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THE SIXTH SCIENTIFIC MEETING OF THE TMJ ASSOCIATION

Comorbid Chronic Pain Conditions - Mechanisms, Diagnosis and Treatments

Meeting Abstracts

Federation of American Societies
for Experimental Biology (FASEB)
Bethesda, Maryland
June 5–7, 2011

TMJA
The TMJ Association, Ltd.

This project is supported by Grant Number R13DE022238-01
from the National Institute of Dental and Craniofacial Research
and by an educational grant from Purdue Pharma L.P.

Association of Central Sensitivity Syndromes with Chronic Diseases Having Structural Pathology

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The mutual associations of a number of conditions without structural pathology, e.g., fibromyalgia syndrome (FMS), irritable bowel syndrome (IBS), temporomandibular disorders, migraine, interstititial cystitis (IC) and restless legs syndrome (RLS) are well known. Collectively they have been called CSS since central sensitization (CS) is a common glue between them.[1] Less recognized are several diseases with structural ("organic") pathology (DWSP) that are associated with CSS, particularly FM. The prevalence of FMS in selected DWSP are shown in the table below:

Disease*	SLE # of studies-10	RA # of studies- 3	pSS # of studies- 5	HCV # of studies- 3	Female AS # of studies-2
Mean % FM (Range)	19.4 (8.2-35.7)	15.0 (13.4-17)	29.8 (5-55)	13.3 (5-19)	30 (10.8-50)
Selected ref.	2,3	4	5	6	7

* SLE- systemic lupus erythematosus; RA- rheumatoid arthritis; pSS- primary Sjogren's syndrome; HCV- hepatitis C virus infection; AS- ankylosing spondylitis

The mean % of FM in other diseases with limited studies are as follows: Osteoarthritis -70; diabetes mellitus- 13; Lyme disease- 45; Crohn's disease- 49; ulcerative colitis- 19. CS with generalized hyperalgesia without FMS was found in osteoarthritis, [8] carpal tunnel syndrome, chronic pancreatitis,[9] RA, and juvenile chronic arthritis.[10] IBS was described in 50% of pSS.[11] 28% of IC had pSS.[12]

Associations do not imply a causal relationship. Of the two associated conditions, which came first, and is there a bidirectional association?

Demonstration of CS in several diseases as above suggests a peripheral source of nociception in many diseases that may subsequently give rise to widespread hyperalgesia and pain. Other mechanisms may involve genetic, endocrine, cytokine, sleep, infection or psychosocial stress factors as well as stress of chronic pain and disease.

In conclusion, a new paradigm is emerging where many chronic conditions with structural pathology have associated FM (and likely other CSS). Many more, yet to be studied (e.g., Parkinson's disease, multiple sclerosis and other neurologic conditions, chronic infectious diseases), are likely to demonstrate CS and association with various members of the CSS family. The implication is enormous for a practicing physician since proper management of these diseases with concomitant CSS must target the central nervous system (central analgesics, addressing psychosocial factors and cognitive behavioral therapy). Such a patient may indeed benefit from a centrally acting drug, such as milnacipran or duloxetine. These associations also provide an opportunity for academicians to study the complexity of chronic diseases and their interaction with CSS.

(Continues on next page)

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Disclosure of Relevant Financial Relationships: None

Fundamentals of What We Know and Do Not Know about Comorbid Chronic Pain Conditions, Including the Role of the Somatomotor and Autonomic Nervous Systems

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Chronic pain can be divided into three large categories: Chronic inflammatory pain, neuropathic pain and complex persistent generalized pain, here called comorbid chronic pain conditions (CCPS). The first two categories of chronic pain are clinically well defined, their underlying mechanisms being related to the biochemical, morphological and physiological changes of the peripheral afferent neurons and of the central representations. CCPS are characterized by deep somatic and/or visceral pain that has the tendency to generalize and is correlated with changes involving the autonomic nervous, the somatomotor and the neuroendocrine systems. The mechanisms underlying CCPS cannot be reduced to a peripheral process (and the subsequent central changes) such as sensitized deep somatic or visceral nociceptors. It is hypothesized that CCPS are the result of central dysregulation involving mechanisms in the spinal cord, brain stem, and forebrain which include the efferent motor systems. The role of the efferent systems in the generation and maintenance of pain must be seen in the context of regulation of protection of the body tissues orchestrated by the brain. This includes fast and slow defense, involves also the immune system and leads to recuperation and healing. Are the centrally regulated autonomic, in particular sympathetic, neuroendocrine and somatomotor changes exaggerated adaptive responses of the body that occur in parallel to the pain, or are these efferent changes causally involved in the generation of CCPS? Are small-diameter afferent neurons activated or enhanced in their activity by the efferent (autonomic, neuroendocrine or somatic motor) outflows to the peripheral deep somatic or visceral tissues in such a way that pain and associated changes are produced? Thus, are pain and changes in the efferent (autonomic and somatic) target tissues parallel events generated by the brain, or under the pathophysiological conditions of CCPS also sequential events leading to body loops via the efferent and afferent systems and mismatch in the communication between the efferent and the afferent central representations? Conceptually, patients with complex regional pain syndrome (CRPS) may serve as an instructive example to be applied to CCPCs. CRPS is a disorder of the brain involving the dysregulation of somatosensory, somatomotor and sympathetic systems. Visceral CCPS, such as irritable bowel syndrome, chronic pelvic pain or other chronic visceral pains, may also involve spinal autonomic systems to the visceral organs, leading to amplification of the afferent signals from the visceral organs without detectable pathology of the visceral organs. The primary cause of these chronic visceral pains may be a central dysregulation of autonomic systems and of ascending visceral sensory systems.

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Disclosure of Relevant Financial Relationships: None

Capturing 3D Tissue Complexity In Vitro

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Tissue engineering is the process of creating functional 3D tissues using cells combined with scaffolds or devices that facilitate cell growth, organization and differentiation(1). The field of tissue engineering is at a crossroads. Straight ahead lies the arduous path to successful clinical therapies for replacing human heart, liver, cartilage and other tissues — a road arguably longer and more challenging than it appeared about two decades ago when the field sprang to life, as fewer than 10 products have made it to the clinic to date(2). The side road, for now less travelled, leads to engineered tissue and organ mimics that will never be implanted directly into patients but will instead be used to transform the way we study human tissue physiology and pathophysiology in vitro. There is an increasing demand for in vitro models that capture more of the relevant complexity than traditional 2D cultures can achieve. Individual cells integrate multiple external cues — including those arising from various extracellular matrix (ECM) components, mechanical stimulation and soluble signals from adjacent and even distant cells — to generate a basal phenotype and respond to perturbations in their environment. A particular challenge is the coupling of chemical and mechanical signals(1). This talk will draw from several examples to illustrate how these signals are coupled quantitatively and describe how advances in synthetic biomaterials, microreactors and quantitative analysis are converging to enable the creation of in vitro models that capture some of these complex features of the in vivo environment, and how they might be applied to chronic pain research.

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Disclosure of Relevant Financial Relationships: None

The Epidemiology of Comorbid Chronic Pain Conditions

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The talk will provide data on:

- Population prevalence of regional and widespread musculoskeletal pain.
- Review the patterns of prevalence by age and gender and how the former differ by regional pain site.

Using population-based epidemiological studies, the talk will examine the hypothesis that:

- Comorbid pain occurs more frequently than one would expect by chance in patients with orofacial pain/ TMJ.
- There are common aspects to aetiology in terms of self-reported factors and sensitivity to pain on examination.

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Disclosure of Relevant Financial Relationships: None

Human Genetic Association Studies of Comorbid Chronic Pain Conditions

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Tremendous individual variability is observed in experimental and clinical settings in both pain sensitivity and susceptibility to chronic pain conditions. Although the sources of variation are not yet well understood, family and twin studies suggest genetic factors contribute to risk for persistent pain. Current evidence supports a heuristic model in which genetic risk factors mediate biological pathways that contribute to domains of enhanced pain amplification and psychological distress. These intermediate phenotypes interact with environmental risk factors leading to the development of chronic pain conditions.

The primary method used to study the genetics of pain and painful diseases to date is to select candidate genes for their known biological relevance to pro-nociceptive processes and look for allelic frequency differences between subjects with variable pain phenotypes. Recent studies have provided evidence that genes related to autonomic response, inflammation, somatization, anxiety, and depression are associated with greater risk of pain disorders such as temporomandibular joint disease (TMJD).

In this talk, I will discuss several recently completed and ongoing case-control and prospective studies designed to examine genetic association with TMJD and a diverse array of intermediate phenotypes. These studies have been performed using a dedicated microarray chip representing 350 genes known to influence psychological and nociceptive pathways, with emphasis on polymorphisms most likely to regulate gene expression and function. These studies may also help to shed light on comorbidity of chronic pain diseases, as well as generate new hypotheses for novel avenues of treatment.

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Disclosure of Relevant Financial Relationships: Consultant for Algynomics, Inc.

Patterns and Impact of Comorbidity of Headache and Other Chronic Pain Conditions in the U.S. General Population

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Background:
Although there is growing information on comorbidity of headache in clinical samples, there has been limited documentation of patterns of comorbidity between migraine with other chronic physical and mental conditions in general population samples of adults and youth in the United States. Migraine and other severe headaches are associated with substantial disability and their impact on disability in general population samples of adults and youth in the United States.

Methods:
Data from three studies are employed to examine patterns of comorbidity of headaches and other pain conditions: (1) the National Comorbidity Survey Replication (NCS-R), a nationally representative, face-to-face household survey of 9,282 respondents aged 18 years or Older; (2) the National Comorbidity Survey-Adolescent Supplement (NCS-A), a nationally representative face-to-face survey of adolescents aged 13-18 years in the continental United States) ; and (3) the National Health Examination and Nutrition Survey 1999-2004, a nationally representative sample of 31,126 U.S. adults.

Measures:
Both the NCS-R and NCS-A interviews included questions about a lifetime and 12-month history of severe headaches or migraine, arthritis or rheumatism, chronic back or neck problems, and a general category of any other chronic pain. The interview also included lifetime and 12-month questions about a wide range of chronic physical and mental conditions. Migraine status in the past 12 months was determined. Presence of headache and other physical and mental conditions was assessed using a questionnaire addressed to a parent or parent surrogate. The NHANES included a standard chronic conditions checklist administered via direct interview.

Results:
The results of all three studies demonstrate substantial comorbidity across chronic physical and pain conditions. There was a strong association between migraine with other pain conditions in both the NCS-R (odds ratio [OR] 3.3), and the NHANES (odds ratio [OR] 2.7), as well as with non-migraine headache in the NCS-R (odds ratio [OR] 3.5). Comorbidity was associated with substantial disability, healthcare utilization and health perception across these studies.

Discussion:
These findings document the importance of capturing the full range of chronic pain conditions and their comorbidity with other physical and mental disorders in evaluating the impact of headaches and their public health significance.

Disclosure of Relevant Financial Relationships:
This work was supported by the Intramural Research Program of the National Institute of Mental Health. The views and opinions expressed in this article are those of the authors and should not be construed to represent the views of any of the sponsoring organizations, agencies, or U.S. Government. All authors report no disclosures.

Chronic Widespread Pain: Models to Mechanisms

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The pathophysiology of chronic widespread pain remains poorly understood, and available therapies are only partially, and mostly unpredictably, effective. Progress has been seriously hindered by the lack of adequate experimental models. Given the strong clinical association between stress and diverse chronic widespread pain syndromes, we have developed animal models based on this association and used them to evaluate pathophysiology. Depending on the nature of the stress, animals develop mechanical hyperalgesia and neuroplasticity in the primary afferent nociceptor. In a model developed to study diffuse musculoskeletal pain (fibromyalgia and temporomandibular disorder), which also demonstrates increased anxiety and visceral hyperalgesia, the neuroplasticity in the nociceptor allows them to respond to levels of cytokines found after exposure to bacterial endotoxin and lesion of both neuroendocrine stress axes – the hypothalamic-pituitary-adrenal and sympathoadrenal – markedly attenuates pain in these models. Importantly, electrophysiological recordings from muscle nociceptors suggest neuropathic changes capable of contributing to enhanced nociceptor function. Thus, animal models of chronic widespread pain, which reproduce many aspects of the clinical syndrome, validate a role of neuroendocrine stress axes and cytokines, as well as suggest a role for neuropathic changes in the primary afferent nociceptor in chronic widespread pain.

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Disclosure of Relevant Financial Relationships: Honoraria from Evotec, Plexxikon, Kai, Merck, Astra Zeneca, Vertex and Roche

Neuronal-Glial Interactions in Pathological Pain

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Over the past decade a body of evidence has emerged indicating that pain behaviours resulting from injury to peripheral nerves are critically dependent upon interactions between neurons and glia in the dorsal horn of the spinal cord. Microglia have been found to play a causal role in neuropathic pain behaviours resulting from peripheral nerve injury, and specific neuron-microglia-neuron signalling pathways have been elucidated. Within the dorsal horn, microglia suppress neuronal inhibition by a sequence of steps involving activation of microglial P2X4 receptors causing the release of BDNF. BDNF acts on trkB receptors which leads to a rise in intracellular chloride concentration in dorsal horn nociceptive output neurons, transforming the response properties of these neurons.

In addition to suppressed inhibition, evidence indicates that following nerve injury there is activity-dependent facilitation at dorsal horn glutamatergic synapses which enhances nociceptive transmission. This enhancement is mediated by intracellular signalling networks involving serine/threonine and tyrosine kinases within nociceptive transmission neurons. Key for this enhancement is facilitation of NMDA receptor function by the non-receptor tyrosine kinase Src. Src is anchored within the NMDA receptor complex by the protein ND2. Disrupting the ND2-Src interaction in vivo attenuates behavioural pain hypersensitivity without the deleterious consequences of directly blocking NMDARs.

Thus, understanding of pathological pain signalling not only within neurons but also in glial cells, and, as well, the interactions between neurons and glia within the dorsal horn may lead to novel strategies for the management of chronic pain states, strategies not previously expected from a solely neuron-centric view of pain.

Supported by the Canadian Institutes of Health Research, the Krembil Foundation and the Howard Hughes Medical Institute.

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Disclosure of Relevant Financial Relationships: Grant – Pfizer Inc. Consultant – Abbott Labs, Endo Pharmaceuticals. Director – NoNO Inc.

Molecular and Genetic Analysis of Pain-Sensing Neurons in Dorsal Root Ganglia

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TMJ can result in significant pain and impairment. It has been proposed that inflammation at temporomandibular joint or damage to the trigeminal nerve causes TMJ–associated chronic pain. Like dorsal root ganglia (DRG) neurons, pain-sensing neurons in trigeminal ganglion are highly diverse. Therefore, it would be essential to determine which subtype of pain-sensing neurons plays a prominent role in TMJ–associated pain. We have isolated several genes which are specifically expressed in different subtypes of pain-sensing neurons in DRG. Some of them are potential drug targets for the treatment of pathological persistent pain states, such as inflammatory and neuropathic pain. Mas-related G-protein-coupled receptors (Mrgprs) encode a large family of orphan receptors specifically expressed in small-diameter nociceptive neurons. To determine the roles of Mrgprs in persistent pathological pain states, we exploited a mouse line in which a chromosomal locus spanning 12 Mrgpr genes was deleted (KO). These KO mice show prolonged mechanical and thermal pain hypersensitivity after hind paw inflammation compared to wild-type (WT) littermates. This mutation also enhances the "windup" response of dorsal horn wide-dynamic-range (WDR) neurons, an electrophysiological model for the triggering of central pain sensitization. Deletion of the Mrgpr cluster also blocked the analgesic effect of intrathecally applied bovine adrenal medulla peptide 8-22 (BAM 8-22), an MrgprC11 agonist, on both inflammatory heat hyperalgesia and neuropathic mechanical allodynia. Spinal application of BAM 8-22 also significantly attenuated windup in WT mice, an effect eliminated in KO mice. These data suggest that members of the Mrgpr family, in particular MrgC11, may constitute a novel endogenous inhibitory mechanism for regulating persistent pain in mice. Agonists for these receptors may therefore represent a new class of anti-hyperalgesics for treating persistent pain, including TMJ–associated pain with minimal side effects, due to the highly specific expression of their targets.

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Disclosure of Relevant Financial Relationships: None

Neural Mechanisms of Pelvic Visceral Pain, Endometriosis, Cannabinoids and Pelvic Pain Organ Function

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Endometriosis is an estrogen-dependent disorder defined by extrauteral growths of endometrial tissue. Major symptoms of endometriosis are severe dysmenorrhea, dyspareunia, and chronic pelvic/abdominal and muscle pain, and/or subfertility/infertility. Symptomatic endometriosis, however, often co-occurs with other, sometimes widespread pain disorders, such as TMJD, headache, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, as well as organ dysfunctions such as bladder hyperreflexia and kidney/ureteral stones. How the growths relate to pain and pelvic organ dysfunction is poorly understood because signs and symptoms do not correlate. Partly due to this lack of understanding, the pain is difficult to alleviate without using hormones that produce intolerable side effects and cannot be used long-term or surgery that fails to provide long-term help. Translational studies with a rat model provide clues for mechanisms and treatments. Growths in the model and women can recruit sensory and sympathetic nerve branches that sprout from nearby fibers, creating a two-way interaction between growths and the CNS. The new fibers are affected by estradiol and become sensitized. This peripherally-dynamic condition is associated with dynamic local and likely remote CNS sensitization influenced by changes in CNS estrogen receptors. Thus, the dynamic and estradiol-responsive nervous system is directly involved in endometriosis, allowing generation of pains and organ dysfunctions that can become widespread and independent of the growths themselves. In studies stimulated by patient reports, results show that cannabinoid receptors are located on neurons innervating the growths, and that treatment with cannabinoids alleviates endometriosis-induced pains. Overall, the findings support a change in focus from pathology to pain, and acknowledgement that the origin of pain, regardless of where the pain is located, is the CNS. This change encourages a multi-therapeutic approach to treatment and recognition that translational research that include basic scientists, clinicians and patients can bring about productive advances.

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Disclosure of Relevant Financial Relationships: None

Epigenetics in Pain and Analgesia – Pharmacogenetics – Implications for Therapeutics

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Pain is a complex trait and differential expression or function of the molecular components contributing to it produces a considerable variability of this phenotype. Expression and function in the nociceptive pathways is under genetic control. This may lead to extreme human phenotypes with complete insensitivity or exaggerated sensitivity to pain (e.g., rare mutations in the SCN9A gene coding for Nav1.7 sodium channels). Common pain phenotypes of pain syndromes are controlled by complex common genotypes producing, however, smaller effect sizes. Genetic research on pain has importantly contributed to identification or verification of molecular targets of new analgesics, of which several have reached clinical testing. Therefore, the few pharmacogenetic modulators of classical opioid and non-opioid analgesics, which have entered clinical practice only marginally (e.g., CYP2D6 genetics modulating the response to codeine via altering its activation to morphine), may be soon completed with genotypes specifically affecting the pharmacology of new analgesics (Lötsch & Geisslinger, 2010) that target genetically variable nociceptive structures and thus allow for a genetics-based personalized therapy. As in other fields, the importance of epigenetic regulation of transcriptional and post-transcriptional processes in the nociceptive system becomes increasingly evident (Doehring et al., 2011). This includes microRNAs and, classically, the methylation of CpG rich DNA island or histone modification (e.g., changes in the methylation or acetylation state), switching the DNA between an accessible and therefore translatable and an inaccessible state. Epigenetics is under environmental control (e.g., nutrition, chemicals), changes with age and may be possibly altered by drugs, including opioid analgesics such as methadone, of which the consequences are unknown as yet. First successful experiments in animals suggest that epigenetically acting drugs altering e.g. histone acetylation might become a new class of analgesics. Therefore, epigenetics and pharmacogenetics will be a basis of the identification and personalized application of analgesic therapeutics.

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Disclosure of Relevant Financial Relationships: None

Epigenetic Regulation of Visceral Pain Due to Neonatal Inflammatory Insult

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Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are two of the major Functional Bowel Disorders (FBD) that afflict about 10 to 15% of the US population. Persistent or recurring abdominal pain and motility dysfunction – gastroparesis, diarrhea/constipation - characterize these disorders. The etiologies of these symptoms are not understood. However, early life adverse events - gut inflammation and psychological stress - are considered risk factors for the development of FBD. The annual episodes of diarrhea in U.S. children less than 5-years-old ranges from 20 to 35 million [1]. These diarrheal episodes lead to about 22,000 hospitalizations per year, indicating the severity of enteritis.

Genome and epigenome are inherited from both parents. As the organisms develop from a single zygote, the genome remains the same, except under extreme changes in cellular environment. During each cell division in fetal and neonatal stages of development, the epigenome programs every gene to set its transcription rate, which imparts cell phenotype. The goal of epigenetic programming is to protect the developing organism and to ensure normal health in adulthood. However, epigenetic programming is highly sensitive to cellular microenvironment, which makes the fetal and neonatal stages of developments highly vulnerable to adverse conditions, such as inflammation and psychological stress. Under these conditions, the epigenome reprograms specific genes to ensure immediate survival. However, this aberrant programming persists into adulthood resulting in complex diseases, such as functional bowel disorders, hypertension and cancer. We tested the hypothesis that inflammatory insult during the neonatal stage of development causes epigenetic dysregulation that alters the transcription of nociceptive genes in the gastric fundus in adulthood, resulting in GHS.

The rats are hypo-responsive to stress during the post-natal days (PND) 4 to 14. The blunted adrenocortical response to stress during this period [2] protects the developing organs from stress hormones, especially corticosterone, from affecting the neonatal programming of genes. We found that colonic inflammation induced by intracolonic administration of trinitrobenzene sulfonic acid on PND 10 in Sprague Dawley rats significantly enhances serum corticosterone (CORT) on PND 15. The CORT levels return to baseline on PND 17 and remain there in adulthood. By contrast, the norepinephrine levels do not change following the neonatal inflammatory insult; however, they are elevated when these rats achieve adulthood (FD rats).

We found significant increase in GHS in 6 and 12 weeks old FD rats vs. age-matched controls in the absence of any increase in MPO activity, oxidative stress, inflammatory cytokines or mast cells. A similar inflammatory insult in 6-week-old adult rats did not induce GHS six weeks later. Gastric-specific DRG neurons showed a 2-fold ($p<0.05$) increase in Brain-derived neurotropic factor (BDNF) mRNA and a 50% decrease in the mRNA of Kv1.1 channels, vs. controls. Intrathecal treatment with a BDNF antagonist, trkB-Fc, significantly reduced GHS in FD rats. Nerve growth factor (NGF) protein expression was 75% ($p<0.05$) greater in fundic muscularis externa of FD rats. Systemic treatment with an NGF antibody significantly attenuated gastric hypersensitivity.

Chromatin immunoprecipitation (ChIP) assays showed increase in RNA polymerase II (RNAP II) binding to the Ngf promoter in the gastric fundus of FD rats, suggesting increase in transcription of this gene. ChIP assays also showed that the association of histone deacetylase 3 (HDAC3) with the Ngf core promoter (-161/-6) is significantly attenuated, suggesting relaxed chromatin structure at this locus to facilitate the formation of preinitiation complex. In addition, the trimethylation of histone 3 lysine 9 (H3K9me3) is suppressed in the core promoter region, which promotes transcription. We conclude that inflammatory stress during the neonatal stage of development causes epigenetic dysregulation in adulthood to induce gastric hypersensitivity, which enhances the afferent signals in primary afferent neurons to induce the sensation of pain in response to gastric distension following a meal.

(Continues on next page)

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Disclosure of Relevant Financial Relationships: None

Vulvodynia and Comorbid Chronic Pain Conditions – A Population-Based Study

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Vulvodynia is a vulvar pain disorder suffered by more than 10 million women in the United States alone. Most women remain undiagnosed, even among those seeking medical attention. Recent data suggest the presence of vulvodynia is increased among women with other chronic pain disorders, including TMD-type pain,[1] fibromyalgia,[2] interstitial cystitis,[3, 4] and irritable bowel disorder.[2] Similarly, studies on genetic polymorphisms,[5, 6] peripheral pain responses,[7-9] and central pain processing[10] provide further evidence of physiologic similarities among these disorders. Although obvious clinical differences exist among these disorders, the similarities between them—in epidemiology, clinical course, and underlying physiology—are just now being elucidated and may provide important clinical insights into etiology and treatment.

Most of the studies reporting an association between these pain disorders have been cross-sectional in design, have compared pairs of diagnoses rather than several at once, and have assessed women with profound symptoms who were presenting for medical care for their pain. While these studies have demonstrated relationships between these pain disorders, they may reflect characteristics of only a select subset of women suffering from these problems. We have been conducting a longitudinal population-based study of vulvodynia among 2500 women in southeast Michigan and have collected data on the diagnoses and/or screening test outcomes for other pain disorders. The associations among these disorders, their relationship to other measures assessed, as well as similarities and differences among the demographic and risk factors noted, will be presented.

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Disclosure of Relevant Financial Relationships: None

Chronic Clinical Pain Conditions are Distinct and Specifically Interact with the Brain

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Non-invasive functional (fMRI) and anatomical brain imaging evidence will be presented pointing to the notion that chronic pain conditions can be differentiated from each other and from acute pain based on brain circuitry. Functional data will be shown to illustrate that brain activity for acute thermal painful stimuli are distinct from brain activity for spontaneous fluctuations of back pain in chronic back pain patients. Similarly, data will be shown that brain activity for acute pressure pain applied to the knee is distinct from spontaneous pain of knee osteoarthritis, and the latter is specifically modulated by COX2-inhibitors that also correlate with brain activity changes. Evidence will also be shown that brain grey matter density decreases in chronic pain in a unique pattern and that the temporal cost of this reorganization is distinct between chronic pain types.

Overall, using multiple brain imaging approaches and investigating multiple types of chronic pain we observe reorganization of brain activity and brain anatomy patterns distinct for each of the conditions studied.

Studies are funded by NIH NINDS NS35115

Disclosure of Relevant Financial Relationships: None

Primary Afferent Nociceptors and the Circuits That They Engage to Produce Chronic Pain

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The primary afferent nociceptor expresses a host of molecules that are not found or are only minimally expressed elsewhere in the CNS. Among these molecules are subtypes of sodium channels, G protein-lined receptors, purinergic receptors and even water channels. Studies in mice with gene deletions established that several of these molecules are important contributors to the processing of pain messages. Another approach to the problem asks whether subtypes of nociceptor, which express a variety of these molecules, contribute to submodalities of pain (e.g. heat, cold, mechanical) or whether any given population is multimodal in its contribution to pain behavior. Our studies indicate that the peptidergic population contributes only to heat pain sensitivity and the non-peptidergic population to mechanical pain. We also found that these subsets of nociceptors can be differentially regulated. In these studies, we reexamined the distribution and function of the mu (MOR) and delta (DOR) opioid receptors in primary afferent nociceptors. Contrary to the prevailing view, which was based almost exclusively on immunocytochemical grounds, using a DOReGFP reporter mouse, we now show that the DOR and MOR are expressed by largely non-overlapping populations of primary afferent fiber. Peptidergic nociceptors express the MOR, and myelinated and non-peptidergic unmyelinated afferents express the DOR. This segregated DOR and MOR distribution is paralleled by a remarkably selective functional contribution of the MOR to the control of heat pain and the DOR to mechanical pain and nerve injury-induced mechanical hypersensitivity. Whether this remarkable degree of specificity for the processing of pain messages at the level of the primary afferent nociceptor is manifest at the level of the CNS circuits engaged by these fibers remains to be determined.

Disclosure of Relevant Financial Relationships: The author has consulted for several pharmaceutical companies and previously served on the Scientific Advisory Board of NeurogesX, Inc.

Cognitive Ontologies for Neuropsychiatric Phenomics Research

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There are potentially informative parallels between pain research and neuropsychiatry research. Both confront syndromes of enormous complexity and aim to identify mechanistic pathways that link basic biological substrates to behavioral states that may elude easy characterization. To gain traction on the myriad paths leading from genomic variation to syndromal manifestations, neuroinformatics strategies are increasingly called upon to navigate across broad domains of knowledge and help researchers find the most important signals. The success of the Gene Ontology project suggests the potential benefits of developing schemata to represent higher levels of phenotypic expression. We have attempted to develop cognitive ontologies to support our work in neuropsychiatric phenomics1, 2. Challenges in cognitive ontology development include the lack of formal definitions of key concepts and relations among entities, the inconsistent use of terminology across investigators and time, and the fact that relations among concepts are not likely to be well represented by simple hierarchical "tree" structures. Because the concept labels are labile, there is a need to represent empirical findings at the test indicator level. This level of description has greater consistency and benefits from operational definitions of its concepts and relations to quantitative data. Considering test indicators as the foundation of these ontologies carries several implications, including the likely utility of task taxonomies. The concept of "test speciation" is introduced to mark the evolution of paradigms sufficiently unique that their results cannot be "mated" productively with others in meta-analysis. Several projects have been initiated to develop cognitive ontologies at the Consortium for Neuropsychiatric Phenomics (www.phenomics.ucla.edu) in the hope that these ultimately will enable more effective collaboration and facilitate connections of information about cognitive phenotypes to other levels of biological knowledge. Several free web applications are available already to support examination and visualization of cognitive concepts in the literature (PubGraph, PubAtlas, PubBrain) and to aid collaborative development of cognitive ontologies (Phenowiki and the Cognitive Atlas). It is hoped that these tools will help formalize inference about cognitive concepts in behavioral and neuroimaging studies and facilitate discovery of the genetic bases of both healthy cognition and cognitive disorders.

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Disclosure of Relevant Financial Relationships: None

Understanding Cell Signaling Dysregulation in Inflammation Contexts: From Qualitative Pathway Maps to Quantitative Network Operations

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Regulation of cellular phenotypic functional behaviors by signaling networks is vitally context-sensitive so that the dynamic operation of regulatory pathways differs from cell type to cell type, between normal and diseased states, and among varied environmental conditions. Data-driven pathway reconstructions have to date largely emphasized production of generic models that hold some potential illustrative validity but are not typically able to provide predictive understanding of cell network operation across different situations. Effective use of network information in the study of disease and therapy requires context-related models for cells and tissues, discerning between normal and dysregulated states.

This presentation will discuss our most recent progress in analysis of cell signaling networks, focusing on operational dysregulation in human epithelial cells under inflammatory contexts, integrating empirical proteomic data with database pathway maps toward predictive, logic-based computational models relating network activities to cell behavior and pathophysiology.

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Disclosure of Relevant Financial Relationships: None

Unraveling Complex Persistent Pain Conditions

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Learning Objectives:
1. To become knowledgeable in current concepts associated with etiological pathways associated with complex persistent pain conditions.
2. To become knowledgeable in how to assess the biopsychosocial and molecular pathways that underlie heterogeneous complex persistent pain conditions.
3. To become knowledgeable of the emerging concepts and technologies that may improve the diagnosis and treatment of patients with complex persistent pain conditions.

Pain perception is one of the most complicated measurable traits because it is an aggregate of several phenotypes associated with peripheral and central nervous system dynamics, stress responsiveness and inflammatory state. As a complex trait, it is expected to have a polygenic nature shaped by environmental pressures. Dr. Maixner will discuss emerging concepts and knowledge of the contribution of genetic variants, including recent discoveries that emphasize a genetic contribution to human pain perception and clinical pain phenotypes[1,2]. He will present findings from recently completed[3,4] and ongoing (see www.oppera.org) cross-sectional and prospective studies that examine the biopsychosocial and genetic factors contributing to the onset and maintenance of a common persistent pain condition that is comorbid with many other common persistent pain conditions. Finally, he will discuss emerging technologies that will prove useful in unraveling the pain genetic networks in subpopulation of patients with persistent pain conditions.

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Disclosure of Relevant Financial Relationships: William Maixner, D.D.S., Ph.D., is the Mary Lily Kenan Flagler Bingham Distinguished Professor and the Director, Center for Neurosensory Disorders at University of North Carolina-Chapel Hill School of Dentistry. He has received federal funding through competitive grants for research endeavors. In addition, Dr. Maixner is an officer and equity stock holder in Algynomics, Inc., a company providing research services in personalized pain medication and diagnostics.

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network

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Background:
Interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) are symptom-based syndromes, defined by chronic recurring pain in the region of the pelvis or urogenital floor. Non-painful lower urinary tract symptoms, such as urinary urgency or frequency, often co-occur in these patients. The etiology, pathophysiology, natural history and association of these syndromes with other persistent pain syndromes, such as IBS, TMD and FM, are incompletely understood, and translational research efforts to develop novel medications have been largely unsuccessful. Traditional research has primarily focused on specific bladder mechanisms, such as inflammation or infection.

Methods:
The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is conducting collaborative, interdisciplinary research on urological chronic pelvic pain disorders, specifically IC/PBS and CP/CPPS. The research network is funded through a consortium grant mechanism (U grant mechanism) by the Kidney and Urology branch of the NIDDK. It involves 6 MAPP discovery sites (Northwestern University, UCLA, University of Iowa, University of Michigan, University of Washington, Washington University, and three additional network projects (Stanford University, Harvard, Queens University, and two MAPP network cores: the data coordinating core (University of Pennsylvania), and tissue analysis and technology core (University of Colorado, Denver). The consortium is organized into three multisite ("transMAPP") projects and several site specific projects.

Research focus and goals:
The goals of the MAPP research network are to advance the understanding of 1) syndrome phenotypes, 2) syndrome etiology , 3) natural history, and relationship of the urinary syndromes with other persistent pain conditions, such as FM, IBS and CFS. The key areas of focus are: 1) epidemiology of disease; 2) phenotyping of urological and non-urological symptoms; 3) biomarkers of disease; 4) neuroimaging/neurobiology; characterization of organ cross talk/pain pathways in preclinical models.

Conclusions: The MAPP consortium is currently in its second year of funding and has been highly successful in meeting its enrollment goals. A wide range of data from structural and functional brain imaging studies to proteonomics, microbiology and clinical phenotyping will be available from all the transMAPP projects which will enable MAPP researchers to address the research goals in an unprecedented way.

References:
www. mappnetwork.org

Disclosure of Relevant Financial Relationships: None

Migraine and TMJ Disorders

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Introduction: Migraine is a chronic pain disorder associated with TMD among other disorders. Migraine may increase in frequency over time in a process best conceptualized in terms of transition models among health states defined by headache frequency.

Methods: The ongoing American Migraine Prevalence and Prevention (AMPP) study provides longitudinal population data collected by annual mailed questionnaires. Launched in 2004, the AMPP study has followed over 10,000 migraine sufferers annually for 5 years. Transition models envision three distinct states: Episodic Migraine (0-14 headache days per month) and Chronic Migraine (CM, 15 or more days/month).

Results: In the AMPP, the prevalence of episodic migraine was about 12%, while the prevalence of CM was 1.5%. Cross-sectional data analysis showed that persons with CM had lower levels of education and household income than persons with EM. CM sufferers tended to be older and had higher body mass indexes.

In its longitudinal phase, the AMPP has assessed a number of potentially remediable risk factors associated with the transition from EM to CM. Risk factors for progression included high attack frequency, obesity, stressful life events, snoring, allodynia, other pain disorders and overuse of certain classes of medication. In particular, opiate and barbiturate combination products contribute to migraine progression. The influence of medication is modified by both attack frequency as well as the frequency of medication use. Depression is a dose-dependent risk factor for progression.

Conclusion: Emerging data suggest that EM is more likely to progress to CM in the presence of risk factors, some of which are remediable. Data on age incidence of migraine and TMD, co-morbidity in clinic-based samples and treatment will be discussed.

Disclosure of Relevant Financial Relationships: Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project Leader), RO1AG025119 (Investigator), RO1AG022374-06A2 (Investigator), RO1AG034119 (Investigator), RO1AG12101 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund, serves on the editorial boards of Neurology and Cephalalgia and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralieve Inc. (a company without commercial products), serves as consultant, advisory board member, or has received honoraria from: Allergan, American Headache Society, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Cognimed, Diamond Headache Clinic, Eli Lilly, Endo, GlaxoSmithKline, Merck, Nautilus Neuroscience, Neuralieve, Novartis, and Pfizer.

Poster Abstracts

Poster A

Subject-specific Modeling and Biomechanical Assessment of the TMJ and TMJ Implants

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Introduction:
Anatomical models of the temporomandibular joint (TMJ) aid better understanding of structure and function of the joint. Finite element analysis (FEA) of anatomical models and implants enable their biomechanical investigation. This poster presents subject-specific anatomical and prosthetic models of the TMJ and biomechanical behavior of the same.

Methods:
A subject-specific 3D model of TMJ was developed from CT scans of a female subject who reported moderate and intermittent pain in both TMJs. To understand the interaction of form and function, FEA of the model were performed under four loading conditions – balanced loading, unbalanced loading, teeth grinding, and clenching – using bite and muscle forces independently. Three FEA simulations for each loading condition were performed and peak von Mises stresses in condylar fibrocartilage were noted. Also, FEA of a commercially available and a patient-fitted TMJ implant were performed. Currently, we are performing biomechanical testing of cadaveric mandibles to validate FEA indications.

Results:
The peak von Mises stresses developed in condylar cartilage during teeth grinding and clenching were found significantly different (p-value <0.0001 at $\alpha = 0.05$) and higher than during balanced loading for bite as well as muscle force simulations. However, the peak stresses in condylar cartilage during unbalanced loading were not significantly different (at $\alpha = 0.05$, p-value = 0.4386 and 0.1967 for bite force and muscle force simulations, respectively) than during balanced loading. Stresses developed in the implant provide insight into structural hot spots of the device.

Conclusion:
FEA of the anatomical model suggest that higher stresses developed in condylar fibrocartilage during teeth grinding and clenching may lead to and/or worsen TMD. The methodology employed for anatomical and prosthetic modeling and FEA can be efficiently used to better understand biomechanical behavior of the complex structures and to improve the design, treatment efficiency, and durability of prostheses.

Poster B

A Population-based Study of Comorbid Conditions of Vulvodynia and Temporomandibular Joint Disorder: Findings from a Pilot Survey of the National Vulvodynia Association

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Introduction: Little is known about the etiology of co-morbid conditions of vulvodynia. We enumerate the prevalence of co-morbid conditions among women with vulvodynia and TMJ and describe potential temporal associations.

Methods: Data collected by the National Vulvodynia Association (NVA) was used. Women who were on the NVA patient listserv were invited to participate in a short, anonymous web-based survey. In addition, the survey is listed on the NVA web site and is open for anyone to respond. 1,457 respondents from 2009 – 2011 who self-reported vulvodynia, time since vulvodynia diagnosis, and age were included.

Results: 63% of women with vulvodynia reported that they had been diagnosed with at least one other pain condition; 325(22%) women reported having TMJ (V-TMJ); however, the most prevalent comorbidity among women with vulvodynia was irritable bowel syndrome (31%). Type of vulvodynia was associated with prevalence of TMJ (20% prevalence among localized vulvodynia, 20% generalized, 30% both, $p<0.001$). Women with V-TMJ were significantly more likely than women with vulvodynia but no TMJ to have all of the comorbidities: interstitial cystitis (27% among V-TMJ vs. 17% vulvodynia without TMJ), fibromyalgia (31% vs. 11%), chronic fatigue syndrome (12% vs. 5%), irritable bowel syndrome (43% vs. 28%), endometriosis (18% vs. 11%), headache (36% vs. 13%) and burning mouth syndrome (10% vs. 3%). Of the 325 V-TMJ women, 216 (66%) reported a TMJ diagnosis prior to her vulvodynia diagnosis, 91 (28%) at the same time, and 18 (6%) after. Among those who later developed TMJ, no woman reported it within the year after her vulvodynia diagnosis (range: 18 – 240 months, mean: 113).

Conclusion: TMJ is common among women who have vulvodynia, particularly women who have both localized and generalized vulvar pain. The overwhelming majority of V-TMJ women developed TMJ prior to or around the time of chronic vulvar pain.

Poster C

Inflammatory Mediator Levels in TMJ Synovial Fluid Increase with Progression of TMJ Disease

Gary Warburton, Robert Utsman, Abhishek Gupta, Ester Kim, Ellen Pauslik, Anahita Shaya, Kimberly Wills, Sharon M. Gordon, Department of Oral-Maxillofacial Surgery, Univ. of Maryland, Baltimore, MD

Introduction: Temporomandibular joint (TMJ) disorders are relatively common, but their pathophysiology is not fully understood. Research has demonstrated the presence of reactive oxidative radical species and various inflammatory mediators in TMJ synovial fluid; however, disease staging and clinical symptoms have not been correlated. The present study investigated the relationship of inflammatory mediators and matrix degradation components in patients (n = 28 females) with various Wilkes stages of TMJ disease and to clinical symptoms.

Methods: Synovial fluid samples were obtained during arthroscopy and processed to remove cells. Total protein concentration was determined prior to protein-specific assay by multiplex protein array. Molecular indicators of inflammation and degradation were correlated with Wilkes classification and clinical pain reports.

Results: Pre-operative pain was rated high and significantly diminished post-operatively in all patients, irrespective of diagnosis. IFN-gamma and COX-2 increased significantly (P = 0.02) with severity of Wilkes classification. TNF-alpha was also elevated in all groups except those with a normal joint, with a positive linear trend for significance (P – 0.08). Matrix degradation represented by MMP-2 and 9 levels demonstrated a significant linear trend for increase that was not significant for median differences.

Conclusion: These data demonstrate an increase in inflammation and degradation processes according to severity of Wilkes staging. Monitoring mediator levels may be predictive of disease progression and provide therapeutic targets.

Abbreviations: n = number; rpm = revolutions per minute; C = Celsius; IFN-gamma = Interferon-gama; COX-2 = cyclooxygenase-2; TNF-alpha = tumor necrosis factor-alpha; IL-6 = interleukin-6; MMP2 = matrix metalloproteinase-2.

Poster D

Investigating Risk Factors for Persistent Pain in Patients with Temporomandibular Joint Implants in The National TMJ Implant Registry and Repository

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Introduction: A variety of therapeutic approaches have evolved for relief of TMJD symptoms ranging from physical therapy and nonsurgical treatments to various surgical procedures including the use of TMJ implants. Knowledge of long-term outcomes assessment of these implants including pain and function remains a major problem. The purpose of this study was to evaluate the association of persistent facial pain with tissue injury as represented by the various surgical study groups in the NIDCR TMJ Implant Registry (TIRR).

Methods: A case control analysis was performed using data from the TIRR to evaluate the association of persistent facial pain with tissue injury as represented by the various TIRR study groups

Results: There were more women than men in the dataset. However women were no more likely than men to have persistent pain. Those in the implant registry reporting any type of surgery (74%) were more likely to report persistent pain. However there was no difference between any surgery type and implant surgery. The association between persistent pain and implant surgery was not modified by whether there was either a planned or removal of implant.

Conclusion: There is an association between surgery for TMJD and persistent pain; however the type of surgery did not modify this relationship. There is need to identify risk factors predictive of persistent pain as an outcome of surgery.