

Utility of animal models for TMJD and orofacial pain

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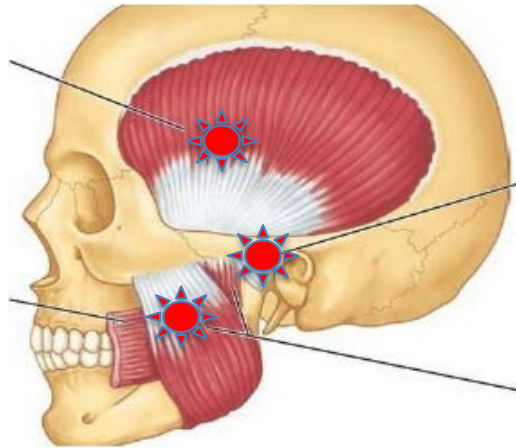
UNIVERSITY of MARYLAND



Disorders of the TMJ and muscles of mastication often result in chronic pain: a major health problem



?



Chronic orofacial pain is highly prevalent in the US, affecting $\approx$ 20% of the population.

The uniqueness of TMJD-related pain

(Similar to) **DEEP PAIN**

CUTANEOUS PAIN

Localization

Diffuse

Localized

Description

**Cramping, Aching,
Throbbing, Dull**

**Sharp, Pricking,
Stabbing, Shooting**

Noxious St.

**Not necessarily
tissue damaging**

**Usually
tissue damaging**

Referred Pain

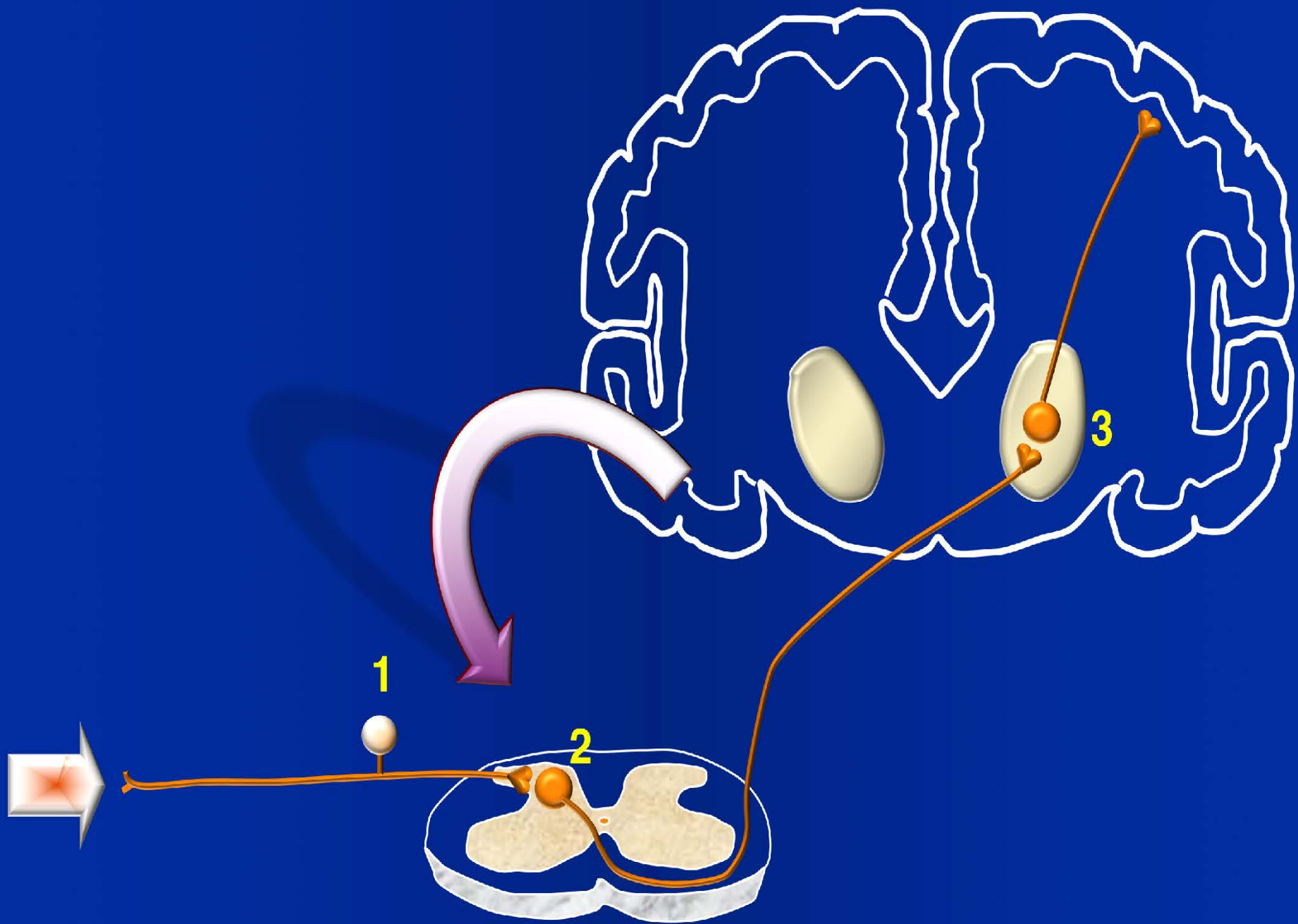
Yes

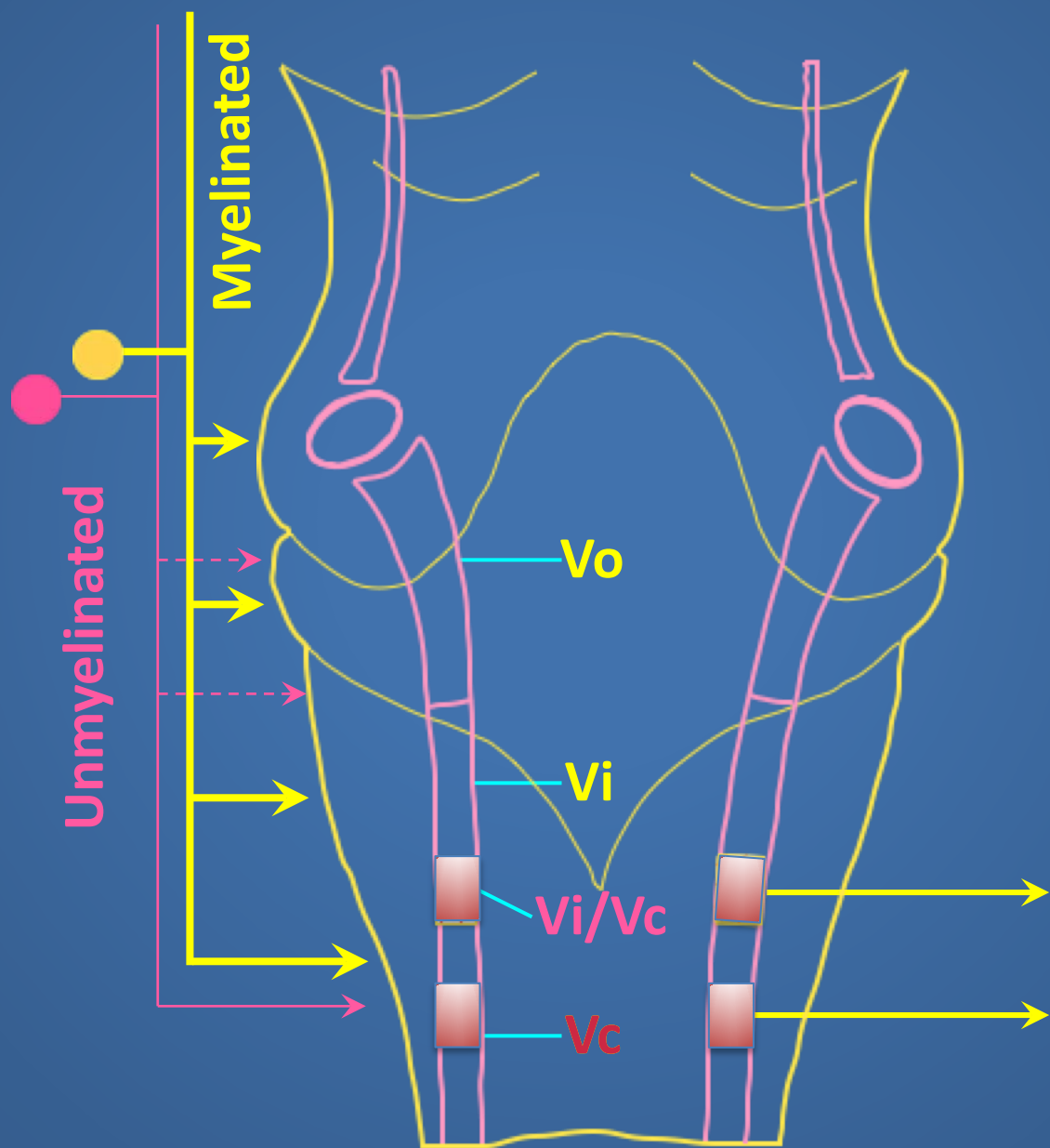
No

**Hyperalgesia/
Allodynia**

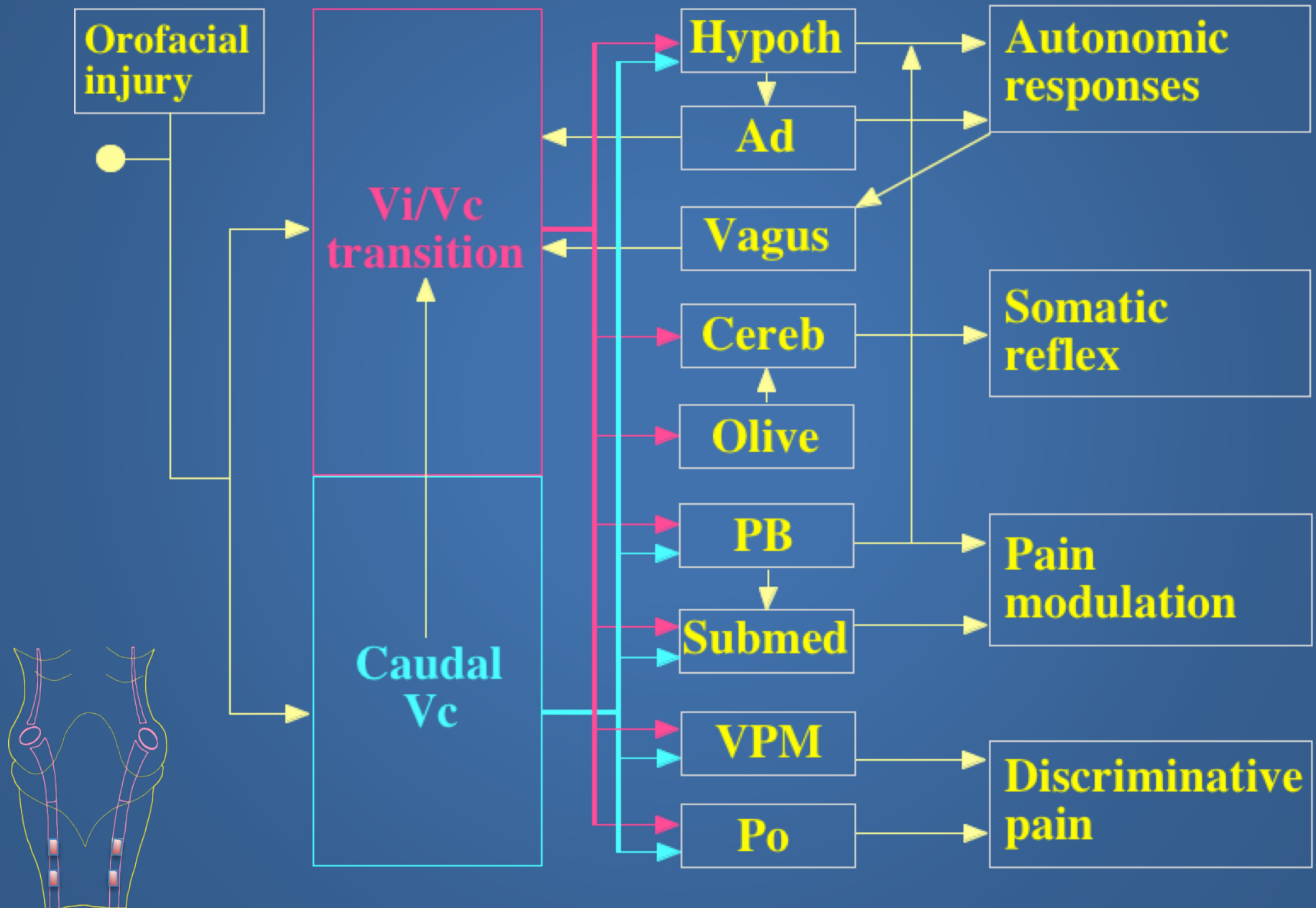
Yes

Yes

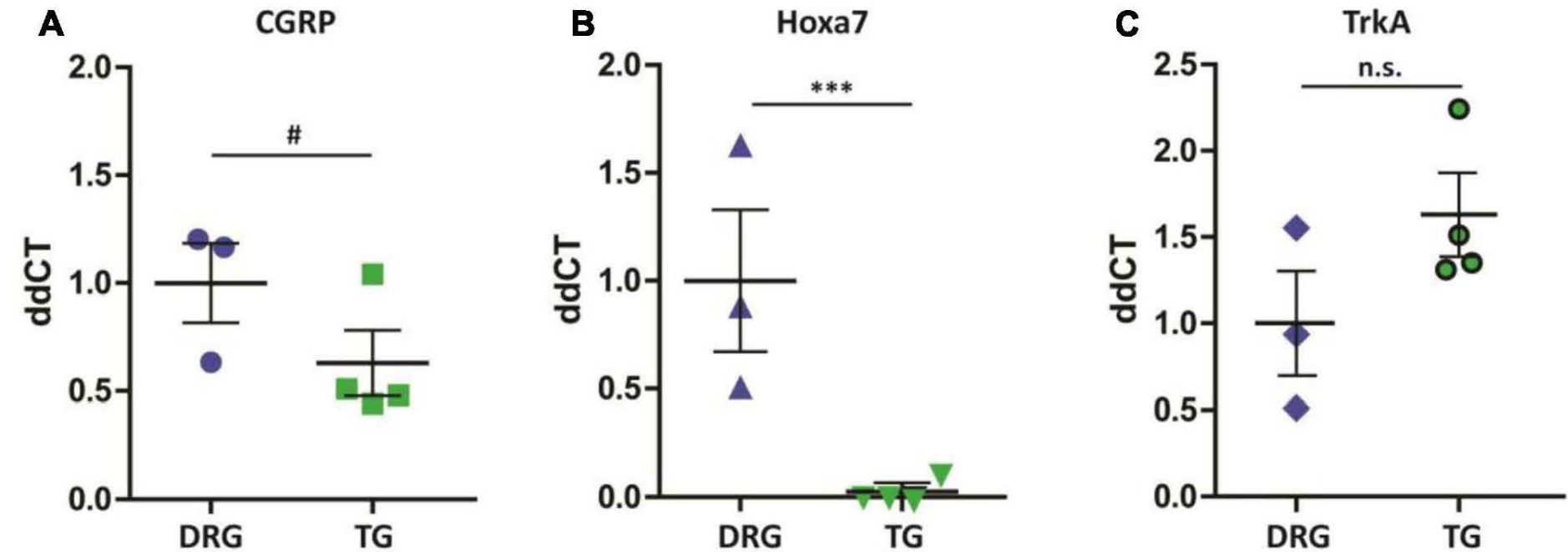




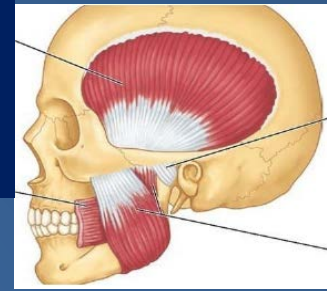
Dual afferent projections



Differential gene expression in trigeminal and dorsal root ganglia

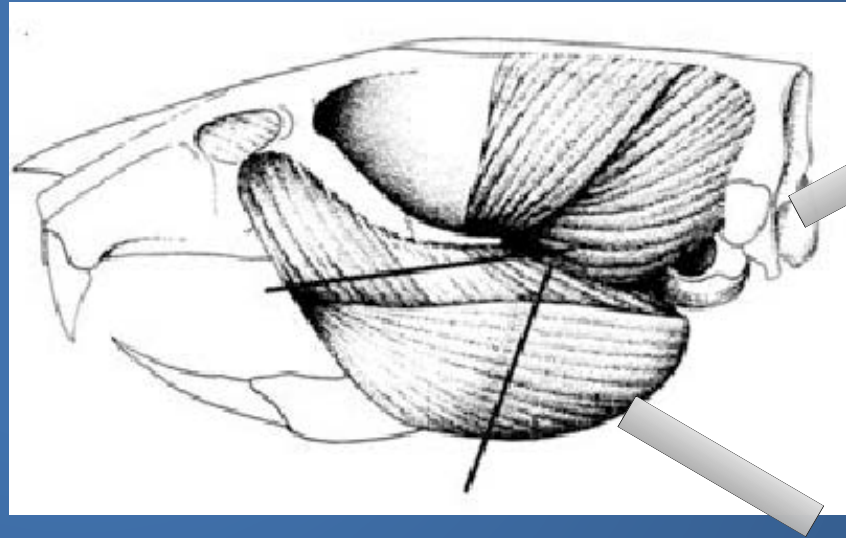


Preclinical models



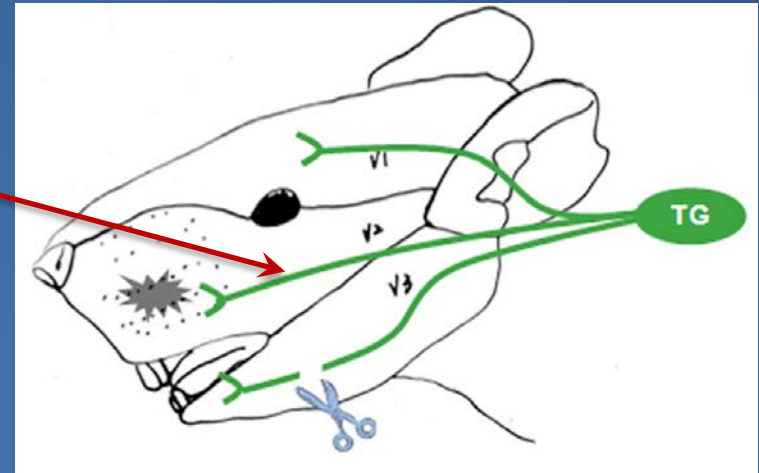
Injection of inflammatory/algesic agents

- Freund's adjuvant/Carrageenan
- Capsaicin
- Formalin
- Serotonin
- NGF
- Hypertonic/acidic saline
- Mustard oil
- Inflammatory soup ...



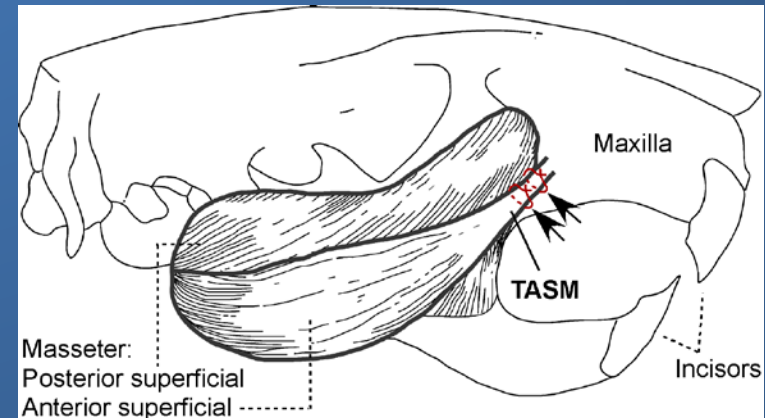
Nerve injury (Constriction, transection, compression...)

- Infraorbital nerve
- Mandibular nerve
- Inferior alveolar nerve
- Mental nerve
- Compression of the trigeminal nerve root
- ...



Muscle injury-Myogenic pain

- Masseter inflammation
- Masseter muscle tendon ligation



Joint loading/TMJ osteoarthritis

- Splint placement
- Mis-placement of dental implant
- Repeated mouth opening
- Disc displacement

Comorbidity conditions

- Masseter inflammation + Stress

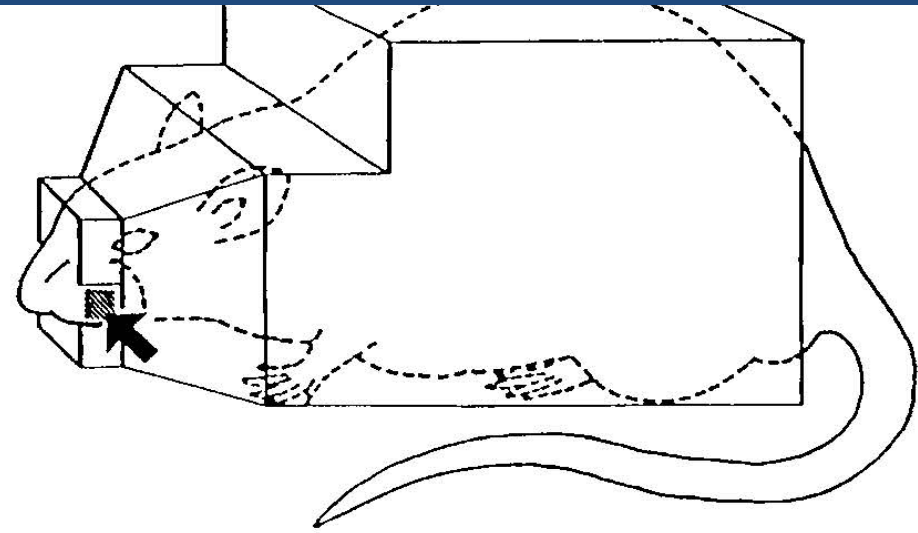
Assessing Orofacial Pain in Preclinical Studies

Nocifensive response

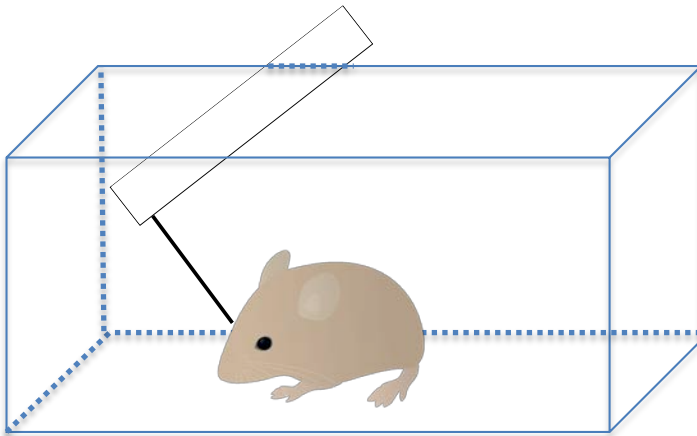


Morris et al., 1982

Rosenfeld et al., 1978



Imamura et al., 1997

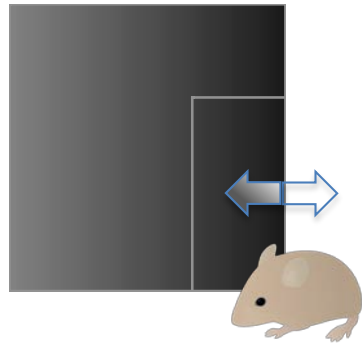


Vos et al., 1994



Ren 1999

Conditioned place avoidance



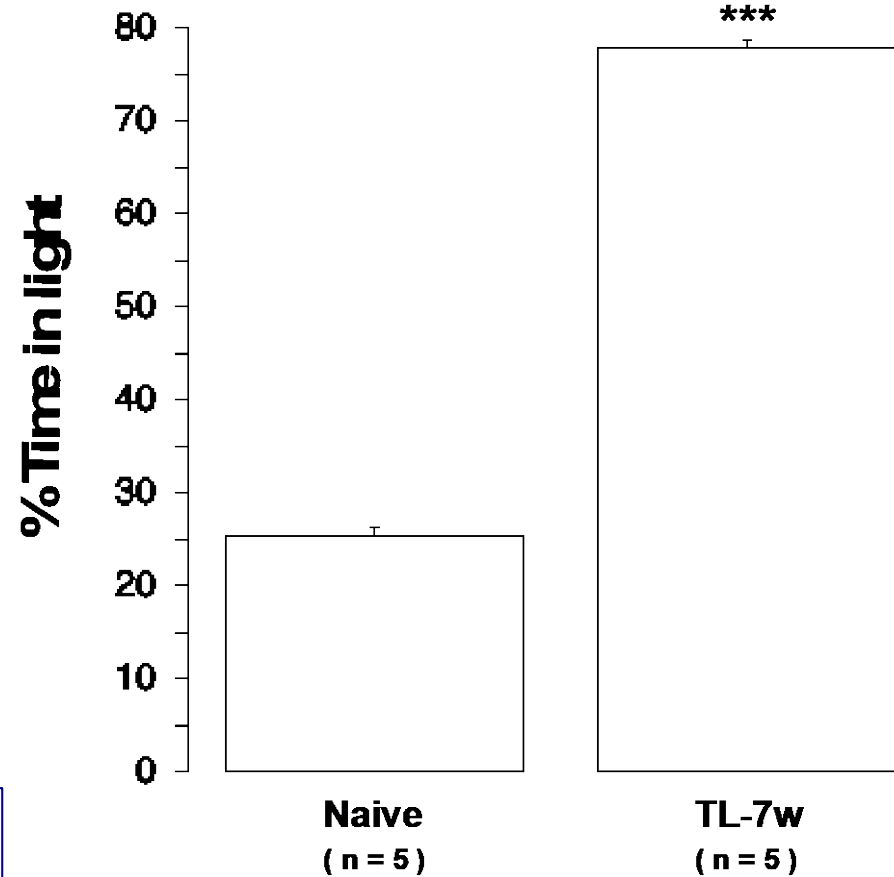
**Injured
side**



**uninjured
side**

Stimulation

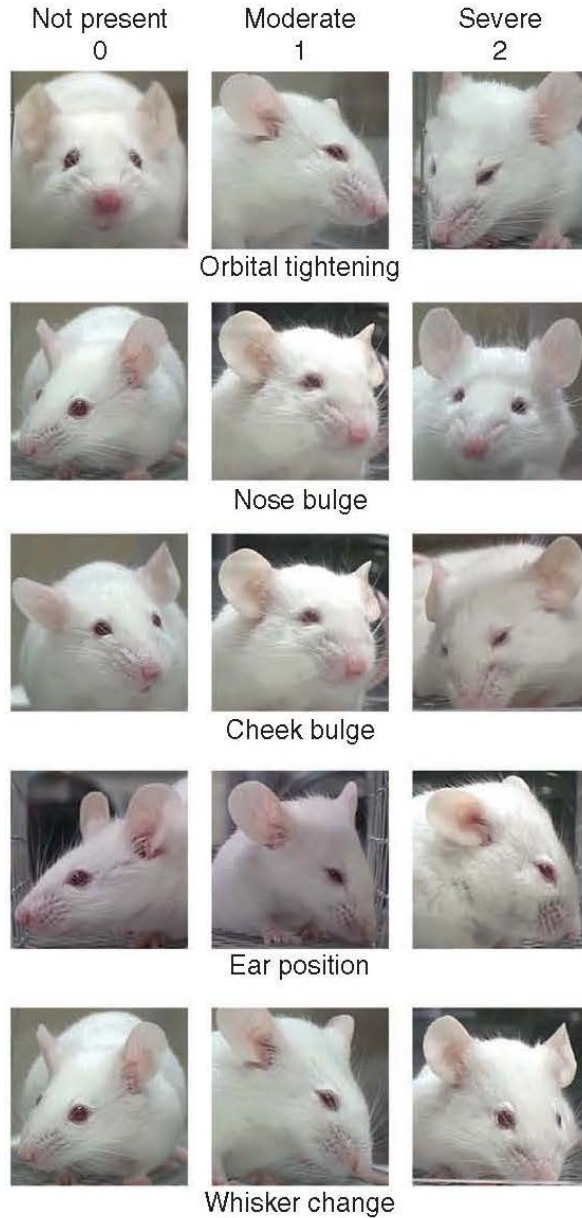
Suprathreshold von Frey filament / 15 s



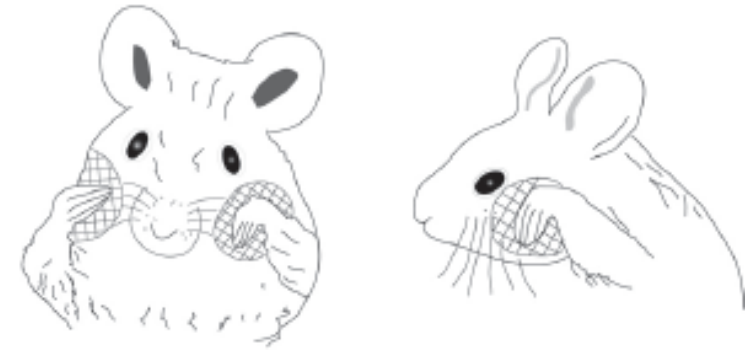
Facial expression

Grooming

Hy Forepaw face rubbing



Lanford et al., 2010



B) Lower lip skin/cheek rubbing against cage surface

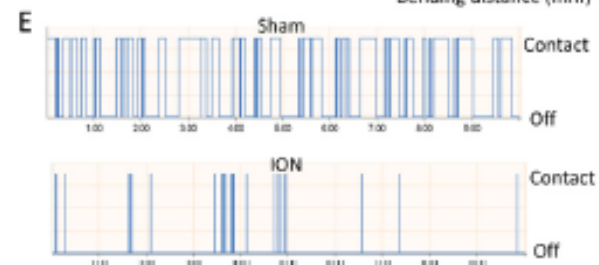
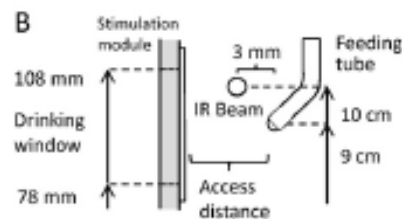
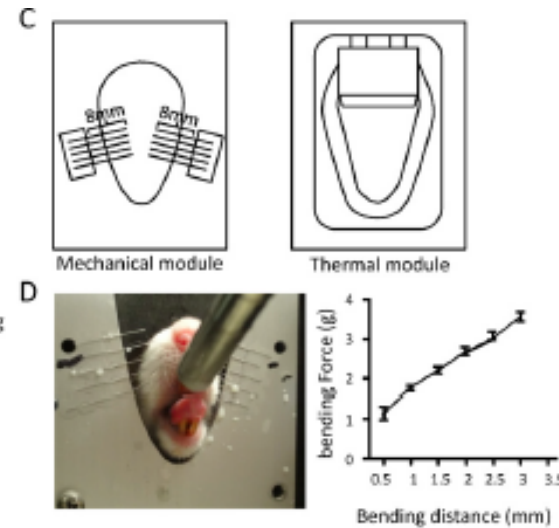
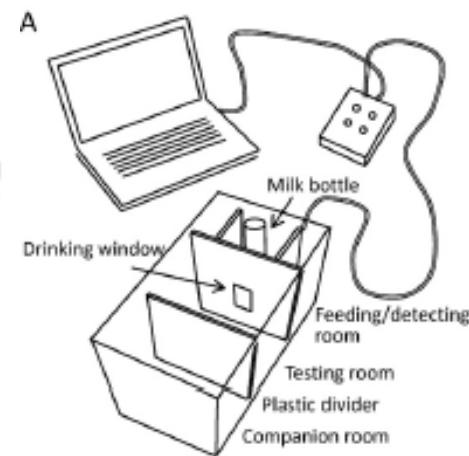
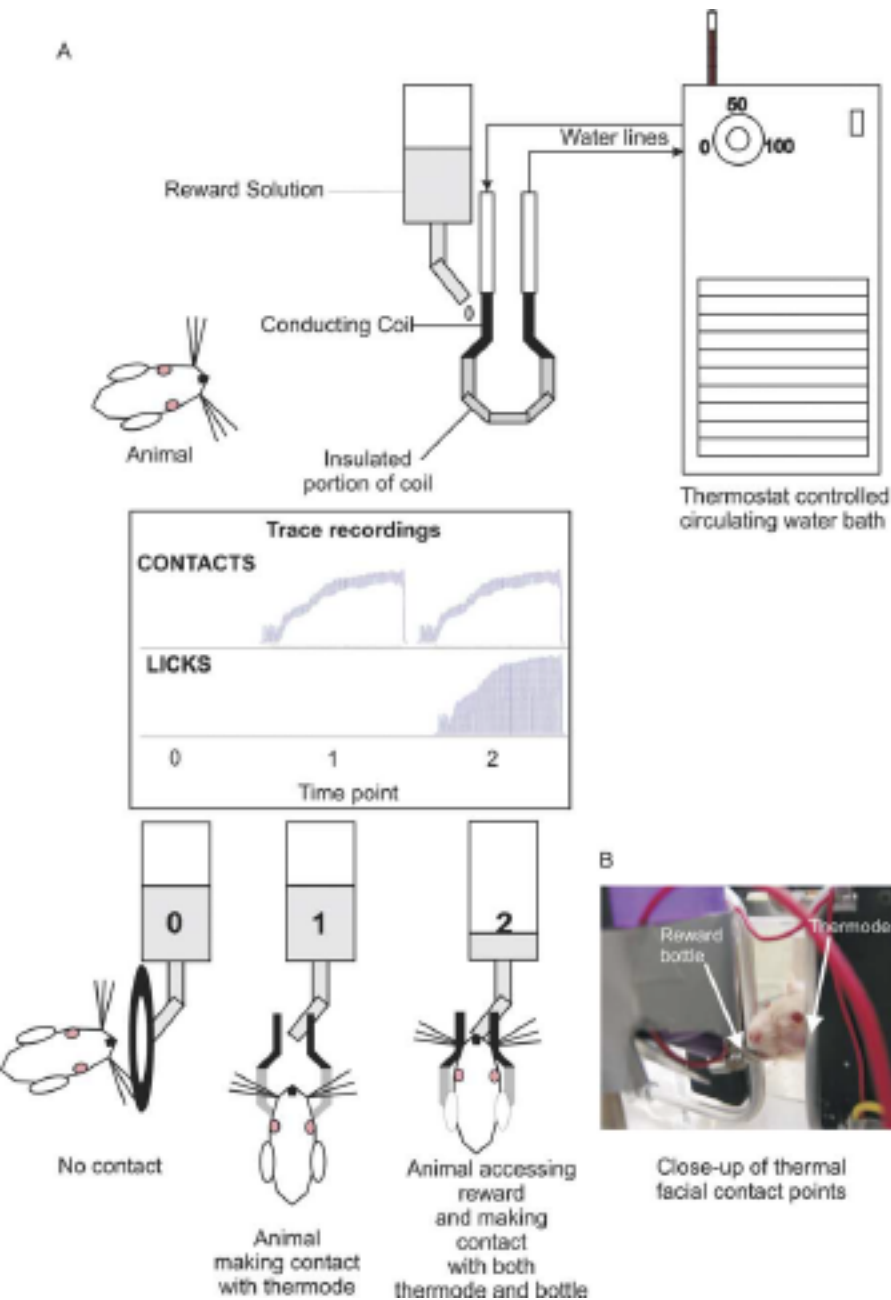


C) Hindpaw face scratching



Romero-Reyes et al., 2013

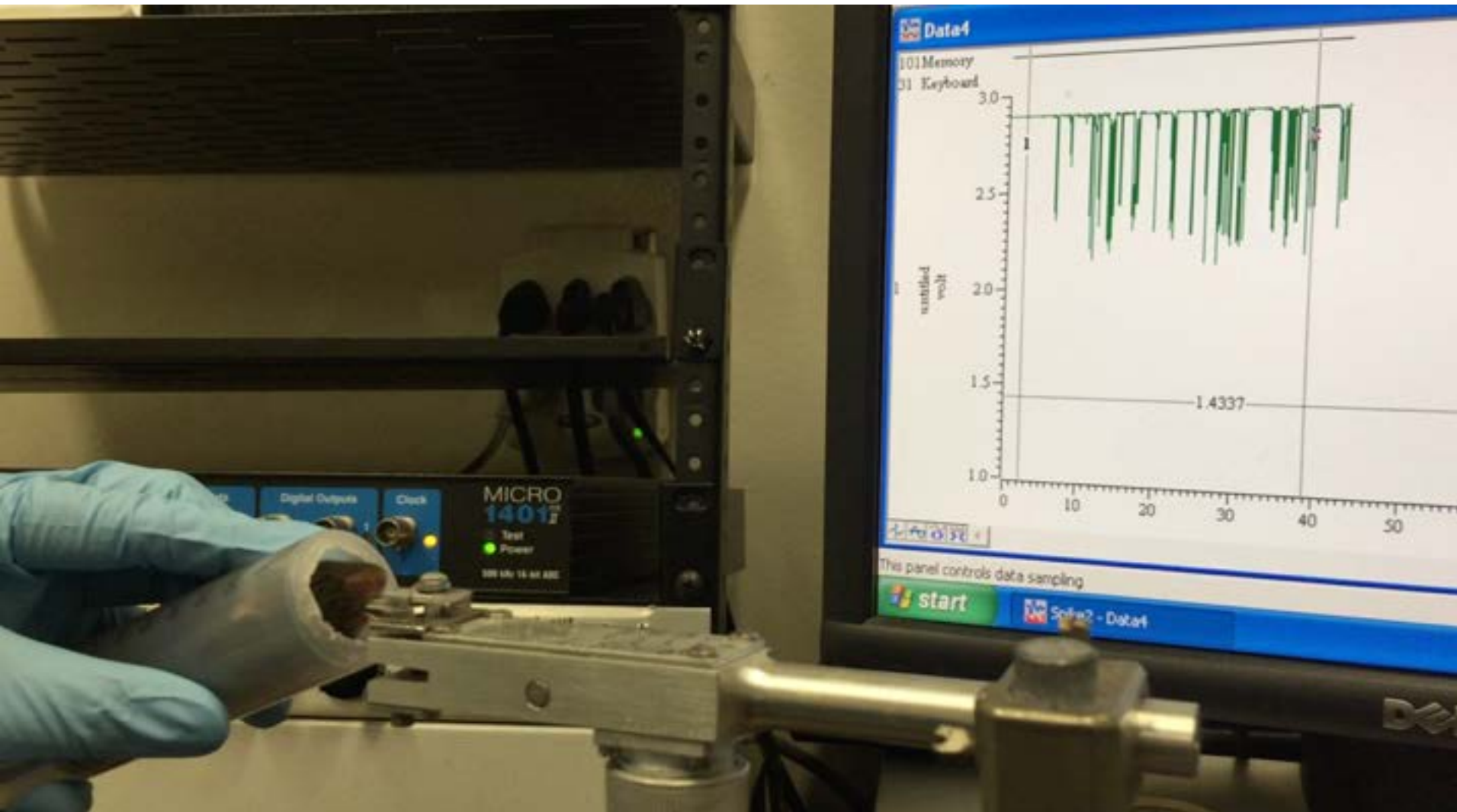
Operant behavioral assay



Cha et al., 2012

Neubert et al., 2005

Biting/Eating Behavior

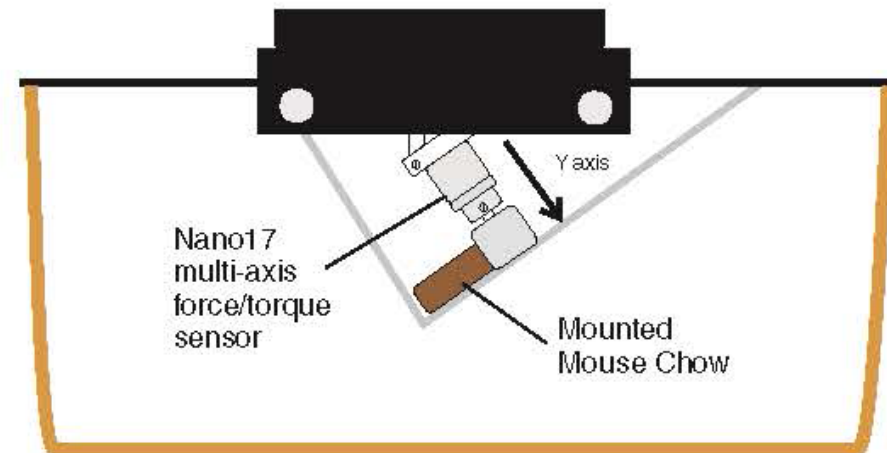
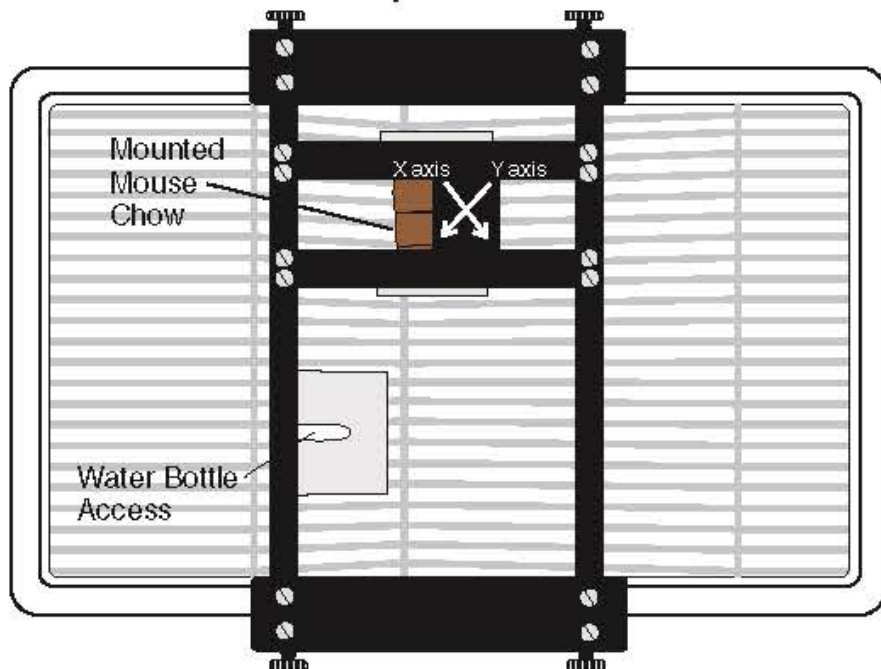




Assessment of incising ethology in the absence and presence of jaw muscle hyperalgesia in a mouse home cage environment

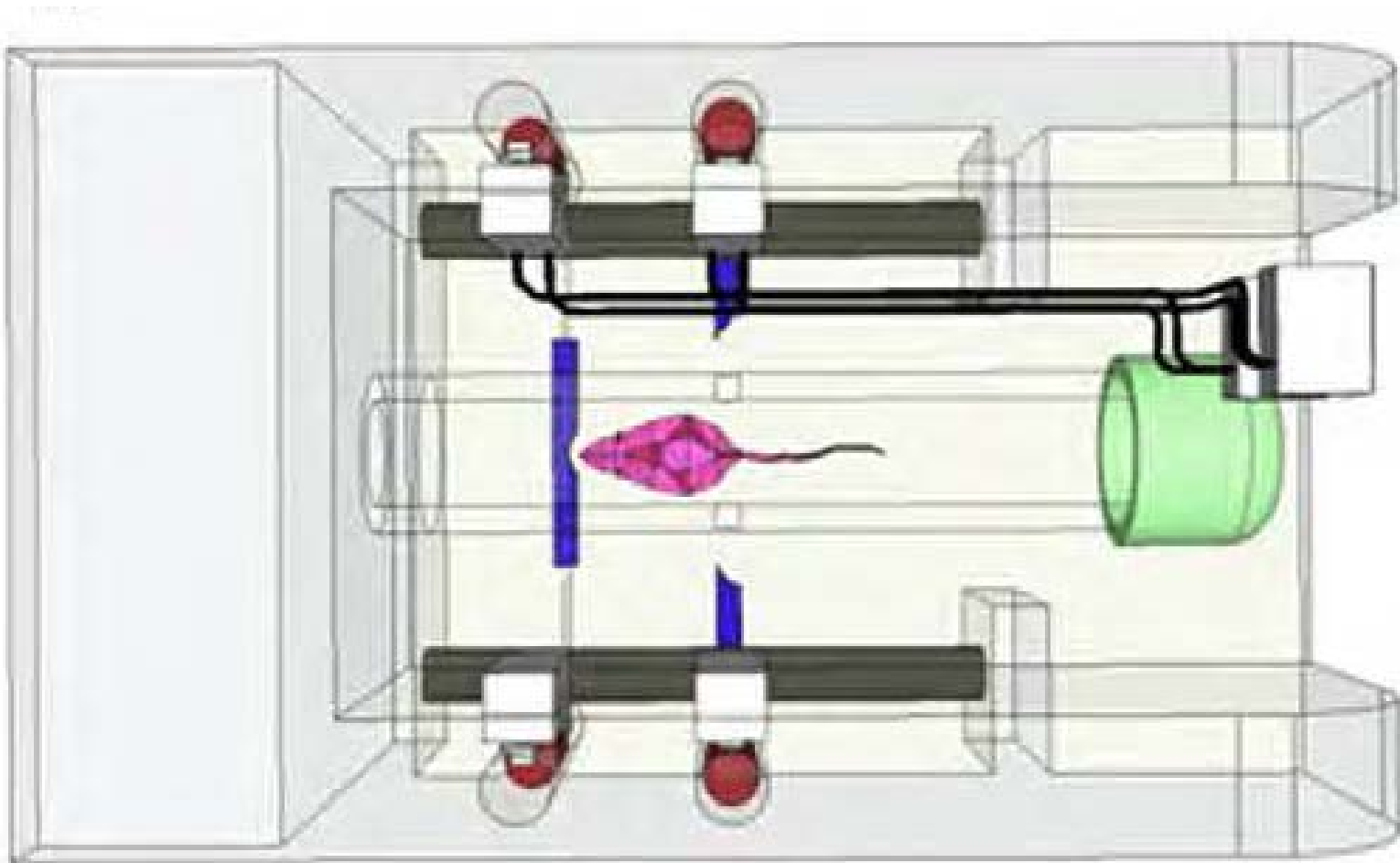
C.G. Widmer ^{a,*}, J. Morris-Wiman ^b

Top View



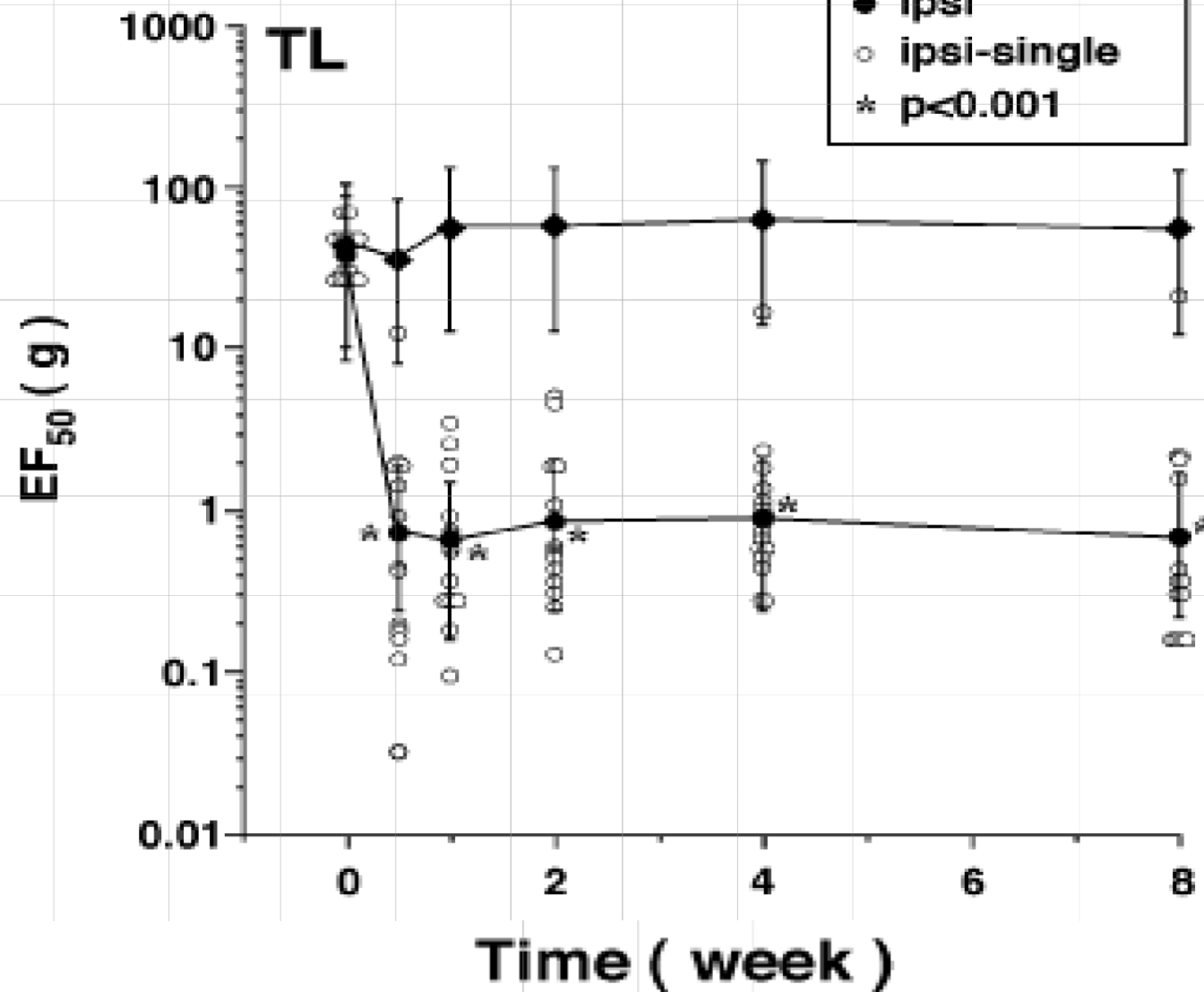
Side View

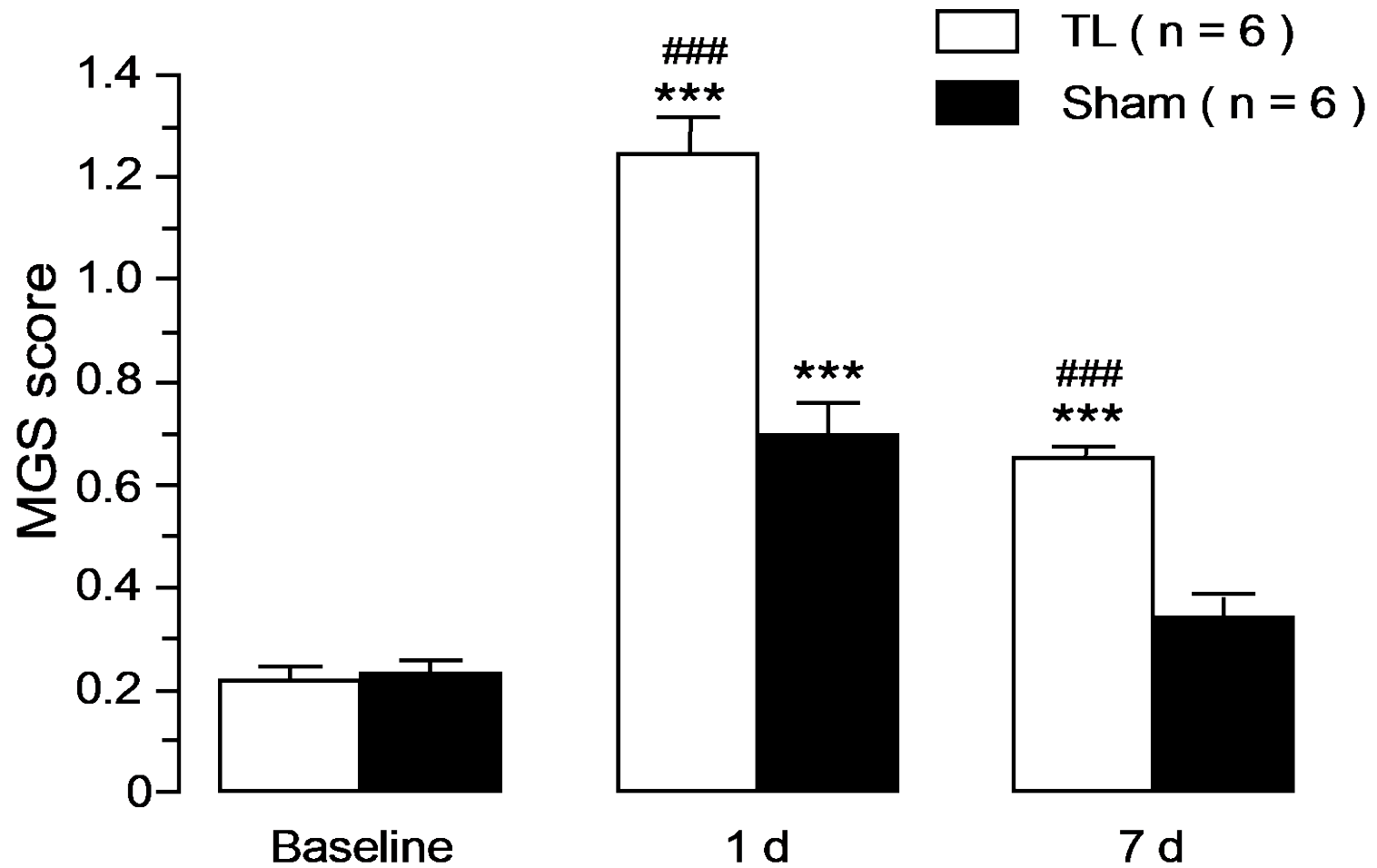
Dolognawmeter



Effect of masseter tendon injury

a



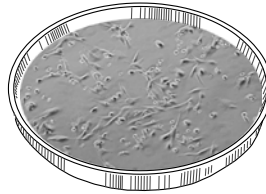
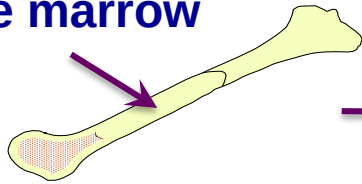


Guo et al., 2019

Lanford et al., 2010

Characterization of BMSCs

Bone marrow



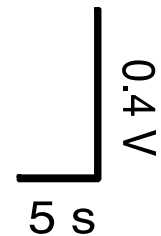
CD90 ⁺	CD45 ⁻
CD105 ⁺	CD11b ⁻
CD73 ⁺	CD34 ⁻
...	...

2d post-BMSCs

TL - BMSC

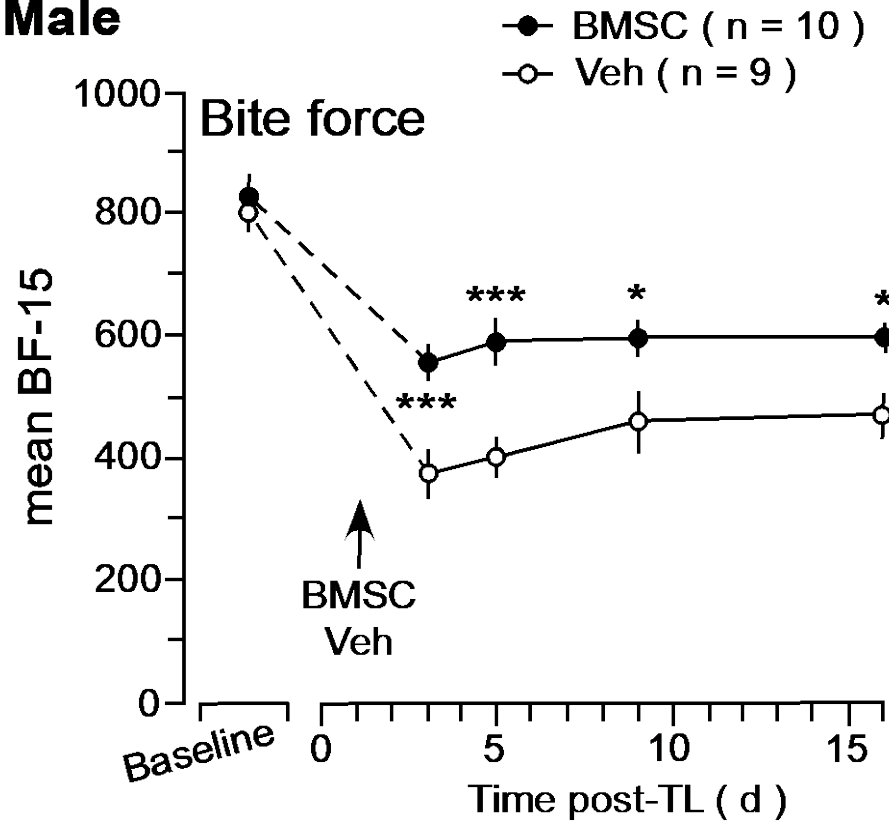


TL - Veh

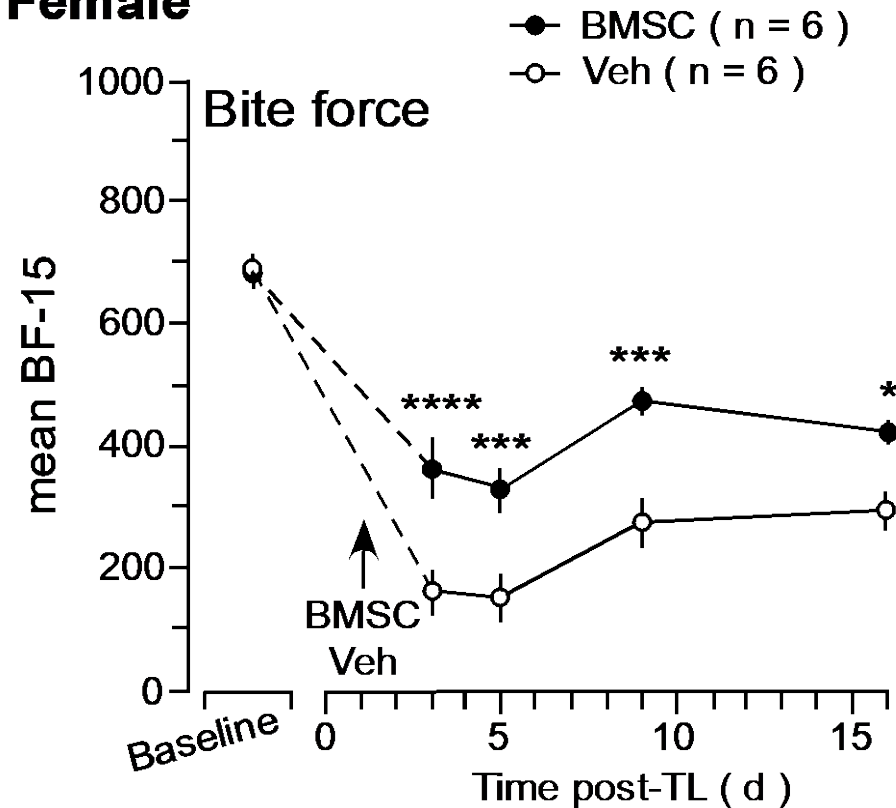


Effect of bone marrow stromal cells

Male

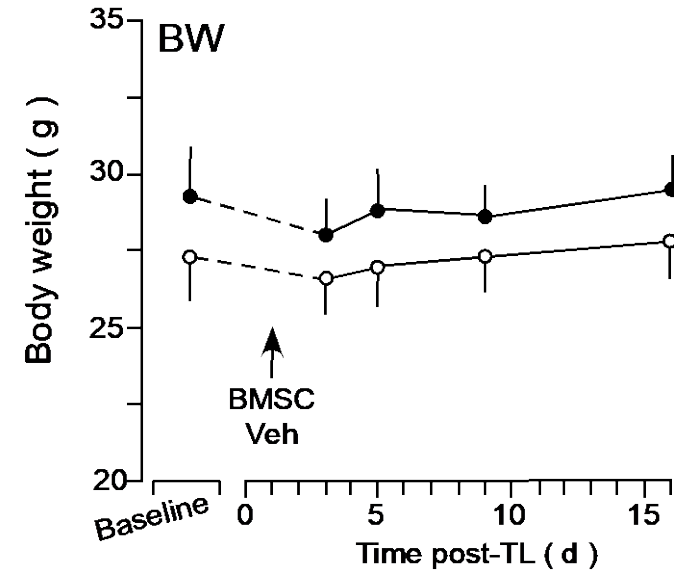
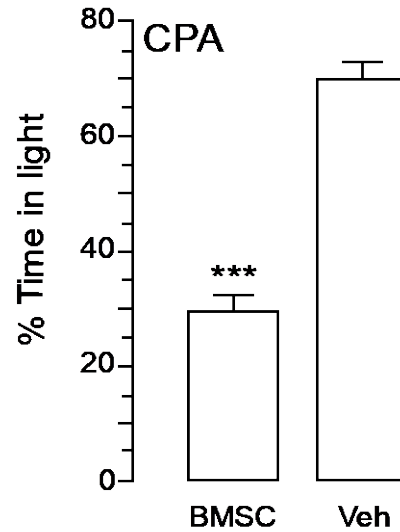
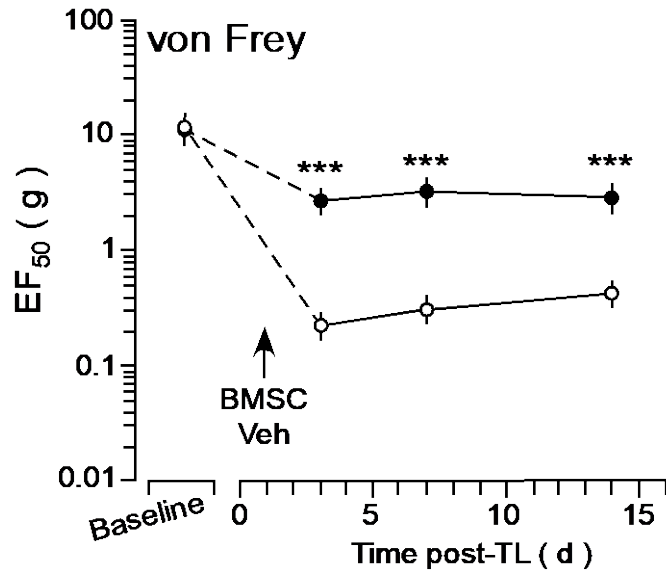


Female

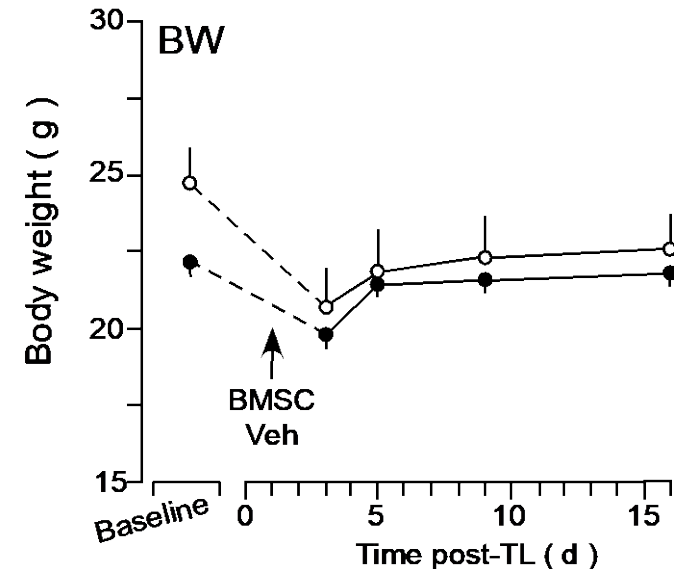
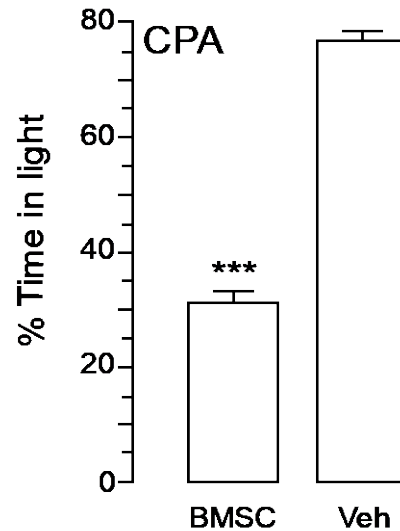
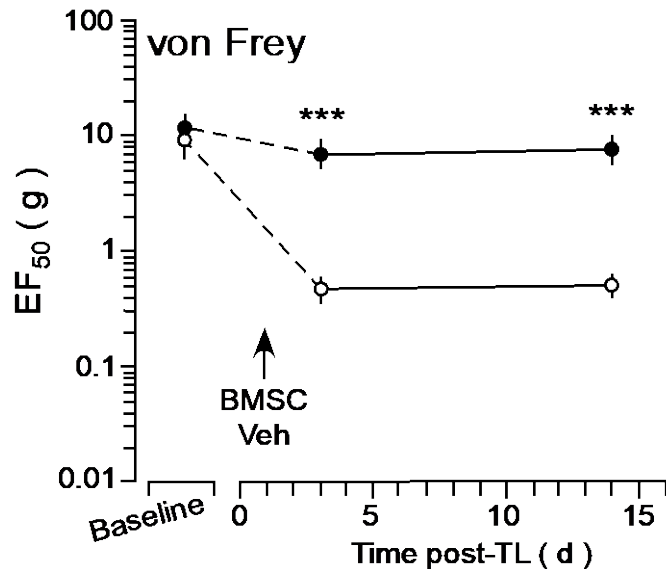


Effect of bone marrow stromal cells

Male

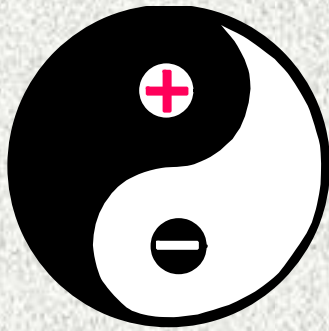


Female

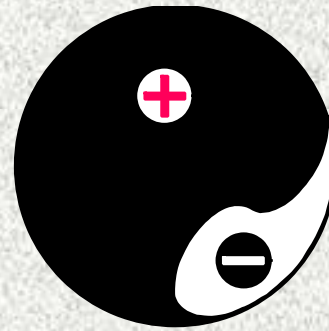


Perspectives

- ❖ **Relevance of animal models**
- ❖ **Relevance of study plan**
- ❖ **Incomplete understanding of mechanisms**



Balanced Immune Regulation



Reduced Inhibitory Regulation

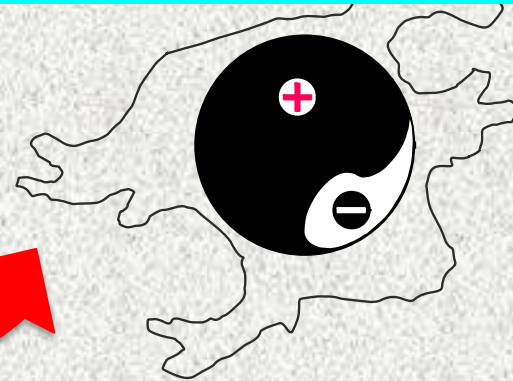
**Balanced Immune
Regulation**



To homeostasis

***Only killing weeds will be
insufficient to make a healthy lawn***

Reactivation



**Reduced Inhibitory
Regulation**

Suggestions/Recommendations

- ❖ Enhance interactions/collaborations between clinical and basic scientist
- ❖ Reversed translational approach to develop models more relevant to TMJD
- ❖ Studying pain chronicity, not only acuteness
- ❖ Immune homeostasis
- ❖ Systematical analyses of big data: -Omics (RNAs, proteins, epigenetics)

Acknowledgement

Wei Guo

Satoshi Imai

Shiping Zou

Jiale Yang

Zaid Mohammad

Feng Wei

Man-Kyo Chung

Jin Ro

Ron Dubner



*Maryland Stem Cell
Foundation*

2014-MSCRFI-0584



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DE025137