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Taking stock: from chasing occlusal contacts to vulnerability alleles

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Dates:
Accepted 25 April 2004

To cite this article:
Orthod Craniofacial Res **7**, 2004; 157–161
Stohler CS:
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Key words: catechol-*O*-transferase; temporomandibular disorder; vulnerability alleles

Over the past 70 years, temporomandibular disorders (TMDs) have been subject to shifts in conceptual understanding. Unable to account for disease patterns, the mismatch between case assignment and treatment need, and very different interventions producing similar treatment outcomes (except for the risk to patients), emerging theories make persuasive arguments in support of alternative explanations.

The change engine

Over the past 70 years, starting with the publication of Costen in 1934 (1), temporomandibular disorders (TMDs) have been subject to shifts in conceptual understanding in response to advances in disease understanding. During this time, often-boiling confrontations have occurred between 'ideological camps', challenging prevailing treatment modalities with each faction committed to win the fight. Unable to account for disease patterns, the mismatch between case assignment and treatment need, and very different interventions producing similar treatment outcomes (except for the risk to patients), new theories make persuasive arguments in support of alternative explanations. The work of Lysle Johnston (and his students) has solidified many concerns regarding the validity of theories dealing with presumably causal factors of TMDs. In addition, Lysle's strong voice positively influenced the orthodontic community to embrace a critical stance in this subject matter, examining new knowledge and the extent to

which it challenges the prevailing theories of temporomandibular joint (TMJ) disease.

Explanatory shifts are not limited to TMDs and reflect the desire of the scientific and practicing community to obtain better concurrence between treatment response and theoretical predictions. Consequently, professional allegiances shift to new foci of discovery and emerging research tools promise a revolution in disease understanding. While any conviction encourages a restrictive scientific inquiry, the breadth of research begins to change when the community starts to acknowledge the deficit of an existing explanatory model. Influenced by trends in science at-large, the research community engages in a new direction and traditional concepts and/or lines of inquiry rapidly loose appeal. Over time, alternative disease constructs succeed because they are biologically more plausible and more successful in explaining the respective disease phenomena.

Although success rates of 75–95% tend to endorse a sense of certainty among respective treatment providers, the fact that so many different types of interventions, presumably addressing very different treatment targets, are indistinguishable when it comes to patients' improvement, should question the explanatory model in support of the presumed treatment action. One of Lysle's favorite slides captured the fact that explanations for successful outcome are not easily consolidated for treatments that range from occlusal appliances, occlusal equilibration, thermal pads, a host of pharmacological interventions, orthodontics, crown and bridge treatments, surgery, physical therapy, relaxation training, acupuncture, biofeedback and psychological interventions. We have yet to learn of a single therapy that is predictably more beneficial than other interventions. In fact, not differences in efficacy but patient's safety seem to be the primary factor that distinguishes available treatments. From this perspective, it makes sense to ask why treatment outcomes seem so strikingly similar.

Evolution of TMD case assignment

Useful TMD taxonomies were developed in response to epidemiological data, calling for refined case definitions to reduce high numbers of false-positive case assignments and to address related concerns of 'over-treatment'. Early 'TMJ' classification systems tended to be overly sensitive but lacked sufficient specificity. Improvements, notably the Research Diagnostic Criteria for TMD (RDC/TMD) (2), have addressed this particular issue (Fig. 1). Newer taxonomies, especially the RDC/TMD system, emphasize anatomical substrates (muscle, joint, disk), assuming that different tissue involvement proves to be significant in terms of natural history, choice of treatment and/or treatment response. However, data gathered during the past decade has not provided evidence in support of this assumption and the limited number of treatments that targeted a particular anatomical structure (e.g. TMJ disk) possibly produced more harm than good on a population average.

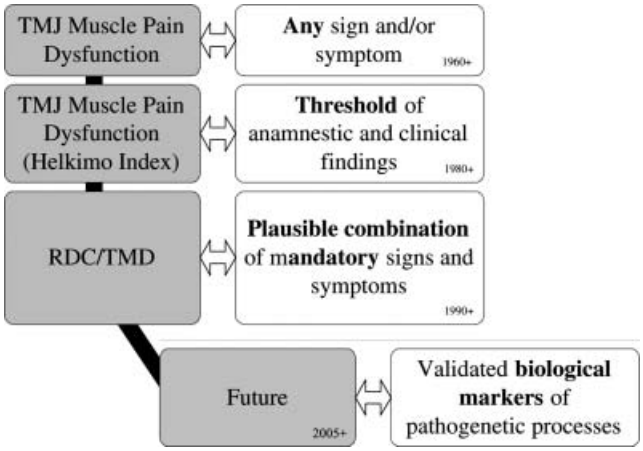

Fig. 1. Evolution of taxonomies of TMJ diseases.

Data generated in the past 15 years have also solidified the view that TMJ diseases are often not limited to a single anatomical domain (e.g., face) and neither is the case assignment to a particular TMJ subset (e.g. muscle, disc, joint) stable over time. Involvement of painful sites outside the topographical boundaries of the masticatory system seems to occur in greater frequency among those patients for whom therapeutic interventions often do not provide the expected outcome (3, 4). Given this significance, greater sensitivity to capture the overlap with related pain conditions (e.g. tension-type headaches, myofascial pain, fibromyalgia, polyarthritides and other ill-defined connective tissue diseases) is required (Fig. 2). Concerns, similar to those for TMDs, regarding the diagnostic validity of taxonomies for these related pain conditions, however, could again be an impediment for the advancement of the field.

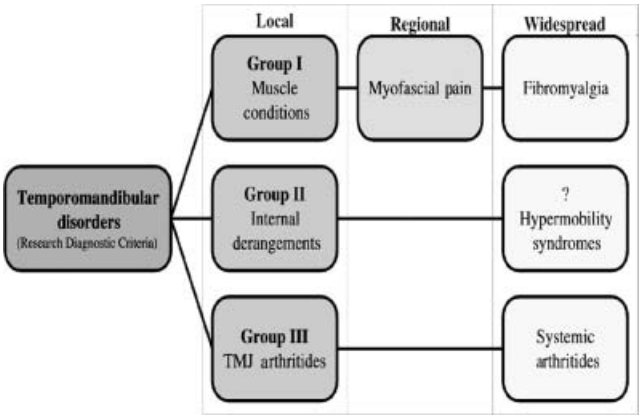

Fig. 2. Jaw muscle, TMJ disc and joint conditions are often not limited to the domain of the masticatory system and include regional and widespread complaints not captured in a systematic fashion by current taxonomies.

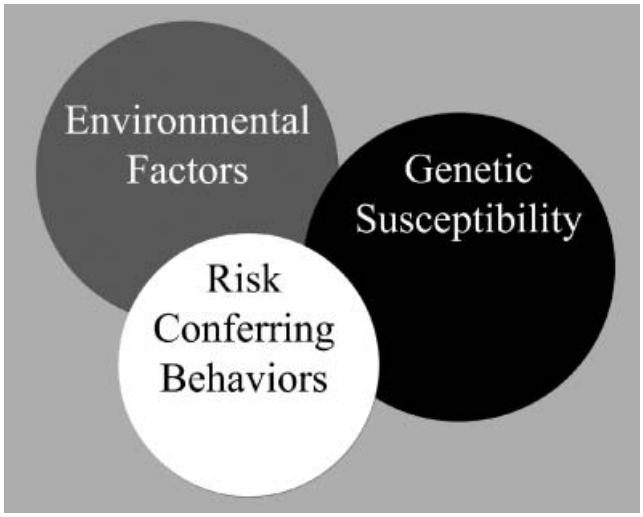

Fig. 3. TMJ conditions conceptualized as a complex disease.

A limitation is also the fact that besides pain and the impairment of jaw motor function, including mechanical hindrance to freely gliding movement of the articular components, symptoms, both relevant to patients and the understanding of TMJ diseases as a system response, are not systematically captured by any TMJ taxonomy today. Although varying from case-to-case in terms of the magnitude of their expression, this includes swelling, numbness, sweating and flushing, sleep disturbances, cardiovascular and gastrointestinal complaints, weight loss or weight gain, loss of libido and reproductive impairment. Unfortunately, symptoms that fall within the anatomical region of a clinician's specialty continue to receive greater weight than case attributes outside the respective topographical domain, reducing the capability to describe TMJ diseases as a complex systemic system response.

Chasing vulnerability alleles

Individuals are not equally susceptible to disease. For example, women in their reproductive years represent the majority of those seeking care and the extent to which genetic and epigenetic factors contribute to TMJ diseases has become a hot research topic. Besides familial risks, different genotypes can involve susceptibility to a particular clinical course of the disease and/or treatment response, including the development of complications (e.g. unfavorable response to environmental challenge, material, etc.) (Fig. 3).

Following deviation from homeostasis, such as the experience of pain, distinct genotypes are expected to produce predictable effects on the stress-response system, including the launch of titrated sensory, affective, neuroendocrine and autonomic messages characteristic for a given subject. The resulting symptoms should be understood as the person's complex response trait with specific complaints being either amplified or attenuated by the unique genetic makeup and/or prior experience. Hormonal milieus are believed to augment the inherent genetic vulnerability to TMJ diseases, explaining the greater likelihood of the condition among women in the childbearing age. Whether or not stimulus specificity (e.g. specific insult) is required to cause a clinically distinct presentation, or whether the exaggerated system response itself should become the focus of clinical attention, remains to be seen.

There is some validity in support of this conceptual framework. When exposed to sustained experimental pain, applied to masseter muscles and matched in terms of perceived pain intensity, human subjects' perceptions depends on the individual level of activation of the endogenous μ-opioid system (5). On the other hand, activation of the μ-opioid system that shapes the subject's response is significantly influenced by the catechol-*O*-transferase (COMT) genotype and linked to distinct traits of pain perception and brain activation (6).

The underlying genetic variance of COMT consists of valine-methionine *(val/met)* substitution at amino acid 108/158 in the soluble or membrane bound COMT proteins that is linked to a difference in thermo-stability, causing a three- to fourfold

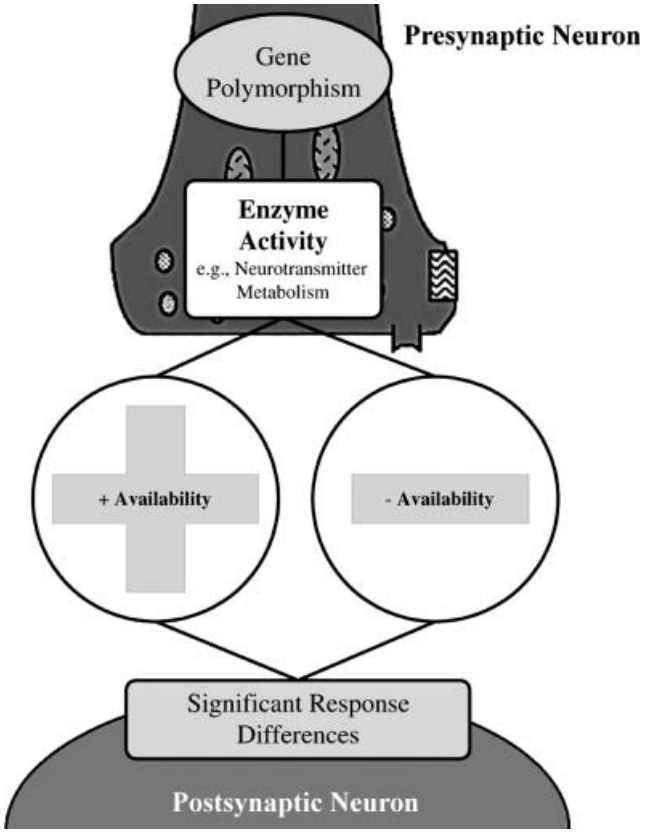

Fig. 4. Genetic variability of enzymes involved in the metabolism of neurotransmitters can result in differences in the synaptic availability of the neurotransmitter, which in turn causes a host of downstream signaling consequences.

reduction in COMT enzyme activity (7, 8). Alleles are co-dominant, so that individuals with the *val/val* genotype have the highest COMT enzyme activity and therefore the most rapid metabolism of catecholamines (Fig. 4). Those with the *met/met* genotype exhibit the lowest activity of COMT, and heterozygous individuals are intermediate.

Differences in COMT metabolic activity have a bearing on central dopaminergic and noradrenergic transmission and respective downstream consequences, including those affecting the state of activation of the μ-opioid system (9–12). Low COMT activity, meaning that catecholamines are metabolized at a slower pace than in the *val/val* genotype, translates into the experience of pain of greater sensory and affective information content due to reduced analgesia mediated by endogenous opioids (6). Regarding gender, COMT activity is 20–30% lower in women than in men (13–16), which is consistent with the greater prevalence and severity of TMJ disease among women in reproductive years.

The emerging conceptual framework

Pain-stress response systems, such as the sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenal (HPA), and antinociceptive systems, including the μ-opioid system, promote adaptive strategies in support of functioning in pain. Emotional and cognitive factors modulated by inherent genetic variance and/or prior experience, influence neurosecretory cells, which in turn impact on hormone synthesis by the pituitary gland with far reaching consequences in central and peripheral tissues.

Not only is the response to pain-stress influenced by molecular individuality, environmental factors and risk-conferring behaviors induce lasting changes in the nervous system and peripheral tissue that can result in non-average reactions to pain-stress. With virtually all of body functions modified by experience, persistent pain, or pain experienced at times of critical developmental stage, modify subsequent response behaviors. Previous experience is incorporated into adaptive response plans, such as the learned appraisal of stressors, modifying the state of activation of the HPA-axis, SNS, antinociceptive and immune systems (Fig. 5). For example, perinatal stressors can cause lifelong changes in receptor profiles and function of the HPA-axis (17–19), and alteration of the response behavior to noxious stimuli have even been observed

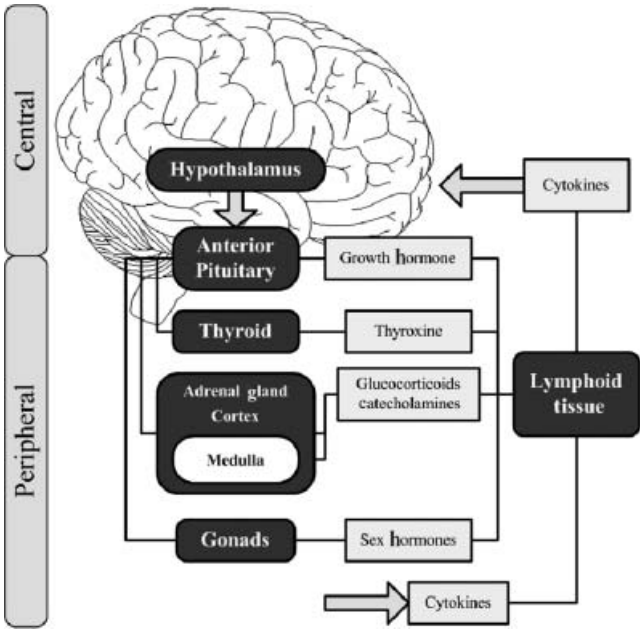

Fig. 5. Pain–stress response system.

in adult rats in which neonatal tissue was exposed to experimentally induced persistent hind paw inflammation (20).

Conclusions

Despite the inability to account for many observations, popular theories regarding the etiopathogenesis of TMJ disease project a false sense of security to the profession. It all boils down to the following quote: 'It ain't what we don't know that gets us into trouble. It's what we do know that ain't so' (21). Blessed are those disciplines that embrace scientific discovery with an open mind. In this respect, discipline representatives with a critical mind and powerful voice, such as Lysle Johnston for Orthodontics and TMJ, are crucial for the integrity and respect of the dental profession in the community of science and health professionals.

Acknowledgments: The Brotman Pain Center is supported through generous gifts from the families of Drs Don Brotman and Sol Brotman, both great alumni of University of Maryland, Dental School. Supported by NIH-NIDCR R01-DE15036 (CSS).

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