TMJA
The TMJ Association, Ltd.

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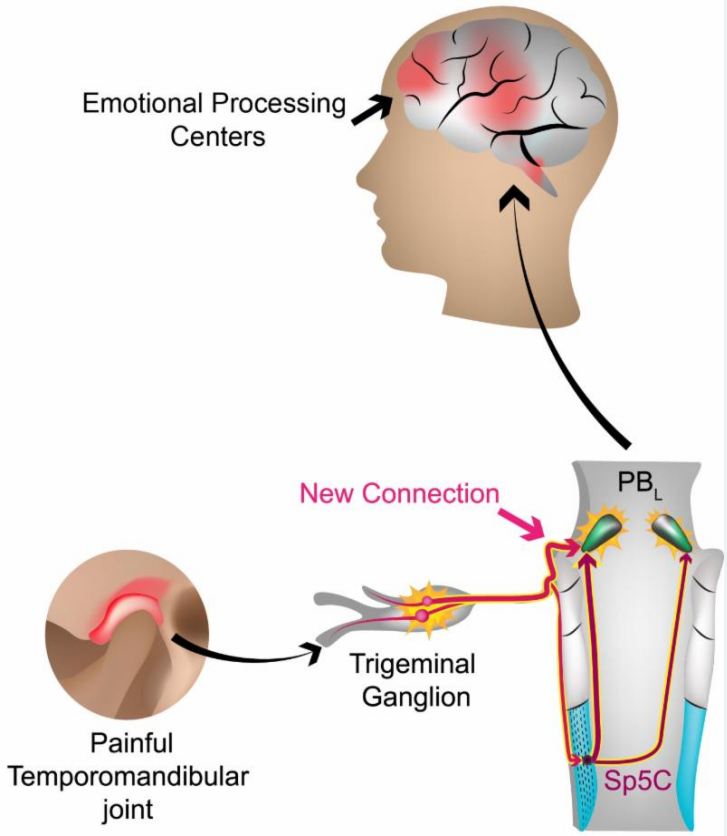
## Pain in Your Head Hurts More Than Elsewhere in the Body

Terrie Cowley, Co-Founder and President of The TMJ Association, often remarks that patients tell her that the pain they feel in their jaws is worse than pain elsewhere in the body. People with migraines, cluster headaches or trigeminal neuralgia would agree. Now you might guess that this is because the face is more generously supplied with nerve endings than other parts of the body (true) and the ratio of nerves to muscles is high. And that is why you can make such exquisitely fine facial movements and expressions. But a more exciting and interesting finding has emerged from experiments by researchers at Duke University in Durham, North Carolina, and reported recently in *Nature Neuroscience*.[1] The team discovered a direct route from the neurons that sense pain in the face or head to neurons in the brain that connect to key emotional centers, areas that evoke the suffering associated with pain and the fear, anxiety and depression that so often go along with it.

You need some neuro-anatomy to understand this. In the head, the neurons that send sensory fibers out to facial and head areas have their cell bodies in the **trigeminal ganglion**, a cluster of neurons that lies just outside of the brain, one on each side of the head.

The ganglion cells include those sensitive to touch, pressure, heat and cold as well as pain, whose fibers contact the meningeal membranes inside the skull, relevant for all headaches, the cornea of the eye, the teeth, tongue, sinuses, lips, and facial skin. From the ganglion the pain-sensing nerve cells, nociceptors, transmit signals along fibers at their other end (their axons) that connect with the brain. Some project to areas where they signal the




The figure depicts a schematic of the novel emotional pain circuit described in the Rodriguez-et-al paper. PBL - lateral parabrachial nucleus Sp5C - trigeminal spinal nucleus nucleus caudalis subsection. Previous understanding indicated that the pain-relaying impulse such as from a

location of your pain and how intense it is.

painful TMJ traveled to the Sp5C where it was synaptically relayed to the PBL. The hitherto unknown direct plugin connect directly to the PBL is then relayed to emotional processing centers in the brain.

Some find their way to cells in the **parabrachial (PB) nucleus** (clusters of neurons in the brain are called nuclei). There are two parabrachial nuclei that hug either side of a portion of the midbrain, a part of the brain under the cortex and over the spinal cord. **The startling finding of the Duke researchers was that there is a direct pathway for facial/head pain signals from the trigeminal ganglion to the lateral part of the parabrachial nucleus and from there to multiple sites in the brain associated with feelings and emotion.** The investigators describe this as a one-synapse ("monosynaptic") pathway-from ganglion cell to lateral PB with no other relay station in between. Of note, this new monosynaptic projection appears to be an exclusive pathway for trigeminally-mediated pain only.

In contrast, pain from the body does not have an express route to feelings but relays to the PB via a way-station in between. Indeed, trigeminal pain neurons were traditionally thought to use an indirect route to the PB through a nucleus in the brain called the spinal trigeminal nucleus caudalis. So what the Duke team discovered is a second streamlined pathway. That in itself offers hope for new ways to treat refractory facial pain because past efforts have only looked at ways to intervene in the traditional pathway. **In addition, the investigators demonstrated that the facial/head pain signals to the PB are more extensive than for an equally intense body pain, and also contact PB nuclei on both sides of the brain, even though the pain may have originated on only one side.**

To demonstrate these properties, new sophisticated technologies were used, including one invented by Fan Wang, senior author of the paper and chief of the laboratory where the experiments were conducted. A major complication the team faced is that the PB nuclei are made up of many different kinds of neurons receiving a range of sensory inputs, including taste stimuli. They also contain neurons involved in regulating hunger and thirst. Moreover, PB neurons, including nociceptors, use a variety of neuro-transmitters in their operations. Other relevant molecules in nociception include TRPV1, a receptor for the hot pepper ingredient capsaicin, and CGRP, calcitonin gene related peptide, which has an established role in migraine headaches and in sustaining neuro-inflammation.

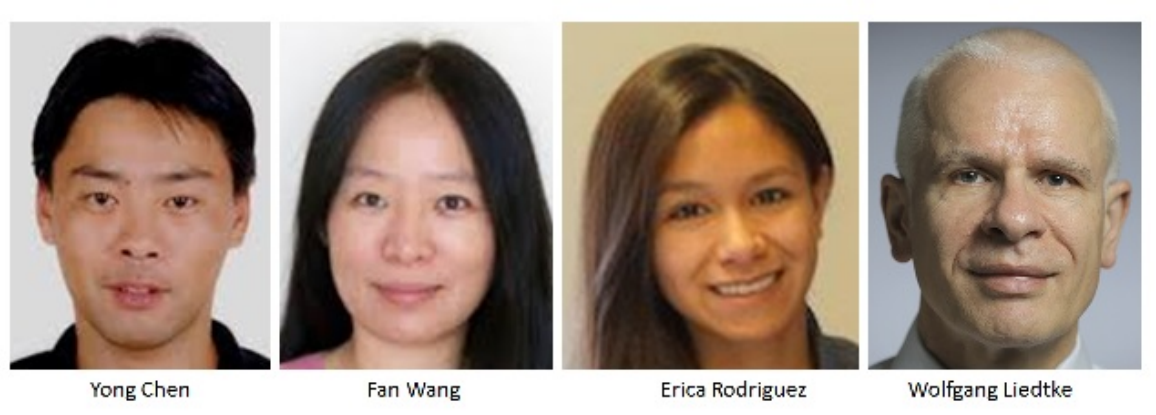
So the first step for the investigators was to determine which parts of the PB might be rich in nociceptive neurons and the neurotransmitters they used. In experiments with mice, the investigators injected equal amounts of a painful chemical irritant such as formalin into either the whisker pads or the hind paws of the mice. This would stimulate nociceptors in the trigeminal ganglion for the whisker pad or a comparable ganglion adjacent to the spinal cord for the hind paw. From there some pain signals would relay to the PB nuclei. To trace which PB neurons were responsive to pain, the researchers made use of a genetic change in affected nerve cells. It turns out that a sensory stimulus triggers the production of an "immediate-early gene" in the nerve cell, generating a protein of a family called Fos, enabling it to be used as a marker for activated neurons. The investigators could inject formalin unilaterally in the mice, wait for the production of Fos, then extract PB brain tissue and stain it to reveal Fos. In this way they located the lateral PB, especially an external sub nucleus, PB-el, as the locus of PB nociceptive neurons. The same staining method demonstrated that pain neurons excited by signals from the whisker pad were more numerous than those from the hind paw and were found in both PB nuclei rather than predominantly on one side.

Now the question was the source of the face pain inputs to the PB. Did they stem from the traditional indirect route through the trigeminal spinal nucleus caudalus or was there a direct trigeminal ganglion to PB route? To do the back tracing of inputs the Duke team

employed a ground-breaking new technology developed by Dr. Wang called **CANE**, for **Capturing Activated Neuronal Ensembles**. The method was used for selectively labeling and remote-controlling a population of pain-activated PB cells. The task to establish the pre-synaptic source for the inputs to the PB-el was more complicated. It required injections of different viral-protein combinations into the PB after formalin injections to mouse whisker pads. These injections were followed two weeks later by yet another combination injection into the same part of the PB. The clincher here was finding that the second injection labelled cells in both the PB-el AND the trigeminal ganglion proving that the ganglion cell was the source of a direct input to the PB nucleus.

Additional experiments established that PB-el neurons project widely to emotional processing centers in the brain such as the amygdala, known to play an important role in generating fear and anxiety. In turn, these same emotional areas also project back into the PB-el in a loop. Finally, the Duke researchers employed yet another sophisticated technique, optogenetics, to investigate pain-related behaviors in mice. They implanted optic fibers in a selected set of trigeminal pain neurons whose axons terminate in the PB-el. When light of the appropriate wave length is shined on the fibers it activates the nerve cells. The team then observed the behavior of mice exposed to a two-chamber spatial arrangement. Without optic stimulation the mice freely explore the space and may choose one of the two chambers as preferred. When the pain stimulation was turned on while the mice were in the preferred chamber, however, they immediately ran to the opposite chamber often vocalizing with typical stress calls. Other experiments showed that silencing optogenetic stimulation could reverse the aversive behavior and had additional analgesic effects in other pain behavioral tests. In sum, the team interprets these experiments as further evidence of the significance of the direct trigeminal PB connection in pain perception and behavior.

**The Future.** As noted earlier, the establishment of a second pathway governing face/head pain in relation to emotions and feelings offers new approaches to treatment, perhaps targeting molecules such as TRPV1 or CGRP. In addition, ways to moderate or even selectively sever connections established by the new monosynaptic pathway may provide relief to patients where previous surgery, for trigeminal neuralgia, for example, has been ineffective.




**About the team.** It is noteworthy that the paper reporting the discovery of the new pathway was based on experiments in Dr. Wang's laboratory executed as part of the PhD thesis of the first author Dr Erica Rodriguez. She herself is no stranger to pain as a result of sports-related herniated discs and surgery. Dr. Wolfgang Liedtke who also sees patients with "refractory" trigeminal pain disorders in his two clinics at Duke University, and Dr. Yong Chen from his laboratory, also contributed important experiments to the paper. Previously, Chen, Wang and Liedtke described a new method to measure TMJ pain equivalents in laboratory mice. Assessment of effects of TMJ injury and TMJ pain on the newly established trigeminal pain circuits will be an appealing logical next step for the Duke team.

[1]A craniofacial-specific monosynaptic circuit enables heightened affective pain. **Rodriguez E, Sakurai K, Xu J,Chen Y, Toda K, Zhao S, Han BX, Ryu D, Yin H,**
**Liedtke W, Wang F. Nat Neurosci. 2017 Dec;20(12):1734-1743. doi: 10.1038/s41593-017-0012-1. Epub 2017 Nov 13.**

**Additional References:**
Temporomandibular joint pain: a critical role for Trpv4 in the trigeminal ganglion.
**Chen** Y, Williams SH, McNulty AL, Hong JH, Lee SH, Rothfusz NE, Parekh PK, Moore C, Gereau RW 4th, Taylor AB, **Wang** F, Guilak F, **Liedtke** W. *Pain.* 2013 Aug;154(8):1295-304. doi: 10.1016/j.pain.2013.04.004. Epub 2013 Apr 6.

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## Stem Cell Study of Jaw Development Could Offer Insight Into Craniofacial Flaws

*The following article appeared in USC University of Southern California News*

Scientists in the USC Stem Cell laboratory of Gage Crump have revealed how key genes guide the development of the jaw in zebrafish. These findings may offer clues for understanding craniofacial anomalies in human patients, who sometimes carry a mutation in equivalent genes.

A time-lapse animation shows skeletal stem cells of the embryonic zebrafish head in green and early-forming cartilaginous facial skeleton in magenta. (Video/Lindsey Barske)

In the study published in Developmental Cell, first author Lindsey Barske and colleagues reported that two related genes, called Nr2f2 and Nr2f5, pattern the jaw by regulating the timing by which stem cells generate skeletal cells.

As in our bodies, the fish skeleton generally starts out as cartilage and is later replaced by bone. However, most upper jaw bones develop without any cartilage template. Nr2f genes prevent stem cells in the developing upper jaw from becoming cartilage early on, so that they are available to make more bone later. This is in contrast to the lower jaw, where another gene called Endothelin1 (Edn1) prevents Nr2f activity and allows for the formation of extensive early cartilage that drives the outgrowth of the lower jaw.

"Our study illustrates the idea that the development of any organ requires a balance between early maturation and maintenance of stem cells. Without inhibitory signals like the Nr2f genes, there probably wouldn't be enough uncommitted precursors left over to make later-forming cell types or maintain adult tissues," said Barske, a postdoctoral fellow and winner of a prestigious Pathway to Independence Award from the National Institutes of Health.

### Taking a novel approach

Prior to this work, little was known about the signals that pattern the upper jaw. The scientists took a novel genomics approach to identify new genes important for upper jaw development, carefully defining all the genes expressed during early jaw development. They then used a powerful type of genome editing to remove many of these genes from the genome, and in so doing discovered that zebrafish mutants lacking several Nr2f genes displayed a second, cartilage-based lower jaw where the

upper jaw should be.

"The power of this approach is that hundreds of genes can be functionally tested in a cost-effective, rapid manner in zebrafish, thus allowing us to assign new functions for the many poorly characterized genes in the genome," said Crump, professor of stem cell biology and regenerative medicine at the Keck School of Medicine of USC.

Additional co-authors include Pauline Rataud, Kasra Behizad, Lisa Del Rio and Samuel G. Cox from USC's Department of Stem Cell Biology and Regenerative Medicine at the Keck School of Medicine.

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Seventy-five percent of the research was supported by $262,500 in federal funding from the National Institute of Dental and Craniofacial Research (R01 DE018405, R35 DE027550 and K99 DE026239), and 25 percent by $87,500 of non-federal funding from the A.P. Giannini Foundation. The USC Office of Research and the USC Norris Medical Library funded the bioinformatics software and computing resources.

## TMD and Burning Mouth Syndrome

A study in the *International Journal of Dental Research* reporting the latest update on Burning Mouth Syndrome (BMS) noted two thirds of BMS patients also had Temporomandibular Disorders (TMD). Burning mouth syndrome is characterized by a recurrent daily burning sensation with no evidence of lesions in the oral mucosa. It is accompanied by subjective dry mouth and dysgeusia (dysfunction of the sense of taste). The tongue is the most commonly affected site, but the condition also affects other sites in the mouth. Its cause and diagnosis is made by exclusion.

We bring this to your attention as we continue to learn about the complexity of TMD as a multi-systems illness with an increasing number of comorbid conditions.

## Study Links Lack of Sleep to Pain Sensitivity

A study in the journal *Nature Medicine* found a strong association between sleep deprivation and pain sensitivity. Researchers said ibuprofen and morphine did not prevent or stop the effects of pain hypersensitivity linked to sleep deprivation. Read more in: Medical News Today.

## NIDCR and Hill Visits

On February 26, TMJA staff participated in the Friends of the National Institute of Dental and Craniofacial Research (NIDCR) Patient Advocacy Council (PAC), an umbrella group comprising non-profit organizations that work together to advance dental, oral, and craniofacial health research and to move that research from the lab to the clinic. The FNIDCR PAC members in attendance represented seven patient advocacy organizations. Attended by NIDCR senior staff, as well as two representatives from the American Dental Education Association, the meeting aimed to foster an ongoing conversation around patient needs and research advances, gaps, and opportunities.

The TMJA also participated in the Advocacy Day on the Hill the following day to advocate for increased

investments in TMJ research. The day included a morning briefing and an afternoon dedicated to meetings with members of Congress and Hill staff.

TMJA staff meets with Senator Grassley of Iowa

## NIH Funding Opportunities

Basic and Clinical Research

In an effort to promote greater understanding of TMD, and to develop safe and effective evidence-based diagnostics and treatments, The TMJ Association promotes and encourages basic and clinical research on Temporomandibular Disorders. Click here to view the latest National Institutes of Health (NIH) funding opportunities for scientists interested in advancing TMJ research. The following NIH research opportunities are currently available:

- Clinical Validation of Candidate Biomarkers for Neurological Diseases (U01 Clinical Trial Optional)
- Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement
- Specialized Centers of Research Excellence (SCORE) on Sex Differences (U54)
- Factors Underlying Differences in Female and Male Presentation for Dental, Oral, and Craniofacial Diseases and Conditions (RO1) (R21)
- NIDCR Small Research Grants for Secondary Analysis of FaceBase Data (RO3)
- Tailoring Dental Treatment for Individuals with Systemic Diseases that Compromise Oral Health (R01) (R21)
- Personalized Strategies to Manage Symptoms of Chronic Illness (R15) (R01) (R21)
- Research on the Mechanisms and/or Behavioral Outcomes of Multisensory Processing (R01)
- Blueprint Neurotherapeutics Network (BPN): Small Molecule Drug Discovery and Development for Disorders of the Nervous System (UH2/UH3) (U44)
- Population Health Interventions: Integrating Individual and Group Level Evidence (R01)
- Family-Centered Self-Management of Chronic Conditions (R21) (R01)
- mHealth Tools for Individuals with Chronic Conditions to Promote Effective Patient-Provider Communication, Adherence to Treatment and Self-Management (R01) (R21)
- The Biomarkers Consortium
- Blueprint Neurotherapeutics Network (BPN): Small Molecule Drug Discovery and Development of Disorders of the Nervous System (UG3/UH3 Clinical Trial Optional)

## In Memorium

Milton and Renee Glass were the Co-Founders of Jaw Joints and Allied

Musculoskeletal Disorders Alliance. Over the years we applauded their advocacy and efforts to get the best science directed toward TMJ. We recently learned of Milton's death and offer our deepest sympathy to Renee and their daughter Jill and son Mikal.

## Research E-Newsletter


*Cutting Edge - COPCs Research Advances*, is an electronic newsletter published by the Chronic Pain Research Alliance, an initiative of The TMJ Association. Developed to keep the medical-scientific community abreast of recent research advances, this publication contains abstracts of recently published studies on the epidemiology, pathophysiology and clinical management of Chronic Overlapping Pain Conditions. These conditions include **temporomandibular disorders**, chronic low back pain, chronic migraine and tension-type headache, endometriosis, myalgic encephalomyelitis/chronic fatigue syndrome, fibromyalgia, vulvodynia, irritable bowel syndrome and interstitial cystitis/painful bladder syndrome.

The most current issues are now available for your review at: http://www.cpralliance.org/New_Findings. If you would like to receive future issues of *COPCs Research Advances*, click here to register.

## Educational Brochures on Chronic Overlapping Pain Conditions

This brochure addresses Chronic Overlapping Pain Conditions (COPCs), how COPCs are diagnosed, the complexity of the chronic pain experience, and how to work with your health care provider to develop a treatment plan. It is available by postal mail or as a PDF on our website.

## Educational Brochures on TMD

*Your Guides for Temporomandibular Disorders* - This brochure written by the TMJA is a straightforward, easy-to-read booklet that guides patients in how to make health care decisions. It is available by mail or as a PDF on our website and we encourage you to share it with your friends, health care professionals and family members.

*TMJ Disorders* - This brochure is produced and distributed by the National Institute of Dental and Craniofacial Research in partnership with the Office of Research on Women's Health, components of the National Institutes of Health (NIH) in Bethesda, Maryland. Part of the U.S. Department of Health and Human Services, NIH is one of the world's foremost medical research centers and the federal focal point for medical research in the United States. This booklet is available in English and Spanish at: https://www.nidcr.nih.gov/OralHealth/Topics/TMJ/TMJDisorders.htm.

## Dental Care Guide

*Temporomandibular Disorders, Dental Care and You*

The TMJ Association developed this guide to provide you with oral hygiene self-care tips that you can do at home, as well as suggestions for future dental appointments. Routine maintenance of your teeth and gums should reduce the risk of dental disease and the need for invasive dental treatments. Click here to view on our website.

## *TMJ Science* Journal

Our latest issue of *TMJ Science*, which includes the summary and recommendations from our 8th scientific meeting-*How Can Precision Medicine Be Applied to Temporomandibular Disorders and Its Comorbidities*–is now available. We hope you're impressed with how far the science of Temporomandibular Disorders has come. We invite you to read this new publication which is available in the publication section of our website as a pdf file.

## *Words of Wisdom*

*If you want to truly understand something, try to change it.*

Kurt Lewin, German-American psychologist

## Support Our Work

The TMJ Association (TMJA) is the only patient advocacy organization fighting for the best science that will lead to a greater understanding of Temporomandibular and related disorders, as well as safe and effective treatments. We cannot c*hange the face of TMJ* without YOU.

Click HERE to make a tax-deductible online contribution today!


## About The TMJ Association

*Changing the Face of TMJ*

The TMJ Association, Ltd. is a nonprofit, patient advocacy organization whose mission is to improve the quality of health care and lives of everyone affected by Temporomandibular Disorders (TMD). For over 25 years, we have shared reliable information on TMD with people like you. We invite you to visit our website, www.tmj.org.

- If you're not currently receiving *TMJ News Bites* and would like to be on our mailing list, sign up here.
- Read Past issues of TMJ News Bites available on our website.

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