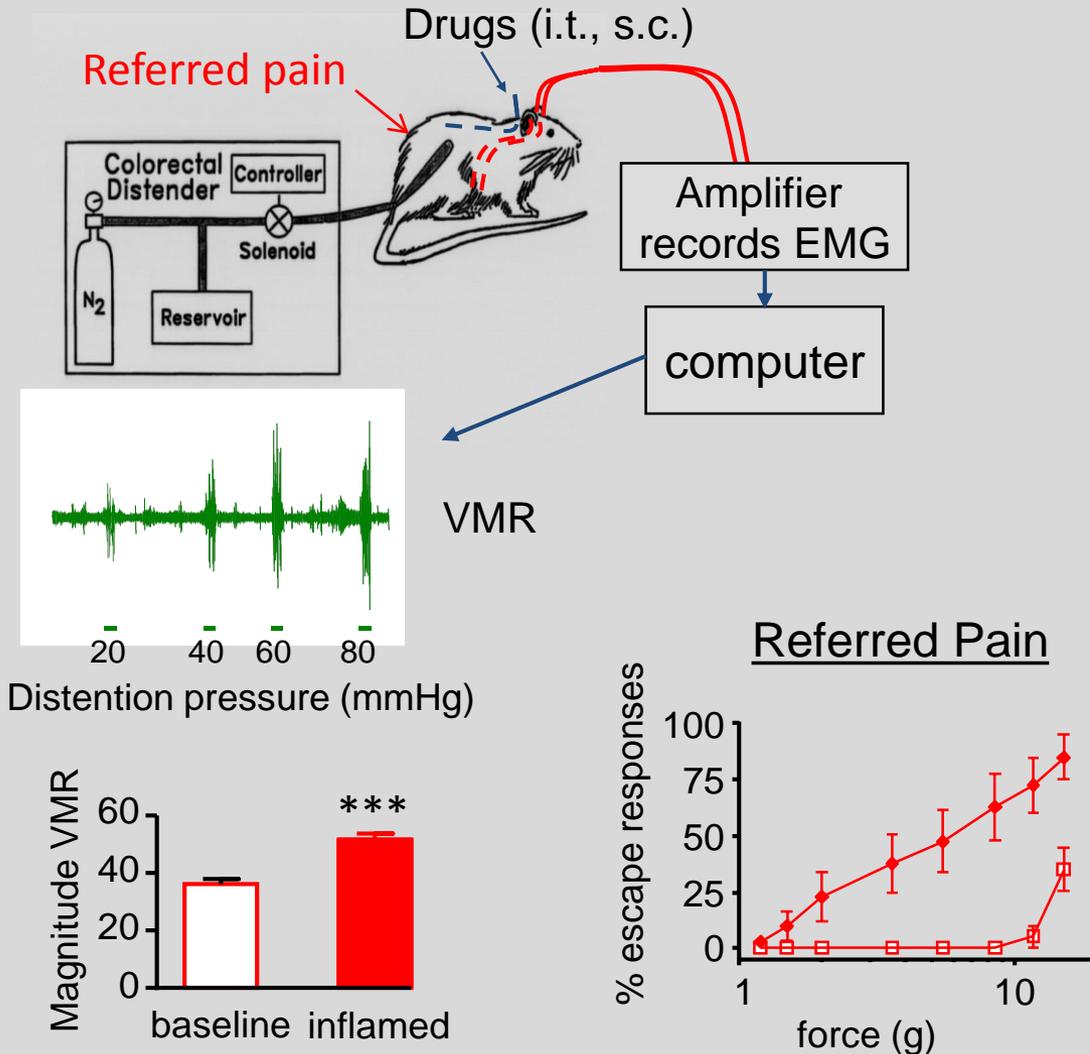
**Pilot study from the
University of Maryland
Organized Research
Center on Persistent
Pain**

Estrogen-dependent visceral hypersensitivity following stress in rats: an fMRI study

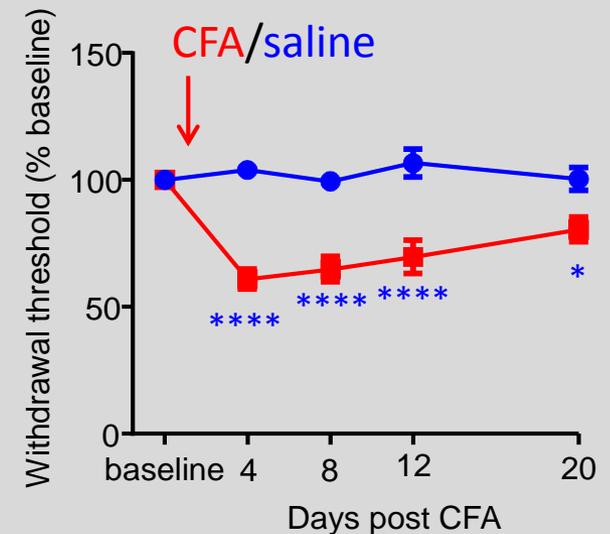
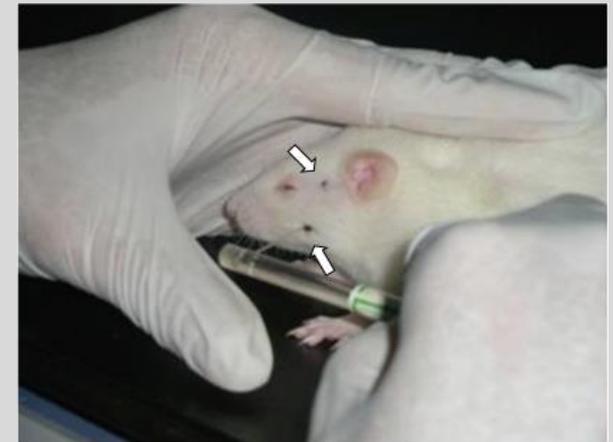


Animal models can be used to examine several aspects of nociceptive processing.

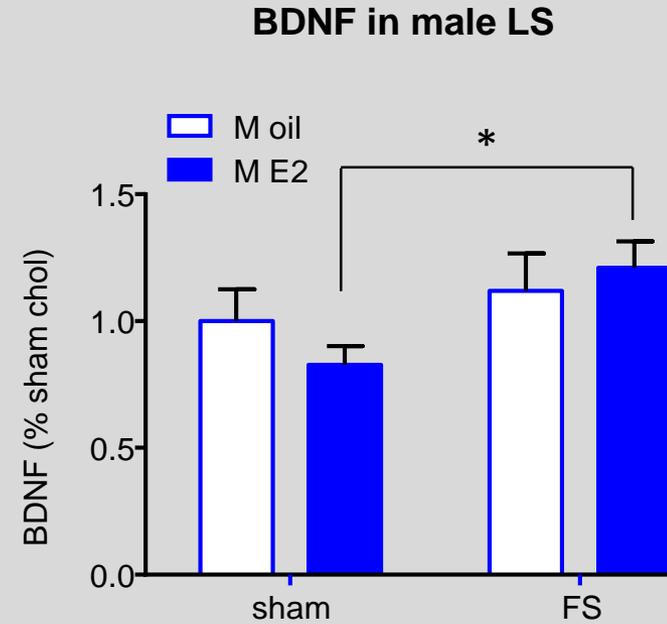
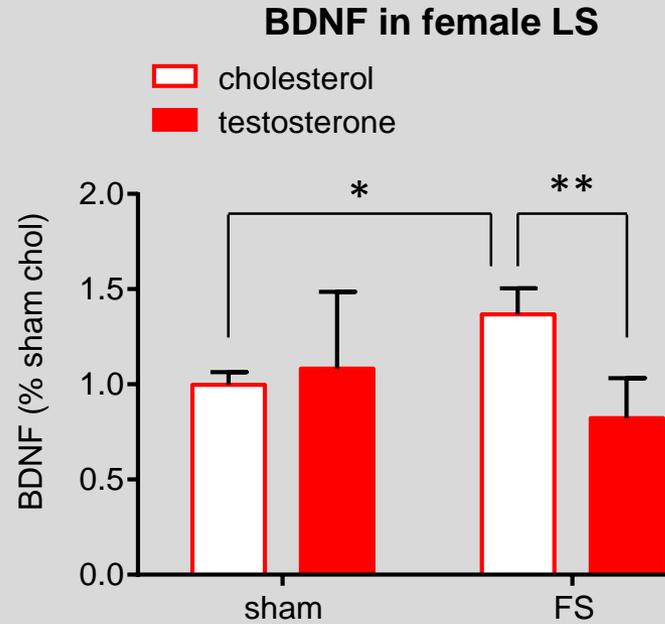
The visceromotor response (VMR) and referred mechanical hypersensitivity to measure visceral pain



von Frey filaments to measure mechanical nociceptive threshold



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



Spinal TrkB blockade attenuates stress-induced hypersensitivity in females

