An Update from the NIH and NIDCR on Temporomandibular Joint Disorders & Pain Research

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NIDCR: Partnering Across NIH and Other Federal Agencies

- NIH Pain Consortium
  https://painconsortium.nih.gov/
- NIH Interagency Pain Research Coordinating Committee
  https://iprcc.nih.gov/
- FDA Medical Device Epidemiology Network TMJ Patient-Led RoundTable
  http://www.mdepinet.org/tmj-patient-led-roundtable-crn/
- NIH Blueprint for Neuroscience Research
  https://neuroscienceblueprint.nih.gov/
- NIH Helping to End Addiction Long-term (HEAL) Initiative
  https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative
NIH Pain Research Funding FY 2008 - 2017

1.5% of NIH total budget in FY2017

Total $516 M

$440 M

$76 M

FY 2017 Distribution Across NIH
FY2017 NIDCR Pain Research

### Funding by Research Type

- **Basic Research**: 53%
- **Clinical Research**: 37%
- **Translational Research**: 10%

### Funding by Mechanism Type

- **Research Project Grants (RPGs)**: 61%
- **Intramural**: 19%
- **Small Business**: 9%
- **Training and Career Development**: 8%
- **Other**: 3%
NIDCR’s Pain Research by Condition

FY2016

- TMD 32%
- Oral Cavity (pulpitis, dental, etc) 7%
- Oral Cancer 10%
- Neuropathic 23%
- Multiple Conditions 16%
- Broad 7%
- Post-surgical 4%

NIDCR pain research is diverse & includes investigation into aspects of:

- Biopsychosocial & genetic determinants of pain
- Neuroimmune interactions
- Sex Differences
- Model development
- Chronic overlapping pain conditions
- Behavioral science approaches
- Transition from acute to chronic pain

NIDCR
Thinking Broadly about NIDCR’s Pain Research Portfolio

FY2016

- TMD 32%
- Neuropathic 23%
- Oral Cancer 10%
- Multiple Conditions 16%
- Oral Cavity (pulpitis, dental, etc) 7%
- Post-surgical 4%
- Broad 7%

Interconnectedness of orofacial pain conditions

- Epigenetic basis for pain vulnerability
- Neuronal and glial interactions of neuropathic pain
- A new animal model for stress-induced transition from acute to chronic pain
- Defining the generators of spontaneous trigeminal pain
- Sex differences in serotonergic modulation of trigeminal pain
- Primary afferent plasticity in chronic pain
FY2017 NIDCR Temporomandibular Muscle/Joint Disorder (TMJD) Research

**Funding by Research Type**
- Clinical Research: 37%
- Basic Research: 57%
- Translational Research: 6%

**Funding by Mechanism Type**
- Research Project Grants: 75%
- Intramural: 14%
- Training and Career Development: 11%
NIDCR & TMD

NIDCR invests in a wide breadth of areas, with the goal of improving the health of those who suffer from TMDs including:

- Genomics and proteomics to compare the characteristics of normal & diseased TMJ tissue
- Systems biology to define the role of nervous, immune & circulatory systems in regulating jaw function in health and disease
- Tools & technologies to model masticatory muscles of the TMJ
- Joint mechanobiology using imaging and jaw tracking to examine TMJ pathology in relationship to loading, tissue nutrition & cell function
- Regenerative medicine
- Behavioral research to improve management of TMDs
- Dissemination and Implementation Research
The Impact of NIDCR’s Diverse Basic Research Portfolio

A craniofacial-specific monosynaptic circuit enables heightened affective pain
Erica Rodriguez 1, Katsuyasu Sakurai1, Jennie Xu1, Yong Chen2, Koji Toda3, Shengli Zhao1, Bao-Xia Han1, David Ryus1, Henry Yin1, Wolfgang Liedtke2 and Fan Wang1*

Different immune cells mediate mechanical pain hypersensitivity in male and female mice
Robert E Sorge1,2,10, Josiane C S Mapplebeck1,3,5,10, Sarah Rosen9, Simon Beggs2,5, Sarah Taves4, Jessica K Alexander3,5, Loren J Martin1, Jean-Sebastien Austin1, Susana G Sotochnical, Di Chen1, Mu Yang7, Xiang Qun Shi1, Hao Huang7, Nicolas J Pillon8, Philip J Bilan8, YuShan Tu3, Amira Klip6, Ru-Rong Ji6, Ji Zhang7,9, Michael W Salter3,5 & Jeffrey S Mogil1,9


Three-dimensional temporomandibular joint muscle attachment morphometry and its impacts on musculoskeletal modeling
Xin She1, Feng Wei4, Brooke J. Damon4,5, Matthew C. Coombs4,5, Daniel G. Lee5, Michael K. Lecholop4, Thierry H. Bacro4, Martin B. Steed4, Naiquan Zheng4, Xiaojing Chen4, Hai Yao4,5

Estrogen Promotes Mandibular Condylar Fibrocartilage Chondrogenesis and Inhibits Degeneration via Estrogen Receptor Alpha in Female Mice
Jennifer L. Robinson1,3, Paola Soria, Manshan Xu2, Mark Vrana1, Jeffrey Luchetti1, Helen H. Lu1, Jing Chen2 & Sunil Wadhwa.

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A Novel Approach: Craniofacial Tissue - Material Interactions

3-dimensional visualization of implant-tissue interface with the polyethylene glycol associated solvent system tissue clearing method

Yating Yi1,2 | Yi Men2 | Dian Jing1,2 | Wenjing Luo2 | Shiwen Zhang1,2 |
Jian Q. Feng3 | Jin Liu4 | Woo-Ping Ge5 | Jun Wang1 | Hu Zhao2

NIH National Institute of Dental and Craniofacial Research
Tissue engineering toward temporomandibular joint disc regeneration

Natalia Vapniarsky1*, Le W. Huwez*, Boaz Arzi3, Meghan K. Houghton4, Mark E. Wong5, James W. Wilsons, David C. Hatcher6, Jerry C. Hu7, Kyriacos A. Athanasiou7†
Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA)

- Genetic risk factors for TMD based on GWAS studies
- Psychological risk factors for TMD including heightened somatic awareness and stress
- Sleep complaints associated with chronic pain
- Differences in clinical pain perception between different ethnic groups
- Women are more likely to transition from acute to chronic pain
Incident injury is strongly associated with subsequent incident temporomandibular disorder: Results from the OPPERA study.

Sonia Sharma; Jean Wactawski-Wende; Michael LaMonte; Jiwei Zhao; Gary Slade; Eric Bair; Joel Greenspan; Roger Fillingim; William Maixner; Richard Ohrbach.

Effect of Human Genetic Variability on Gene Expression in Dorsal Root Ganglia and Association with Pain Phenotypes

Marc Parisien, Samar Khoury, Anne-Julie Chabot-Dore´, ..., Jeffrey S. Mogil, Inna Belfer, Luda Diatchenko

Cell Reports

PAIN. Incident injury is strongly associated with subsequent incident temporomandibular disorder: Results from the OPPERA study.

Sonia Sharma; Jean Wactawski-Wende; Michael LaMonte; Jiwei Zhao; Gary Slade; Eric Bair; Joel Greenspan; Roger Fillingim; William Maixner; Richard Ohrbach.
NIDCR Supported TMD Clinical Research

**Pharmacologic**
- Effect of COMT genetic polymorphisms on responses to propranalol therapy in Temporomandibular Disorder (SOPPRANO study)
- Preliminary Safety Study of Botulinum Toxin for Treatment of Myofascial TMJD Pain
- Genetic effects on expectancy-induced analgesia (placebo) in TMD

**Non-Pharmacologic**
- High-definition transcranial direct stimulation (HD-tDCS) for endogenous μ-opioid receptor modulation and lasting pain relief in chronic TMD
- Patient-centered, web-based program, to educate and engage TMD patients in a personalized program to improve exercise, diet, sleep, and oral health behaviors aimed at decreasing and preventing pain.
Lessons Learned

• Studies indicate TMDS are multifactorial conditions influenced by genetics, sex and gender, environmental and psychological factors but significant gaps remain in our mechanistic understanding of peripheral and central adaptations and psychosocial influences that promote chronification or resolution of TMDs.

• TMD patients with the most severe symptoms exhibit the greatest burden of comorbid conditions pointing to a multi-system disorder.

• The absence of a firm mechanistic understanding of TMD and clear etiological targets has precluded development and clinical implementation of safe and effective evidence-based treatments.

• TMDs are highly complex necessitating effective patient stratification approaches to facilitate precision medicine approaches.

• TMD models that recapitulate human pathophysiology are critical to development of safe and effective therapeutic interventions.

• Determination of the mechanisms that sustain or promote resolution of chronic TMD pain and strategies to intrinsically and/or extrinsically modulate these mechanisms present therapeutic opportunities.

• A fuller understanding of sex-based differences/influences underlying TMDs will facilitate development of therapeutic interventions.

• Leveraging recent technological advances and resources developed through the NIH BRAIN, Blueprint, and SPARC Initiatives are poised to enable significant advances.
Thank You!