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Review

Neuroplasticity and Central Sensitization in Orofacial Pain and TMD

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Abstract

Temporomandibular disorders (TMD) are a group of musculoskeletal and neuromuscular conditions that involve the temporomandibular joint (TMJ), the masticatory muscles, and branches of the trigeminal nerve. TMD is the most common chronic oral facial pain disorder. Pain associated with TMD can be clinically expressed as myogenous or arthrogenous in etiology. The myogenous variant of TMD is characterized by pain in the muscles of mastication. The arthrogenous form of TMD is caused by pain in the joint leading to synovitis, capsulitis, or arthritis. Classically, mastication activity aggravates musculoskeletal pain. TMD pain is frequently associated with biomechanical dysfunction of the temporomandibular joint. This includes clicking or locking of the TMJ due to an anterior displaced disk, resulting in limited range of motion of the mandible. The diagnosis is based on the presence of symptoms such as periauricular pain related to mastication, joint noises (popping/clicking), limited mandible opening, jaw locking, and headaches. Orofacial pain includes several diagnoses: odontogenic, musculoskeletal, neurovascular, persistent idiopathic facial pain (PIFP), neuropathic pain,

neuralgia, TMD, and headache. When there is a persistent and intense nociceptive input in a sensitized central nervous system, the patient becomes more reactive and experiences more pain with less provocation. Practitioners should have knowledge of this type of heterotopic pain when determining the origins of orofacial pain. Without deep understanding of the trigeminal system and mechanisms differentiating nociceptive and non-nociceptive pain, clinicians will most likely treat the reported symptoms instead of the underlying cause.

Keywords
Neuroplasticity; central sensitization; orofacial pain; temporomandibular joint dysfunction; TMD; TMJ-D; trigeminal nerve

1. Introduction

Temporomandibular disorders (TMD) are a group of musculoskeletal and neuromuscular conditions that involve the temporomandibular joint (TMJ), the masticatory muscles, and branches of the trigeminal nerve. The American Academy of Orofacial Pain defines TMD as a group of disorders involving the masticatory muscles, the TMJ and associated structures [1]. Pain associated with TMD can be clinically expressed as myogenous or arthrogenous in etiology [2, 3]. The myogenous variant of TMD is characterized by pain in the muscles of mastication, while the arthrogenous variant of TMD is characterized by pain the joint [4-6]. The biomechanical dysfunction of the TMJ includes clicking or locking of the TMJ due to an anterior displaced disk, resulting in limited range of motion of the mandible [1, 4, 5, 7, 8]. The diagnosis is based on periauricular pain triggered by mastication, joint noises (popping/clicking), limited opening, jaw locking, and headaches [1, 2, 7, 9].

There is difficulty with establishing evidence based TMD guidelines due to the numerous confounding variables and comorbidities present. TMD is one type of orofacial pain condition that is a chronic, debilitating, and difficult to treat due to the lack of identified underlying mechanisms. Although several key contributing processes have been described at the level of the articular disc and spinal cord, very few studies have discussed the functional and structural changes of cortical areas involved in various pain pathways [8, 10-12].

The recognition of the roles of central sensitization and neuroplasticity, (whether it is being driven by ongoing nociceptive input or it is occurring in the absence of a peripheral driver), is critical for effective pain management [13-15]. Accumulating evidence supports the clinical importance of central sensitization in patients with chronic orofacial pain; they tend to not respond to local treatment and will become less compliant with their treatment plans. These patients may be referred to several medical and dental specialists with a narrow approach to care, without resolution of the patients' chief complaint. Therefore, it is extremely important that clinicians identify those patients during the initial examination [13, 16-18].

The following review presents TMJ anatomy, diagnosis, with discussion on the roles of central sensitization and neuroplasticity in orofacial pain. The aim is to discuss criteria to determine the presence of central sensitization to improved treatment outcomes.

2. Orofacial Pain and TMD

Orofacial pain includes several diagnoses: odontogenic, musculoskeletal, neurovascular, persistent idiopathic facial pain (PIFP), neuropathic pain, neuralgia, TMD, and headache [19]. Chronic orofacial pain may originate from peripheral injury (nociceptive and inflammatory pain), neuropathy, or functional abnormality (central pain, neuropathic pain, projected pain or referred pain) [20-22]. When there is a persistent and intense nociceptive input in a sensitized nervous system, the patient becomes more reactive and experiences more pain with less provocation [17, 23, 24] due to central sensitization. Practitioners should have knowledge of this type of heterotopic pain when determining the origins of orofacial pain. Without deep understanding of the trigeminal system and mechanisms differentiating nociceptive and non-nociceptive pain, clinicians will most likely treat the reported symptoms instead of the underlying cause. Clinical evaluation findings may not provide enough clues to support the correct action.

Centralized pain is often found in a set of idiopathic chronic pain conditions, including fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, headache, TMD, and interstitial cystitis [25-27]. Prior reports have studied the heterogeneity in TMD in Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) [28, 29]. This effort recognized variations in pain sensitivity and demonstrated a change in the mentality in treatment to include the degree in which an individual's pain has been centralized [29, 30]. However, in terms of peripheral receptors, the dentoalveolar region is more densely innervated [31-33]. This sensory abundance is linked to the key role of oral sensorimotor control in mastication, deglutition, and speaking [34].

The signs of TMD include muscle and/or TMJ tenderness to palpation, limited ROM (range of motion) and/or incoordination of mandibular movements and/or joint noises that may be transient [1, 35]. Currently, the definition encompasses a broader category that includes pain and/or decreased functionality of the mandible, either due to pathology within the joint or surrounding musculature [1, 28, 29, 35]. The cause is multifactorial due to biomechanical, neurologic, and psychosocial components contributing to the pathology [5].

3. Temporomandibular Joint (TMJ) Components

The TMJ is innervated by the mesenteric and auricular temporal nerves and is connected to the dentition and the contralateral joint. The TMJ and articular disc is attached to the lateral and medial poles of the condyle. When the mandible approaches maximal incisal opening, the upper compartment (consisting of condyle-articular disc complex) moves in a sliding movement relative to the infratemporal bone or just beyond the articular eminence (Figure 1). The lower compartment (consisting of the condyle) rotates underneath the disc. Therefore, the TMJ shares characteristics of both a hinge and gliding joint fibrocartilaginous disc (translational) and ginglyomoarthrodial components (rotational movement).

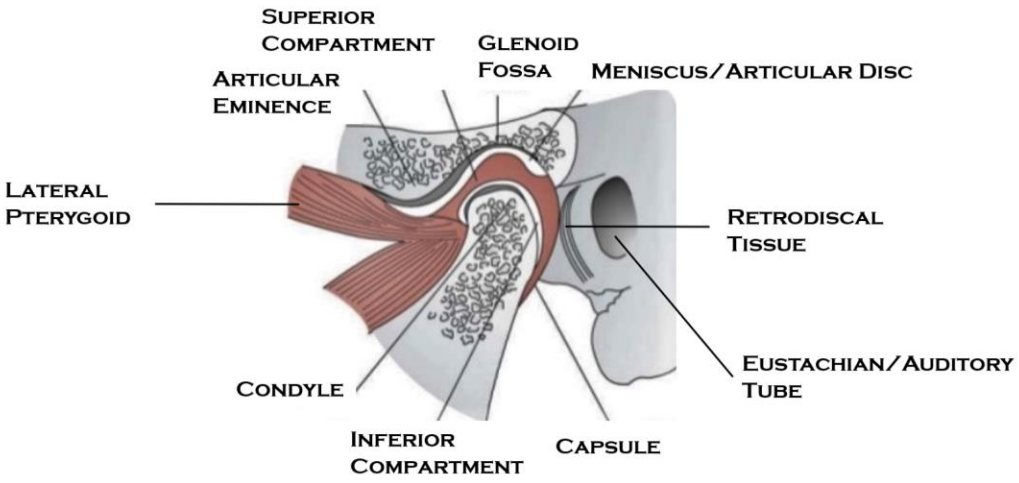

Figure 1 Components of the temporomandibular joint.

The TMJ Arthrogenous temporomandibular disorder is clinically characterized by sharp pain of moderate to severe intensity, localized to the TMJ and surrounding tissues that may radiate to the ear [8]. The pain is aggravated during loading and functioning of the joint with accompanied trismus. This condition may be associated with an anterior displaced disc and/or dysfunctional articular disk causing joint locking, which may be an additional cause of limited movement (Figure 2).

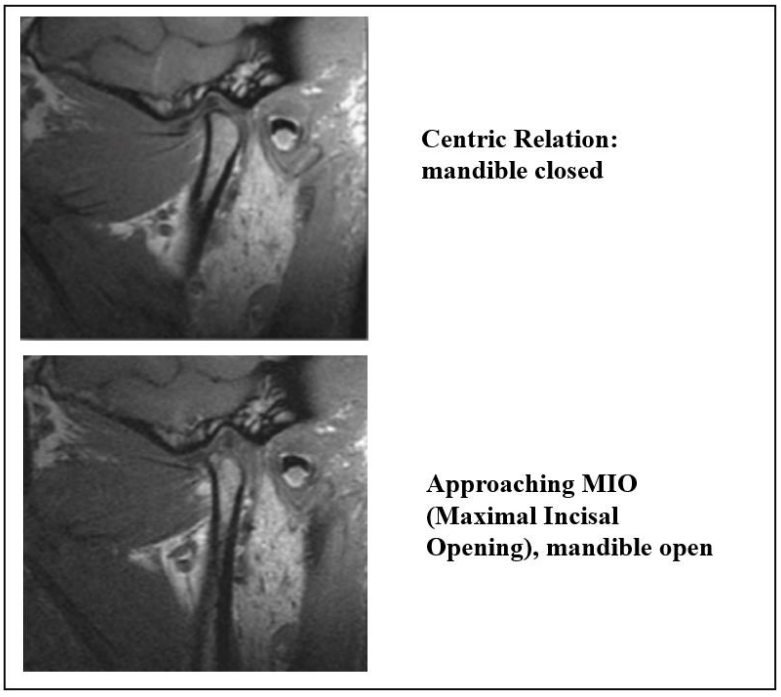

Figure 2 MRI of TMJ and articular disc in open and closed positions of the mandible.

Pain is a dominant feature of TMD and the patient's ability to cope and adapt determine progress. Reduced adaptive capabilities are suggested in all TMD patients. There is inconsistent association of bruxism and TMD in the literature, as some bruxers report masticatory pain [1, 7, 36, 37]. Interestingly, high activity bruxers tend to report less masticatory pain [2, 7, 30, 37]. In the general population, oral parafunctional habits are common and usually do not result in TMD symptoms [2, 6, 25, 26]. Additional reports have suggested oral parafunctional habits are initiating or perpetuating factors for certain subgroups of TMD patients [2, 22, 30]. Therefore, a causal relationship is unclear because few studies directly assess these behaviors on TMD [4, 31]. Some even claim that technical occlusal approaches successfully treat TMD. TMD has a complex multifactorial origin involving macro and micro trauma, psychosocial distress, sleep disturbances, altered resting brain-network connectivity, and sustained muscle activation during sleep [13, 21, 37]. Additionally, patients with persistent TMD pain suffering from depression and anxiety have an increased risk of feeling joint and muscle pain, respectively [8, 31, 38]. Recent studies have shown the pain is mediated by central sensitization, involving neuroplasticity, oxidative stresses, and enzymatic changes [11, 12, 16, 39, 40]. In central sensitization, localized stress factors such as ischemia and hypoperfusion cause the release of glutamate, histamine, and other substances from cells and afferent nerve fibers leading to excitation and sensitization of nociceptors [6, 17, 18, 24-26, 39].

4. Neuroplasticity

On the one hand neuroplasticity may optimize neural networks, on the other hand in an unhelpful form can result in central sensitization. Neuroplasticity is a continuous process allowing remodeling of synaptic networks to perceived experiences to the environment. This reorganization appears to be linked to the presence of pain; it may help explain the basis for transitioning from an acute state to a chronic condition. A meta-analytic study of experimental and chronic orofacial pain excluding headache disorders consistently identified changes in the structural and functional brain abnormalities in chronic orofacial pain subjects [9]. In the trigeminal system, neuroplasticity of caudalis nociceptive neurons may be induced either by direct stimulation of peripheral nerves by a neuropathic injury/inflammation, or through nerve damage [32].

5. The Trigeminal Nerve System

The trigeminal nerve system (CNV) involves a complex arrangement of interneurons, synaptic connections, and transmission fibers. It contains sensory branches V1, V2, and sensory/motor branches V3 (Figure 3). The trigeminal nerve also receives afferent axons from the facial, C2-C3 cervical, glossopharyngeal, and vagus nerves [23]. After trigeminal nerve injury, primary afferent neurons are activated and relayed to the central nervous system [32]. Orofacial negative stimuli cause activation in the nociceptive neurons corresponding to areas innervated by each branch of the trigeminal nerve [32]. Nociceptive neurons in trigeminal spinal subnucleus caudalis and upper cervical spinal cord are strongly enhanced after trigeminal nerve injury [41, 42]. Neuropeptides, neurotrophic, glutamate, and ATP modulate neuronal activity in uninjured neurons as well as injured neurons after trigeminal nerve injury [43, 44].

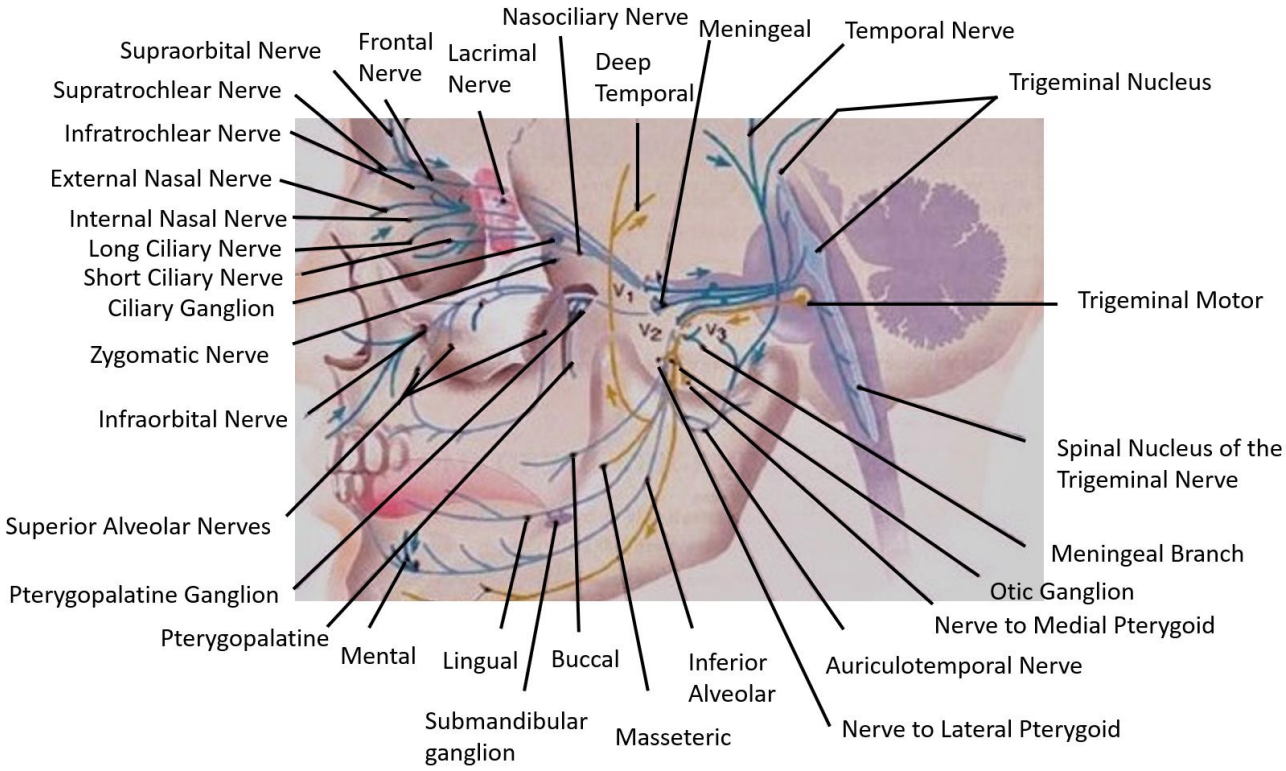

Figure 3 Trigeminal nerve system. V1: ophthalmic branch; V2: maxillary branch; V3 mandibular branch.

6. Central Sensitization and Clinical Practice

Central sensitization refers to the amplification of pain by central nervous system mechanisms [13, 22]. For example, neuropathic pain is associated with nociceptor sensitization, changes in the molecular expression of neurotransmitters and receptors in the nociceptive axons, as well as in the dorsal root ganglia neurons [27]. Additionally, there are changes involving the dysregulation of the inhibitory interneurons in the dorsal horn and the descending modulatory pathways, glial cell activation following the synthesis and release of proinflammatory cytokines [27]. This morphological and functional reorganization of the afferent projections in the dorsal horn contributes to hypersensitivity, hyperalgesia, dysesthesia, and allodynia which perpetuates a chronic pain state. At the cellular level, the underlying mechanism is neuroinflammatory resulting from glial cell activation. [12, 26]. This hyperactive state of the central nervous system may reduce vulnerability to future environmental stresses. It is noteworthy to differentiate central sensitization ~~is distinct~~ from hypersensitivity. Sensitization is the progressive increase in the response to a repeated stimulus, as opposed to hypersensitivity, which is ~~as~~ an increased ability to detect stimuli and react to it. Since the brain's ability to adapt its synaptic connections is based on the environmental demands, it suggests patients can override the maladaptive neuroplasticity through stress reducing coping mechanisms and application of self-management strategies [4, 16]. Perception of environmental stressors and behaviors such as, sleep quality, caffeine intake, nicotine intake, anxiety, depression, somatization,

bruxism, all affect and modify the central nervous system through neuroplasticity and central sensitization [4, 8, 12, 30, 31]. Studies have shown that nociceptive facilitatory pathways in the brain are activated by emotional factors from stress to include, hypervigilance, depressive thoughts, and maladaptive perceptions [22]. Behavioral responses attributed to stress, such as anxiety and tension would cause an increase in activity of the hypothalamic pituitary adrenal axis, with an increase in ACTH, cortisol, and adrenaline secretion by supradrenal glands, both during sleep and wakefulness [22]. Release of adrenaline facilitates neuromuscular tonus, reduction in the salivary secretion, and increase in basal activity of the sympathetic nervous system. There is an increase in muscular contraction, and bruxism during sleep [37]. Even when dental malocclusion is corrected, many individuals displaying these behavioral factors continue to brux and experience allodynia [22]. This group has higher somatic awareness and are hypervigilant.

Markers of pain centralization can be identified through history, physical examination, and motivational interviewing. It requires a deep understanding of the patient's underlying pain mechanism by assessing the pain threshold in asymptomatic areas. Patients with central sensitization and chronic pain have overactive nociceptive facilitatory pathways and poor functioning antinociceptive mechanisms. This results in exaggerated central nervous system response (severe jaw pain often accompanied by various other symptoms, such as chronic neck pain, insomnia, and stress intolerance) to normal somatosensory input. There are three features required for diagnosing central sensitization: 1) pain experience that is disproportionate to the extent of injury/pathology, 2) neuroanatomically illogical pain pattern, and 3) hypersensitivity of senses unrelated to the musculoskeletal system [24]. Clinically this can be measured and quantified using simple graded chronic pain status scores from 0 (No pain or discomfort) to 10 (Worst pain imaginable) scale as well as pain diagrams to document and recognize the pain pattern (Figure 4). Others have reported graded pain severity into four hierarchical classes: Grade I, low disability-low intensity; Grade II, low disability-high intensity; Grade III, high disability-moderately limiting; and Grade IV, high disability-severely limiting [45].

Both medicine and dentistry will encounter patients with central sensitization; it is critically important for physicians and dentists to recognize it in clinical practice. Given the overall hyperresponsiveness of central nervous system neurons, it may explain the altered sensitivity to many environmental stimuli.

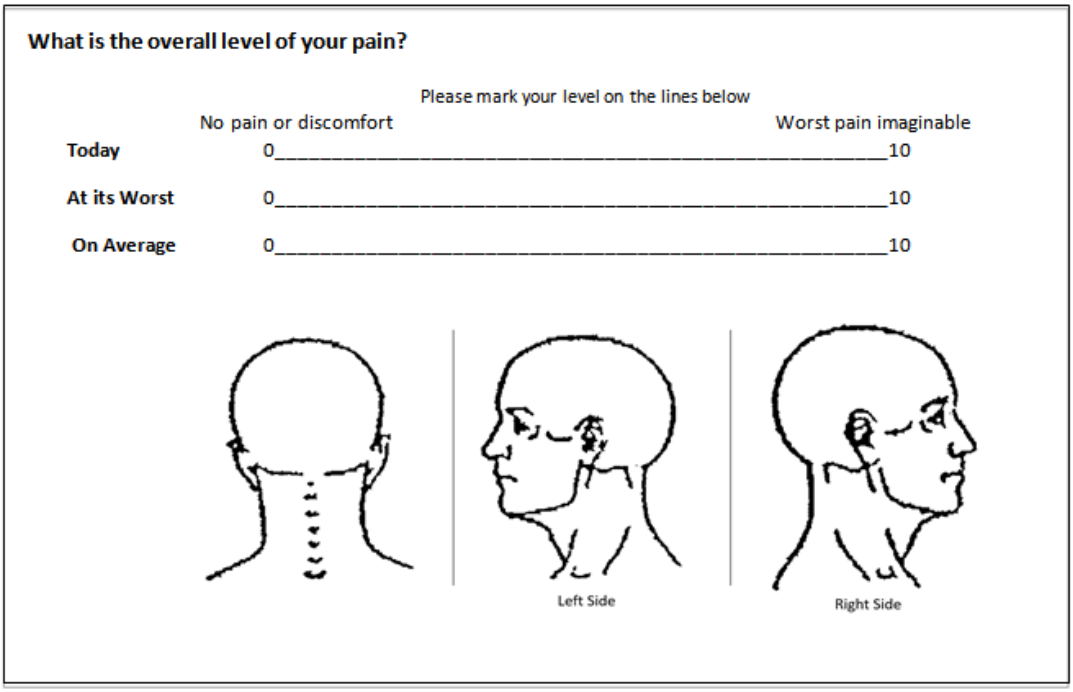

Figure 4 Excerpt from patient intake questionnaire for simple graded chronic pain status.

7. Conclusion

Neuroplasticity, central sensitization, and pain types exemplifies the importance of addressing the anatomical and functional complexities of the TMJ. Acute TMD pain is the result of primarily peripheral mechanisms, whereas chronic TMD pain is a central problem leading to neuroplastic changes and impaired central inhibition. TMD must be examined as a complex disorder determined by interacting and redundant systems. Focusing ~~from~~ on one perspective (e.g. disc derangement in joint, trismus) is insufficient. Advances in the basic sciences related to TMD need to involve collaborations between medical and dental institutions. Future studies should identify specific neuroplastic changes due to sensory input from the environment.

Author Contributions

The author did all the research work in this study.

Competing Interests

The author declares this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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