Center for Pain Research

The Ernest J. Del Monte Institute for Neuroscience

Eli Eliav, DMD, PhD

UNIVERSITY of ROCHESTER MEDICAL CENTER

EASTMAN INSTITUTE for ORAL HEALTH OUR FIRST 100 YEARS Leading. Caring. Discovering.

UR MEDICINE

EASTMAN INSTITUTE FOR ORAL HEALTH

Table 1. Proportion of U.S. Adult Population With Persistent Pain, 2010

	Estimated Number (Millions)	*Persistent Pain, %*	*AOR (95% CI)*
Total adult population	207.7	19.0	
Sociodemographic attributes			
Age 18–29	46.0	7.6	Ref
Age 30–39	36.3	14.4	2.1* (1.4–3.1)
Age 40–49	39.2	17.6	2.7* (1.8–3.8)
Age 50–59	35.8	25.7	3.6* (2.5–5.2)
Age 60–69	26.8	29.6	4.0* (2.7–5.8)
Age 70–79	14.5	27.8	3.4* (2.2–5.2)
Age 80 or older	9.1	28.5	3.4* (2.3–5.1)
Male	100.5	16.2	Ref
Female	107.2	21.6	1.4* (1.2–1.7)

Kennedy et al. The Journal of Pain, Vol 15, No 10 (October), 2014: pp 979-984

In 2012, health care providers wrote 259 million prescriptions for opioid pain medication, enough for every adult in the United States to have a bottle of pills…

Drug overdose is the leading cause of accidental death in the US, with 47,055 lethal drug overdoses in 2014. Opioid addiction is driving this epidemic, with 18,893 overdose deaths related to prescription pain relievers, and 10,574 overdose deaths related to heroin in 2014

Center for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, Mortality File. (2015). Number and Age-Adjusted Rates of Drug-poisoning Deaths Involving Opioid Analgesics and Heroin: United States, 2000–2014. Atlanta, GA: Center for Disease Control and Prevention.

Research and treatment should aim to improve pain and/or pain management, and also to improve patient physical, psychological, and work and social role functioning

Multidisciplinary Pain Center

Multidisciplinary Diagnosis and Treatment

Clinicians work in the same space:

- Physician(Neurologists, Anesthesiologists, Oncologists, pediatricians)
- Nurses
- Mental health professionals
- Physical therapists
- Dentists (orofacial pain, OMFS)

Methods:

- Sensory Testing
- Nerve Blocks
- Pharmacological treatment
- Surgical Interventions
- Physical Therapy/Exercise
- Non-surgical intervention
- Brain imaging

Examples for Chronic Pain Conditions:

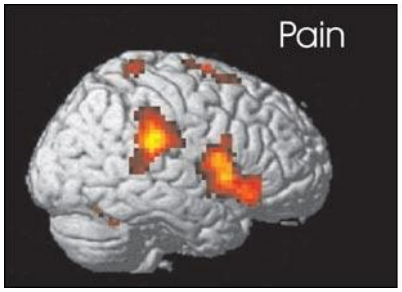
Back Pain, Headaches, CRPS, Neropathic Pain, Cancer pain, Chronic Abdominal and Pelvic pain, Orofacial Pain (TMD), Post tramatic neuropathies

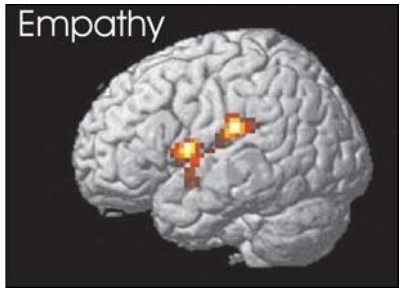
Research

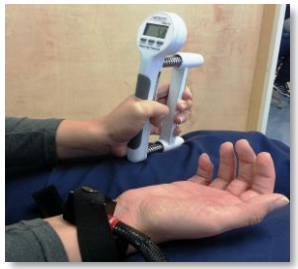
- Animal studies
- Brain imaging
- Clinical research
- Clinical trials
- Precision medicine

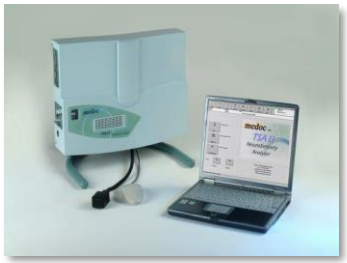
Education

- Patients
- Health care professionals









Pain Research and Clinics at URMC

EIOH

Research

XiuXin Liu DDS PhD
Yanfang Ren DMD PhD
} Acute Pain

Jund Khan BDS MPH PhD
Eli Eliav DMD PhD
Takano Takahiro PhD
} Chronic Pain

Clinical research assistants
Laboratory assistants

Orofacial Pain and Sensory Testing Clinic

Ross Tallents DDS
Jund Khan BDS MPH PhD
Eli Eliav DMD PhD

Neurosurgery

Neuromedicine Pain Management Program
Drs. Markman and Villareal

Translational Pain Research
Dr. John Markman

Anesthesiology

Pain treatment Center
Drs. Kent, Thakur, Koh, Philip and Smith

Dr. Robert Dworkin

Center for Translational Neuromedicine
Dr. Nedegaard lab

Physical Medicine Rehabilitation

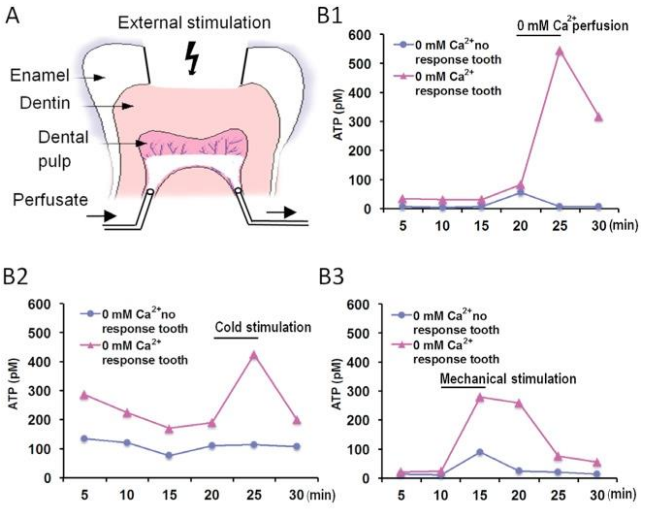
Orthopedics

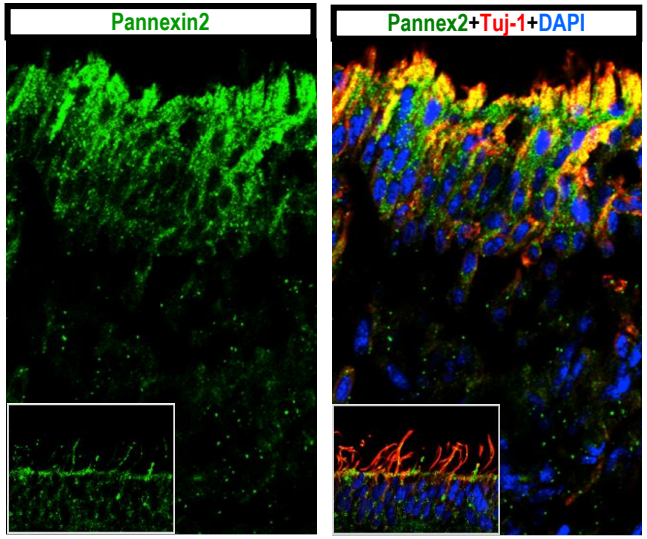
Neurology
Dr. Villanueva

XiuXin Liu's / Yanfang Ren Lab

Nociceptive transduction mechanism for Dentine Hypersensitivity

Environmental stimulation triggers ATP release from odontoblasts via pannexin channels to activate P2X3 receptors on adjacent nerve fibers and induce pain.





Liu, et al., 2015, J. Dental Research.

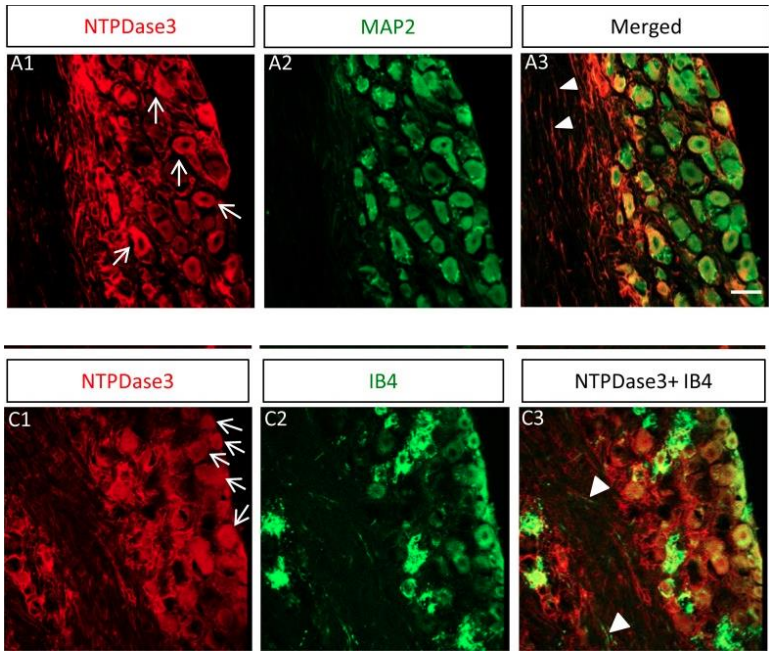
Pannexin Channel Blocker Reduces External Dentin Stimulation-induced ATP release

XiuXin Liu's Lab

The role of ecto-nucleotidases in the pathogenesis of orofacial neuropathic pain.

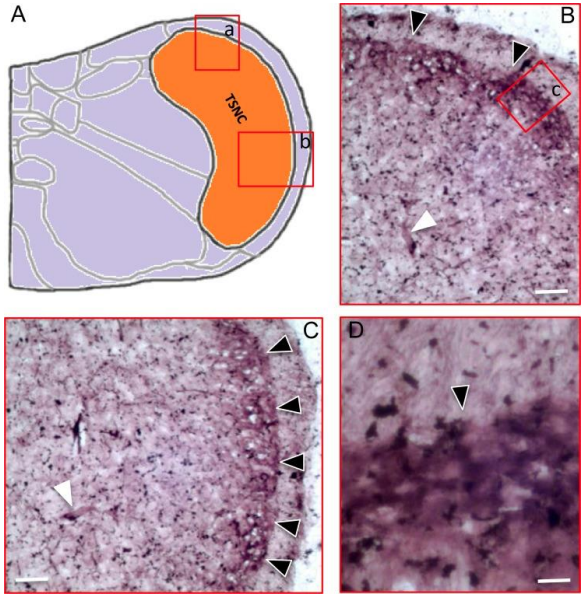
Purinergic signaling are determined by ecto-nucleotidases that control ATP degradation and adenosine generation.

Expression of NTPDase3 in TG Nociceptive Neurons



Ma, et al., 2016, PLoS One

Detection of Ecto-ATPase in Nociceptive Lamina of the Trigeminal Subnucleus Caudalis



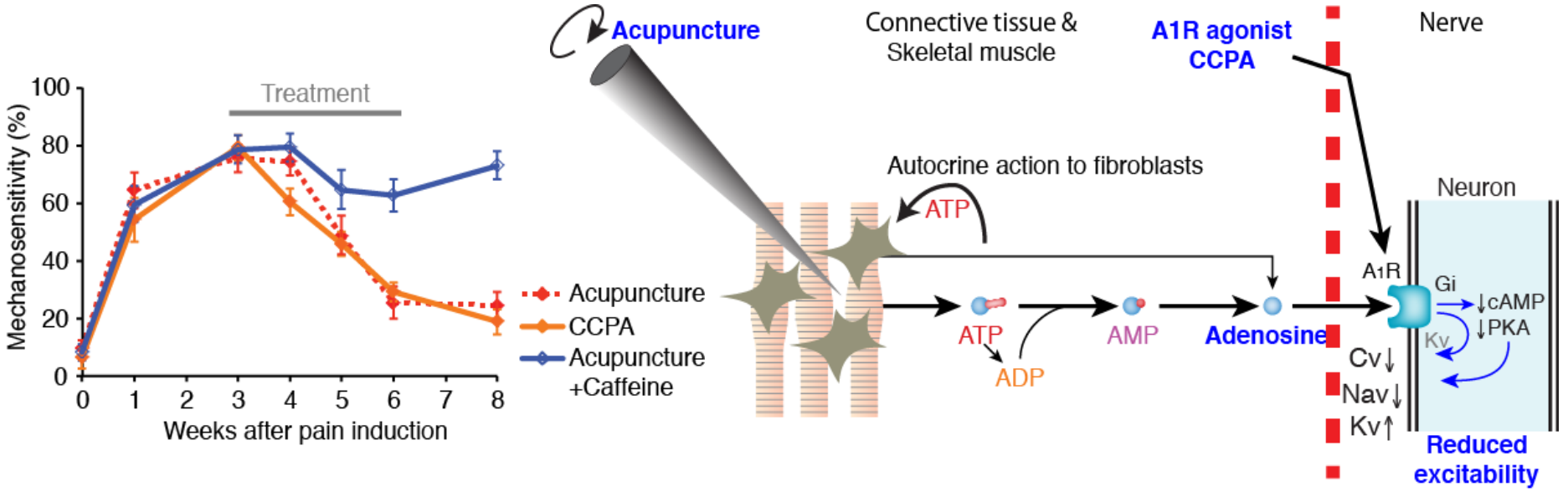
Ma, et al., 2016, PLoS One

Disruption of ecto-nucleotidase (NTPDase3 and CD73) trigeminal neuronal expression and presynaptic terminal localization caused by chronic inflammation, local constriction and trigeminal nerves injury may contribute to the pathogenesis of orofacial neuropathic pain.

Takano lab
Adenosine-mediated acupuncture analgesia

•We discovered that repetitive acupuncture treatments induce an increase of extracellular adenosine at acupuncture point, which lead to a long-term pain suppression

•We hope to develop a novel therapeutic strategy to treat both acute and chronic pain condition.



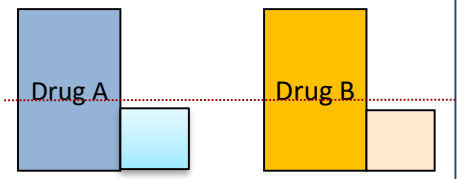
Khan / Eliav Lab

Treatment
Basic and clinical studies

Use of Topical Medications for Neuropathic Pain
Pregabalin
Diclofenac
Duloxetine
Ibuprofen
Amitriptyline

Combination Drug Therapy

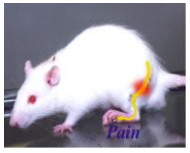
Pregabalin
Duloxetine
Diclofenac
Ibuprofen
Ketoprofen



The role of inflammation in neuropathic pain
Pro/Anti inflammatory Cytokines : (IL-6, IL-1, IL-12, IL-17, IL-18, IL-10, IL-2, IL-4, IL-27)

Mechanisms
-Opioid System (Kappa receptor)
-Anti Inflammatory System

Cytokines as treatment for Pain?
-Local and Systemic Injections



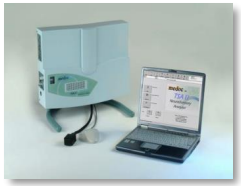
Diagnosis

Quantitative Sensory Testing (QST) for the Diagnosis and Evaluation of Chronic Pain Conditions

Peripheral Nervous System
- Thermal Detection and Pain Threshold
- Electrical Detection Threshold
- Mechanical Stimulus Test
- Cold Test

Central Nervous System
- Temporal Summation
- DNIC: Diffuse Noxious Inhibitory Control
- CPM: Conditioned pain Modulation

QSTs can support assessment of BMS, Maxillary Sinusitis, Atypical Odontalgia and Post Implant Neuropathy



Pain Modulation and Precision Medicine Approach
Basic and clinical studies

Pain Modulation System
- HIV Subjects
- Muscle Pain
- TMJ Disorders
- Headaches
- Acute Dental Procedures

Exercise Induced Hypoalgesia
Basic Science
- Endo Cannabinoid System
- Opioid System
- Inflammation

Clinical
- Orofacial Pain conditions

Orofacial Pain Genetics Analysis
Burning Mouth Syndrome :
- Tumor Necrosis Alpha receptor (TNFRSF1B) and Lacto Erin (LTF)

Atypical Odontalgia:
- Tumor Necrosis Alpha receptor (TNFRSF1B)

HIV Related Myalgia:
- GTP cyclohydrolase 1 (GCH1), nuclear factor kappa- B, subunit 1 (NFKB1) and oxytocin receptor (OXTR

In order to execute the research, what new human capital might be needed to engage in the work

- Interaction with all the pain clinics / Labs
- Brain Imaging
- Geneticist
- Psychologist
- Physical Therapy

What it would take to get a group of scientists working in the area to a point where they might be able to submit a program project grant. Are there key facility or major equipment needs?

- Establish a team and collaborative work
- Define a common theme (precision, tailored treatment for chronic pain patients)

Briefly provide as concrete a plan as possible for how to grow the idea, program or center over the coming 36-48 months.

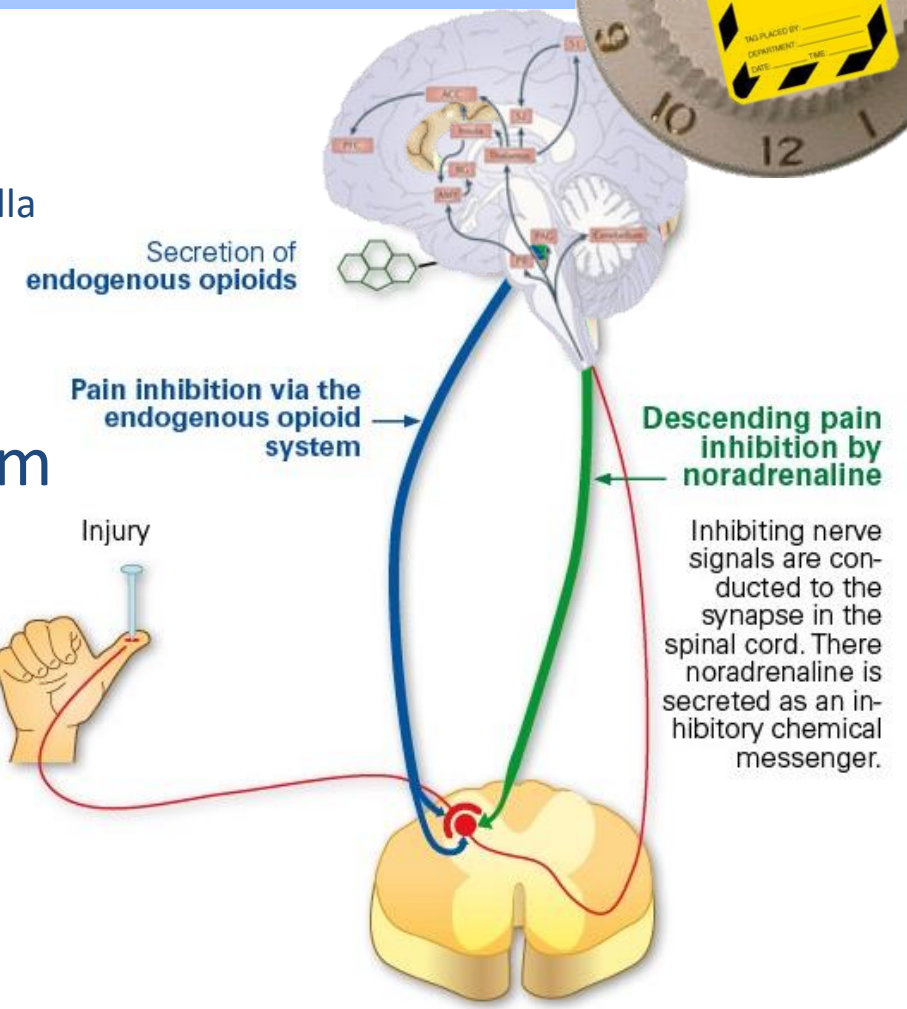
- Recruitments
- Establish URMC pain group, common research projects
- Publications

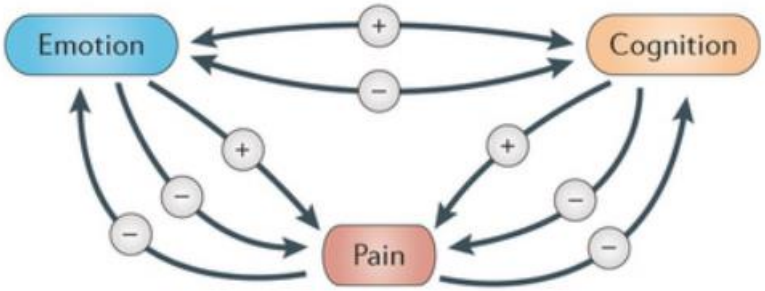
Pain Modulation
Inhibition of Pain

- PAG/RVM

Periaqueductal gray/Rostral ventromedial medulla

  - Down regulating pain inhibitory system
- Endogenous opioid system
- Serotonin
- Noradrenaline





Inhibitory Pain Modulation is known to be activated by:

Exercise

Aerobic

Isometric contraction

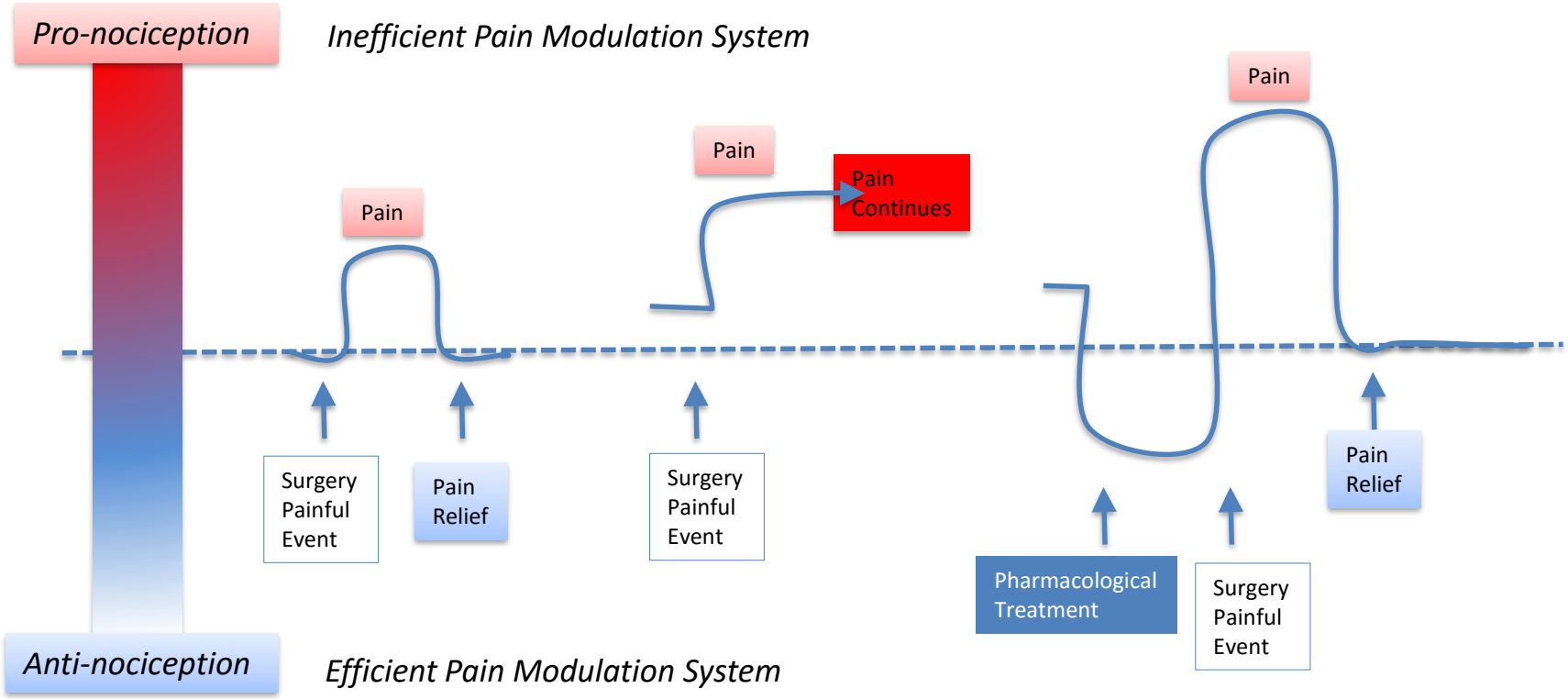
Painful stimulus

Cold

Hot

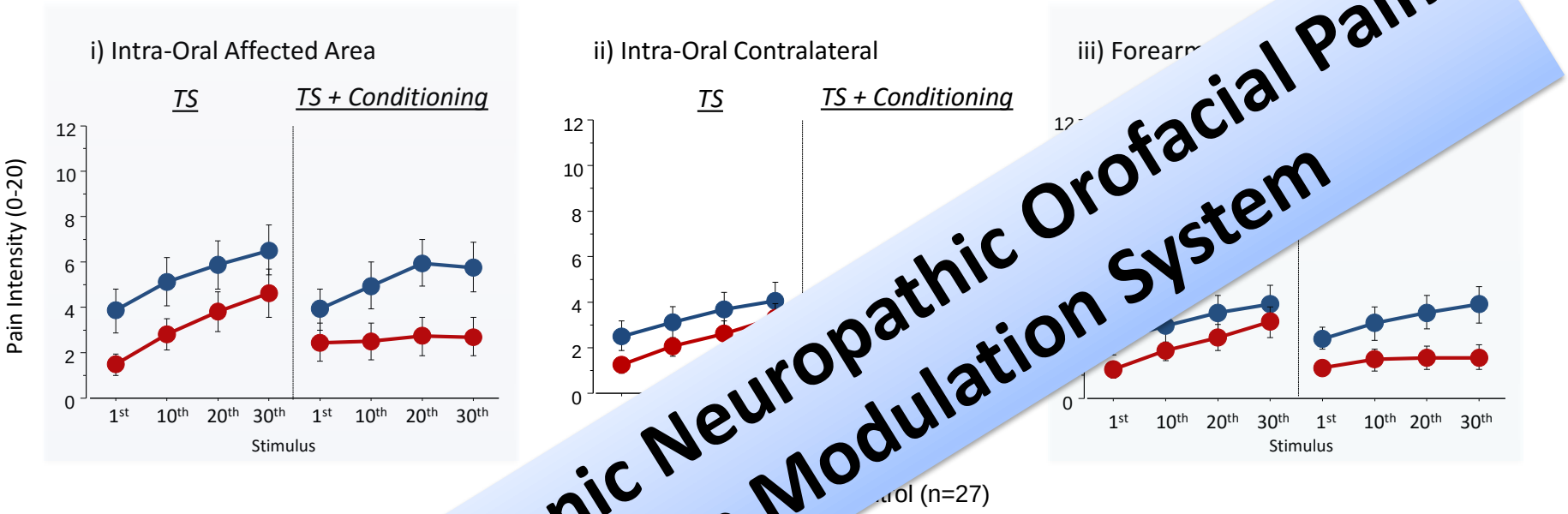
Mechanical

Electrical



David Yarnitsky,
Role of Endogenous modulation in Chronic Pain mechanisms and treatment.
PAIN 156 (2015)

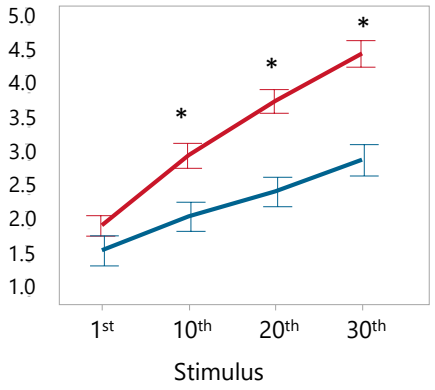
Posttraumatic Trigeminal Neuropathy



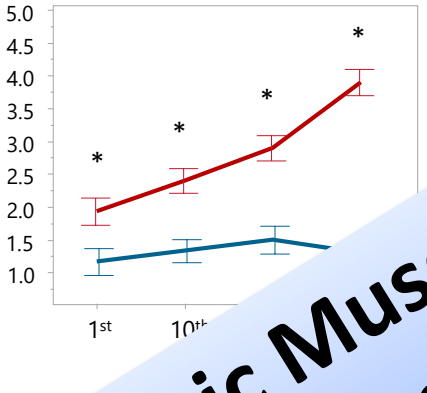
Patients with Chronic Neuropathic Orofacial Pain Have Less Efficient Pain Modulation System

Patients with Chronic Masticatory Muscles myalgia

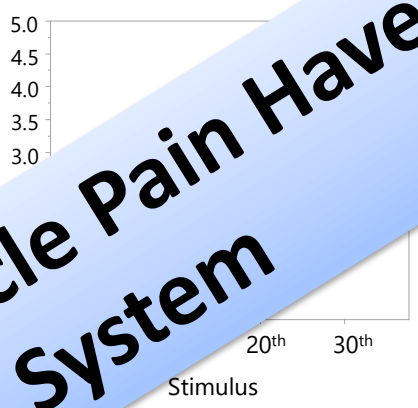
Baseline Pain Level



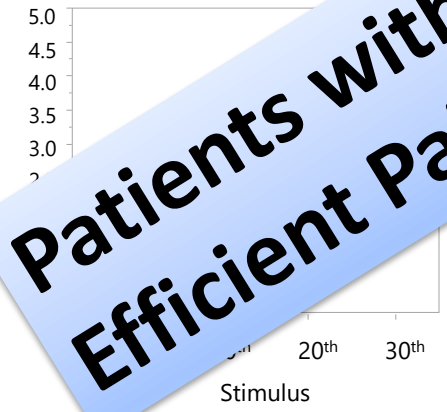
1 Min Following Exercise

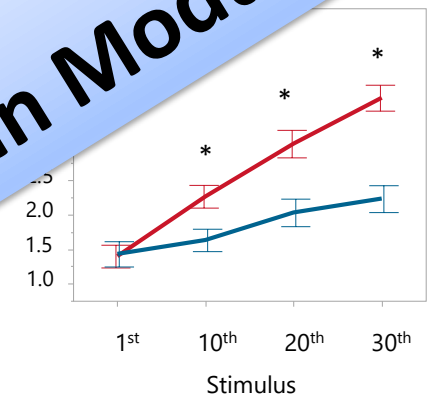


5 Min Following Exercise

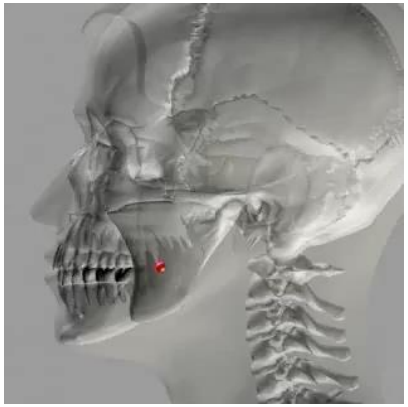


15 Min Following Exerci





CMMP
HC



5 minutes, 50% max

30 stimuli 26g

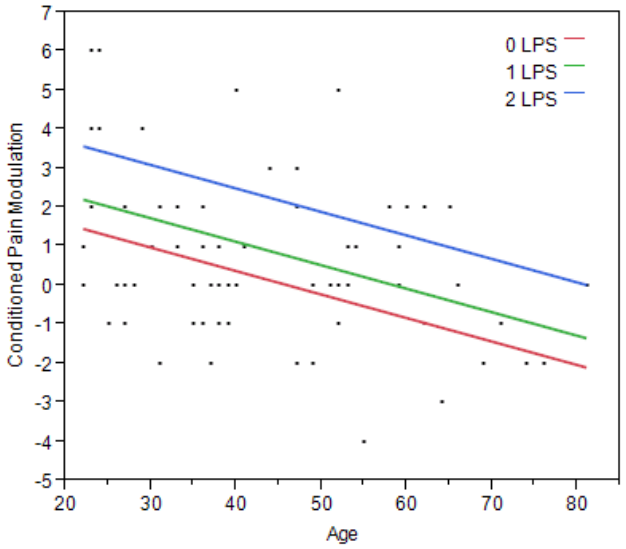
Patients with Chronic Muscle Pain Have Less Efficient Pain Modulation System

Pain Modulation Genotyping

DNA - white blood c
shedding of ora

Modulation (CPM) in the dominant
reases with age (P=0.0005) and is associated
bjects' number of *COMT* Low Pain Sensitivity (LPS)
plotypes (P=0.006 for additive model)

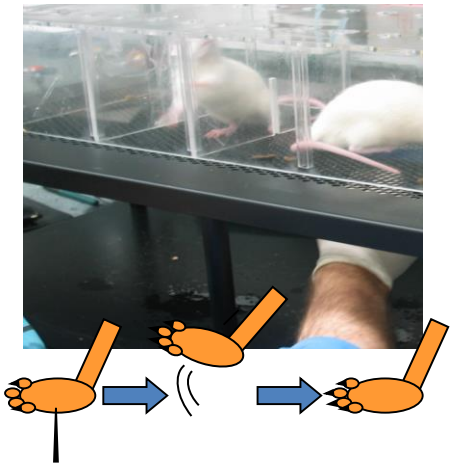
Specific genotypes are associated with pain modulation and chronic pain



Not all patients are on even playing field

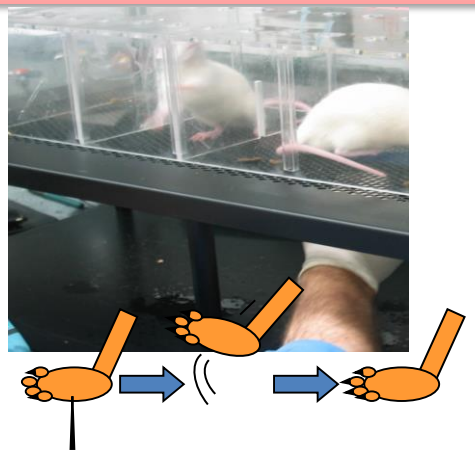
Exercise Induced Hypoalgesia, Rat Model

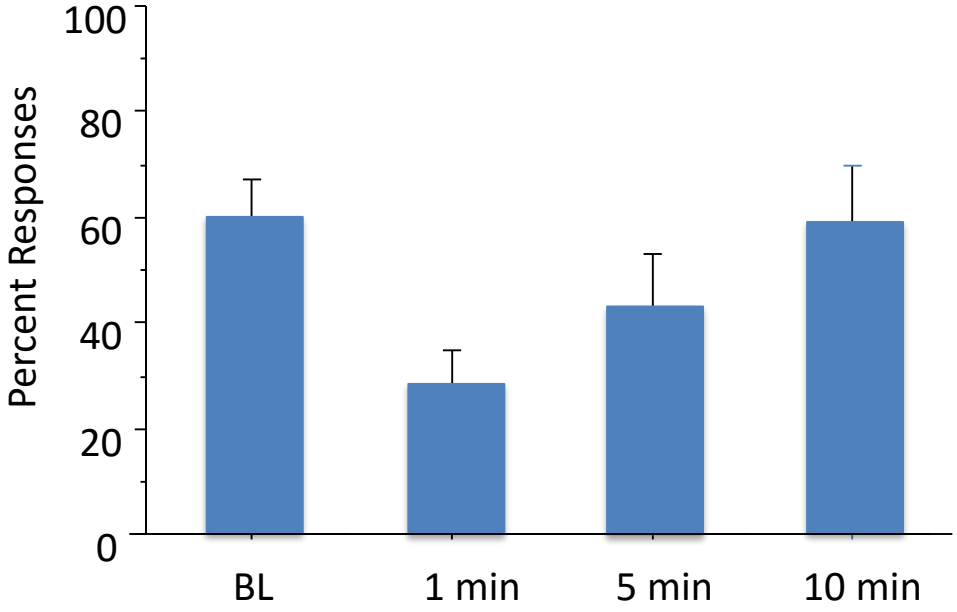
BL % responses



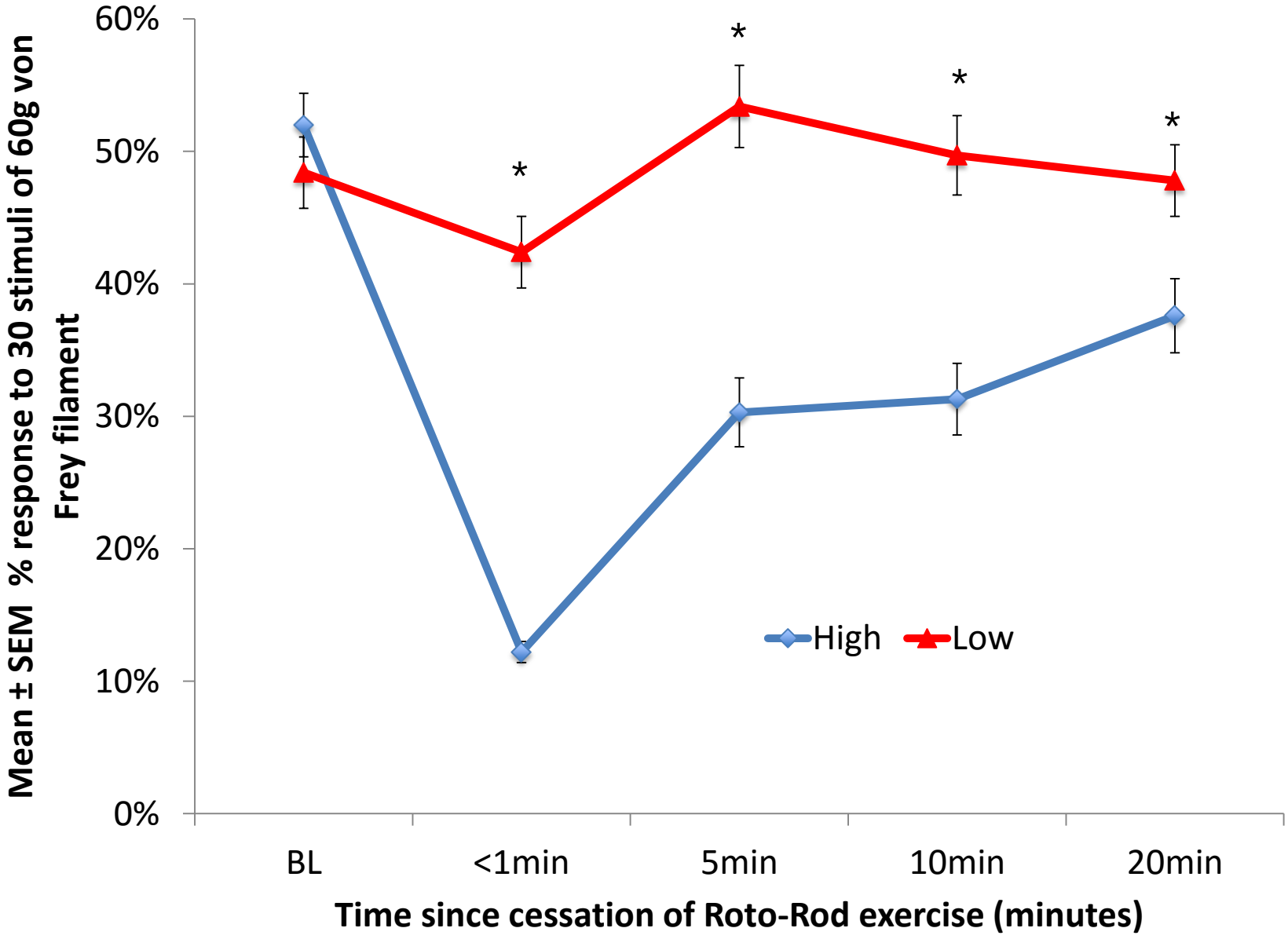
3 min exercise on Rotarod

% responses
1, 5, 10 min following exercise





EIH by High, Low



Exercise Induced Hypoalgesia, Rat Model

Low Pain Modulation rats develop significantly more pain

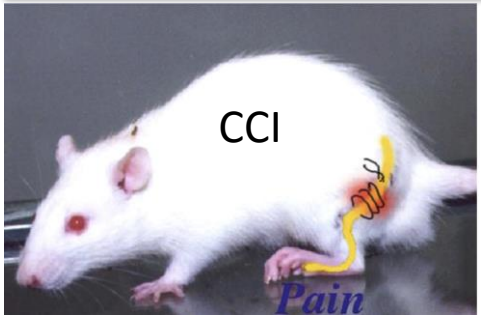
Only Low Pain Modulation rats develop mirror-image pain

Low Pain Modulation Rats Respond Better to Duloxetine

Cannabinoid antagonists reverse exercise effect on Pain

Phase 2

Pain Assessment Baseline



Pain Assessment, 7 Days following surgery

Summary

- Central modulation of pain can be activated by external stimuli and exercise
- Pain modulation profile assessment
  - May predict development of chronic pain
  - May support more targeted treatment selection
- Pre-emptive pharmacological treatment prior surgery in patients at risk should be further studied
- Activation of the inhibitory pain modualtion system may alleviate pain