Received: 1 April 2021 | Revised: 24 June 2021 | Accepted: 17 July 2021

DOI: 10.1111/joor.13236

REVIEW

JOURNAL OF ORAL REHABILITATION WILEY

# Occlusal disharmony and chronic oro-facial pain: from clinical observation to animal study

Ye Cao[1,2,3]

[1]Department of Prosthodontics, Center for Oral and Jaw Functional Diagnosis, Treatment and Research, Peking University School and Hospital of Stomatology, Beijing, China

[2]Center for TMD & Orofacial Pain, Peking University School and Hospital of Stomatology, Beijing, China

[3]National Clinical Research Center for Oral Diseases, National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing Key Laboratory of Digital Stomatology, Beijing, China

**Correspondence**
Ye Cao, Department of Prosthodontics, Center for Oral and Jaw Functional Diagnosis, Treatment and Research, Peking University School and Hospital of Stomatology, No. 22 Zhong Guan Cun South Ave, Beijing 100081, China.
Email: ye.cao@bjmu.edu.cn

**Funding Information**
This research was supported by the Natural Science Foundation of China (No. 81970955, Y. Cao) and the Natural Science Foundation of Beijing, China (No. 7192231, Y. Cao)

## Abstract

**Background:** Occlusion can be viewed as the most sensitive susceptor of the central nervous system in the oro-facial region. Its inalienable relationships to the temporomandibular joint, the muscles, the stomatognathic system and even the central nervous system are self-evident. Almost all the dental treatments inevitably change the occlusion, potentially or actually, locally or extensively, and immediately or gradually.

**Objective:** The objective of this study was to present a narrative literature on occlusal disharmony and chronic oro-facial pain.

**Methods:** Literature reviews focusing on clinical studies about the relationship between occlusal disharmony and myofascial oro-facial pain, and related preclinical studies about the animal models of, as well as the peripheral and central mechanisms underlying this condition related to, occlusal disharmony were used as starting point and guidelines to describe the topics mentioned. A search of the PubMed database was performed mainly with the following search terms: "occlusion," "occlusal interference," "occlusal disharmony," "occlusal change," "oro-facial pain" and "myofascial pain."

**Results:** Relevant literature from the past 70 years until the present day was meticulously studied. The literature review together with three related characteristic clinical cases revealed an intimate association between occlusal disharmony and chronic oro-facial pain, involving pathological changes, extending from the peripheral tissues to the central nervous system. The patients suffered from psychological distress, sleep disturbance and poor life quality.

**Conclusion:** Occlusal disharmony–related oro-facial pain is a clinical problem that deserves attention, although there are no universally accepted clinical protocols. The existing literature provides some constructive suggestions, but further research is needed.

KEYWORDS

Chronic oro-facial pain, experimental occlusal, interference, occlusal disharmony

## 1 | INTRODUCTION

Temporomandibular disorders (TMDs) are a cluster of medical and dental conditions involving temporomandibular joints, masticatory musculature and the accompanying structures.[1] Despite their high occurrence in population studies, the disorders are self-limiting, and only 3.6–7.0% of patients with TMDs require treatment, with pain being the most common reason for seeking treatment.[2-5] Painful

TMDs affect up to 10% of the general population and 45–60% of patients with TMDs.[6-8] Among the different subtypes of painful TMDs, chronic and muscular subtypes most markedly affect patients' quality of life and mental health. Chronic TMD, especially myofascial TMD, is even considered a functional pain syndrome, similar to fibromyalgia and chronic fatigue syndrome.[8-10] The tremendous impact of chronic painful TMDs led to their inclusion in the International Classification of Diseases (ICD-11) of the World Health Organization.[11]

Chronic oro-facial pain is associated with extreme discomfort and economic burden and must be given sufficient attention. In the first edition of the International Classification of Orofacial Pain (ICOP) published in 2020 by the International Association for the Study of Pain (IASP), there was a major focus on chronic oro-facial pain.[12] The ICOP is a comprehensive classification of oro-facial pain, in which chronic primary myofascial pain was first proposed as a diagnosis. Chronic primary myofascial pain is an important supplement to the muscular oro-facial pain and defined as 'mild to moderate levels of deep aching or pressing pain in the masticatory muscles, occurring episodically or unremittingly, often associated with chewing and/or yawning, etc., and with onset more than three months ago'. It is often associated with psychosocial distress. Similar symptoms were previously termed as 'persistent oro-facial muscle pain', 'chronic masticatory myofascial pain' or 'chronic myalgia'.[13,14]

In nearly 100 years of research on TMD, the viewpoint about the underlying aetiology has transformed from mechanically based theories to a biopsychosocial model. The role of occlusion in the pathogenesis of TMD has changed from a causative factor to a contributing factor. Occlusion has been defined as the 'static relationship between the incising or masticating surfaces of the maxillary or mandibular teeth or tooth analogs'.[15] Occlusal change induced by tooth loss, periodontal disease, and various dental practices including filling, prosthodontic treatment and orthodontics can cause occlusal disharmony, which is defined as 'a phenomenon in which contacts of opposing occlusal surfaces are not in harmony with other tooth contacts and/or the anatomic and physiologic components of the craniomandibular complex'.

## 1.1 | Occlusion disharmony intimately associated with chronic myofascial oro-facial pain

The relationship between occlusion and TMD has long been a controversial topic. During the 1930s and 1940s, the aetiology of TMD was mainly understood as a mechanical/occlusal problem. Later, the aetiology of TMD was revised from the viewpoint of mechanics to a biopsychosocial model.[16] Furthermore, the relationship between occlusion and TMD has gained extensive attention. Despite abundant epidemiological and experimental human studies, no definite causal relationship has been established between occlusion and TMDs.[17-19] However, clinical observations have led some dentists to agree that there is an important relationship between occlusal features and TMDs. Why do some patients experience long-lasting pain and discomfort after occlusal changes? Why does occlusal treatment relieve some TMD symptoms?

Among the findings of the many studies reported thus far, some deserve extra attention. Randomised controlled trials have shown that participants with and without a history of TMDs showed different adaptations to artificial interferences. Those with a history of TMD and true interferences reported more severe symptoms and clinical signs compared to those reported by patients without TMD history and placebo interferences.[20,21] Moreover, one case-control study compared 222 controls with 196 patients with TMDs, which were divided into different diagnostic subgroups. The study reported that selective occlusal variables appeared to be associated with some specific TMD subtypes.[22] We believe it is crucial to clarify the concept when discussing the relationship between occlusion and TMDs. Regarding 'occlusion', it is necessary to clarify the specific subtype, that is whether it is malocclusion, naturally occlusal interference, abrupt occlusal change, posterior occluding teeth loss or artificial occlusal interference.

There has been an abundant clinical focus on the relationship between acute occlusal disharmony and TMDs. Acute occlusal disharmony (including that related to dental treatment) can be considered an initial contributing factor to TMDs. In a study conducted in 230 patients with TMDs, 7% of the patients attributed the onset of their symptoms to dental treatment (orthodontic and other dental procedures), which was identified as the second most common cause.[23] In one of our earlier studies, we consecutively studied 12 patients with chronic masticatory muscle pain, of whom 10 reported symptoms related to acute occlusal changes.[24] In a recent study in 131 patients with perceived dental-related causes of TMDs, 27.5% specifically reported prior dental treatment as the cause of TMDs. What is more noteworthy is that in 67.3% of the cases, the TMDs were myogenic.[25] Perceptions of illness have been shown to be markedly associated with outcomes in a range of acute and chronic diseases.[26] The recognition that dental treatments could be the cause of patients' TMD symptoms, according to patients' beliefs, is a newly emerging issue.

## 1.2 | Clinical characteristics of occlusal disharmony–related oro-facial pain: Three representative cases

Clinical treatment strategies should be customised for occlusion-related oro-facial pain based on patients' symptoms and systematic evaluations. Table 1 and Figures 1-3 show three cases in which dental treatments resulted in occlusion disharmony, which in turn induced oro-facial pain. In case A, oro-facial pain was caused by stimulation of nociceptors due to potential or actual damage in the periodontium, muscle or TMJ.[27,28] The pain was localised to the injured area, and the pain experience was perceptually proportional to the amount of the incoming peripheral nociceptive input.[29] Case A can be categorised as a peripheral nociceptive mechanism, which is clinically manageable and has a good prognosis. The symptoms are generally reversible.[30,31] In contrast, oro-facial pain in case B was not merely generated and maintained by a peripheral nociceptive drive, but could also be attributable to changes in the central nervous system. A complete mismatch between occlusal factors and perceived

**TABLE 1** Cases of occlusal-related oro-facial pain

| | Chief complaint and history | Sign and symptoms | Treatments |
|---|---|---|---|
| **Case A Prognosis:good** | A 38-year-old man with no history of systemic medical problems. His main complaint was that he could not bite his teeth together after a #46 crown restoration. He also complained of mild bilateral pain in the masseters for a month. His crown had been adjusted by another dentist three times, but the open bite became progressively worse. Occlusal splint therapy and equilibrations were conducted. The occlusion was restored to its former position, and the #46 crown was renewed.<br>Figure 1A-D Clinical photographs of the patient at his first visit. An open bite was detected, and merely, contacts of #17- #47, #27- #37 existed. Figure 1E-H Clinical photographs of the patient after splint therapy and #46 crown restoration. The intercuspal occlusion was rehabilitated. | • Localised pain in TMJ or the masticatory muscle<br>• Tender on palpation<br>• Acute occlusal disharmony | • NSAID<br>• Physical therapy<br>• Occlusal splint<br>• Occlusal equilibration<br>• Prosthodontic treatment |
| **Case B Prognosis:bad** | A 40-year-old woman with no history of systemic medical problems. She had her anterior teeth restored by crowns due to aesthetic problems 3 years ago. She felt discomfortable in her TMJ and muscles after the treatments. Since then, the crowns have been removed and redone several times, but the symptoms sustained. Her dentist conducted occlusal adjustments on her posterior teeth, which caused an ultima disaster for her. Now, her main complaints were widespread moderate-to-severe pain in her face and neck, accompanied by a numb sensation in the oro-facial region. She experienced severe sleep disturbance and psychological distress. She was frustrated with her disease and claimed that her daily life was disrupted after the fixed restorations were inserted into her mouth. We conducted occlusal splint therapy on her, but it only showed a temporary relief. The combination of occlusal splint and acupuncture treatment had a relatively good effect on her. The sleep disturbances and pain improved significantly, but symptoms were recurrent.<br>Figure 2A Photograph provided by the patient showed her anterior teeth before prosthodontic treatment. Figure 2B-F Clinical photographs of the patient at her first visit, and Figure 2E, F shows the occluding contacts. | • Regional or diffused pain, widespread hyperalgesia<br>• High somatic awareness or hypervigilance<br>• Psychological distress<br>• Chronic occlusal disharmony<br>• Experience of multiple failed treatments | • Pregabalin, gabapentin, tricyclics<br>• Psychiatric treatment<br>• Cognitive behavioural therapy<br>• Pain coping skills<br>• Acupuncture treatment<br>• Occlusal splint |
| **Case C Prognosis:poor** | A 53-year-old woman with a 2-year history of problems that began after orthodontic treatment. She reported that her teeth kept moving every minute and she could not find a comfortable position for her mandible. She complained of widespread oro-facial pain, with trouble in breathing, swallowing and sleeping. These symptoms have seriously affected her normal life. She believed that the 'bite change' was the cause of all her ongoing problems. She had consulted several orthodontic specialists, prosthodontic specialists and TMD specialists in the past 2 years. She had received psychiatric and occlusal splint treatments; however, her symptoms are getting worse.<br>Figure 3A-C Photographs provided by the patient before her orthodontics treatment. Crossbites of #12- #42 #43, #14- #44 #45 were existed. Figure 3 Clinical photographs of the patient at her first visit. | • Persistent complaint of bite discomfort with no matched occlusal discrepancy<br>• A long history of unsuccessful dental treatments<br>• Severe psychological distress<br>• Poor compliance with dentists<br>• OD is highly suspected | • Divergent management approaches<br>• Dental or irreversible occlusal treatment should be avoided |

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; OD, occlusal dysesthesia; TMD, temporomandibular disorders; TMJ, temporomandibular joint.

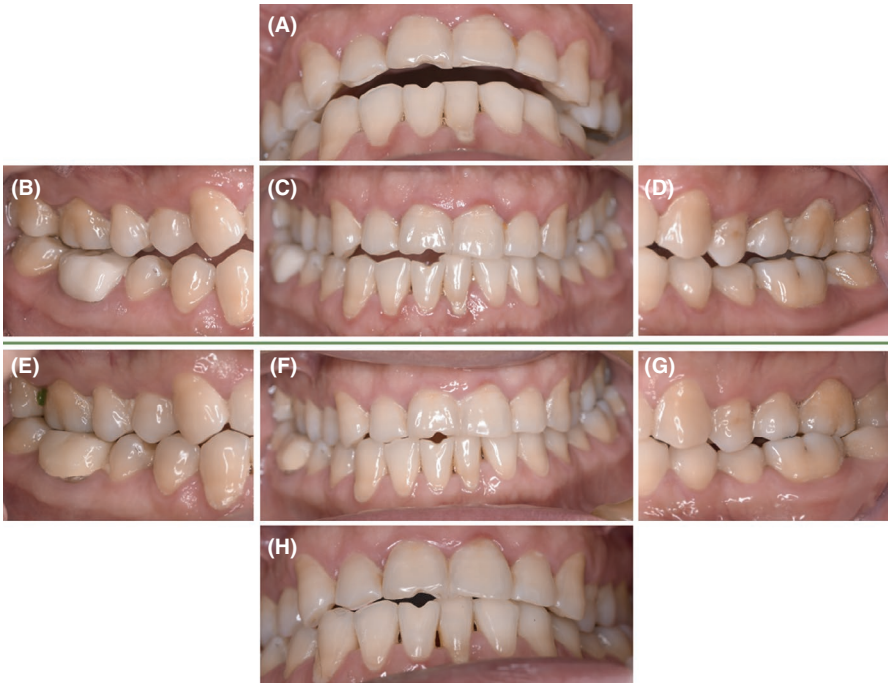


**FIGURE 1** Clinical photographs of case A

pain is observed in centralised pain, which is challenging to treat and has a substantial negative impact on patients, including emotional disturbance, sleep impairment, and a disaster of daily life.[29]

Sometimes, occlusal changes can also cause very rare conditions, such as occlusal dysesthesia (OD) or phantom bite syndrome, as in case C. OD refers to a persistent complaint of an uncomfortable bite sensation with no obvious occlusal discrepancy. It is a rare condition and usually associated with emotional distress and triggered by dental treatments. The main complaint of OD patients is 'the bite is off' accompanied by a long history of an uncomfortable bite position and unsuccessful dental treatment.[32-34] OD is often noted as a comorbidity with TMDs, especially myofascial oro-facial pain related to occlusal alteration.[35-37] The diagnosis and management of OD remain a major challenge for dental practitioners. Besides, the differential diagnosis of OD and TMDs is also important because the managements for the two conditions differ entirely.

## 1.3 | Animal models of myofascial oro-facial pain

Preclinical research is an important way to understand the mechanism of a disease and explore therapeutic methods. The study of pain relies extensively on animal models to assess the sensory aspects, understand the pathophysiology and design novel drugs and therapies. Several models have been developed and reported in the literature to study the various features of myofascial oro-facial pain.

### 1.3.1 | Inflammatory muscle pain model

Injection of chemical irritants into the masticatory muscles of animals could induce allodynia/hyperalgesia for varying durations. The common algesics include complete Freund's adjuvant (CFA), mustard oil, acidic saline, and glutamate.[38-40] Models such as those involving the use of CFA evoke a massive inflammatory response with tissue erosion that does not correspond to known muscle pathologies. Injection of chemical irritants into muscle simulates myofascial oro-facial pain attributes to myositis according to the ICOP.

### 1.3.2 | Eccentric muscle contraction

The masseter muscle is rapidly stretched or electrically stimulated during forced lengthening to produce eccentric muscle contractions. Mechanical hyperalgesia is detected in the muscle for hours to days, depending on the number of eccentric contraction bouts.[41] This model simulates myofascial oro-facial pain attributed to muscle spasm according to the ICOP.

### 1.3.3 | Ligation of the tendon of the masseter muscle

Unilateral ligation of the tendon of the anterior superficial part of the rat masseter muscle yields long-lasting and constant mechanical hypersensitivity of myogenic origin. Mechanical sensitivity is significantly reduced and maintained throughout the eight-week observation period, suggesting the presence of mechanical hyperalgesia/allodynia.[42] This model simulates the myofascial oro-facial pain attributable to tendonitis according to ICOP.

### 1.3.4 | Experimental tooth movement model

Experimental tooth movement (ETM) models are caused by artificial movement of teeth in animals and then induce the occlusal

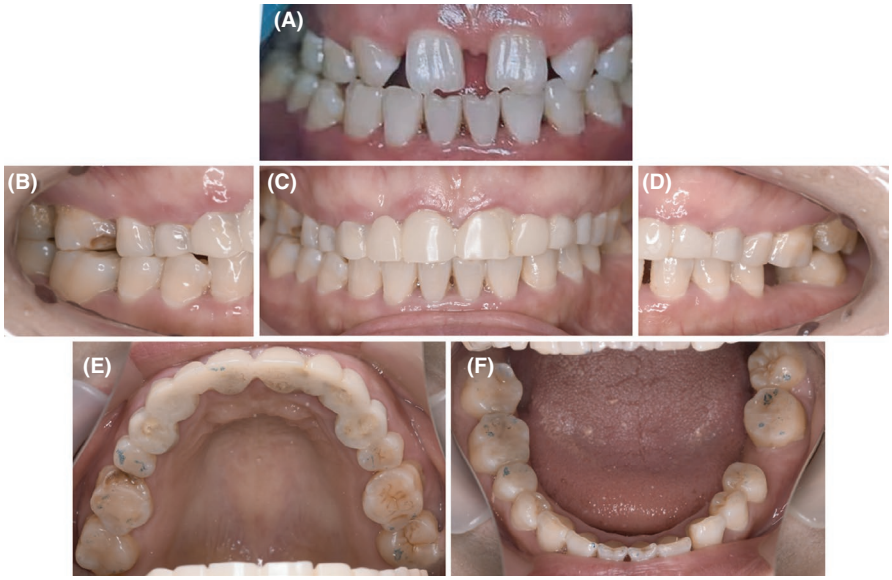


**FIGURE 2** Clinical photographs of case B

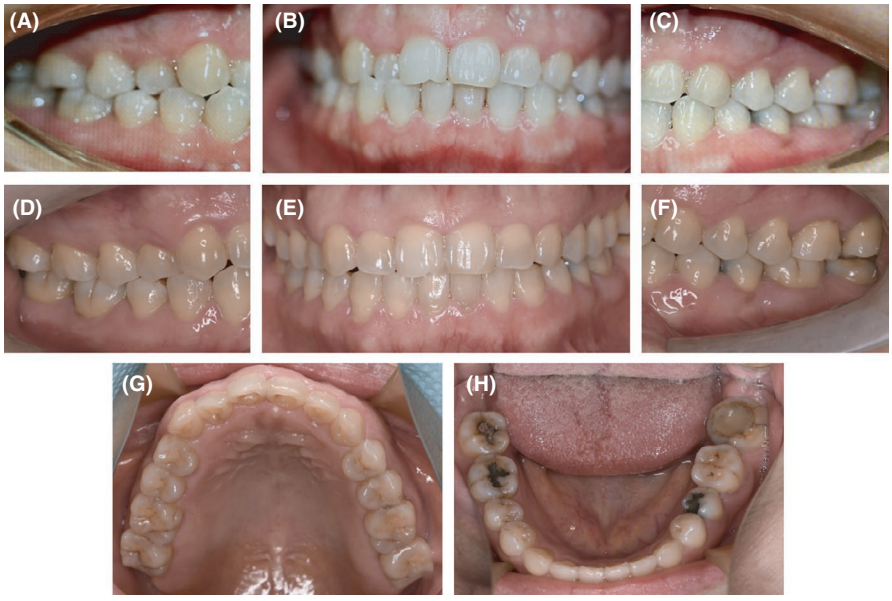


**FIGURE 3** Clinical photographs of case C

disharmony. The ETM is usually induced by inserting a piece of elastic band between the left upper first and second molars of rats, with the aim to move the first molar mesially.[43,44] A significant reduction in pressure pain threshold can be observed in the ETM group from 4 to 13 days after the application of tooth movement.[43] This model simulates the primary myofascial oro-facial pain according to ICOP.

### 1.3.5 | Unilateral anterior crossbite model

Occlusal disharmony can also be led by unilateral anterior crossbite (UAC) animal model. Metal tubes are bonded to maxillary and mandibular incisors on ipsilateral side, by which an anterior teeth crossbite will be induced.[45,46] Masseter's atrophy and TMJ catabolic degradative changes accompanied by short-term mechanical hyperalgesia in masticatory muscles are observed in this model.[45,47] This model simulates the acute primary myofascial oro-facial pain according to ICOP.

### 1.3.6 | Experimental model of occlusal interference

The bite-raising model was first used to study periodontal diseases approximately 90 years ago.[48] Many appliances such as pins, filling materials, or orthodontic wires are bonded on the tooth to induce occlusion changes.[49,50] Some studies have shown that hyperalgesia occurs in rats after 1- to 2-mm occlusal raising.[51,52] However, the design of the bite raise in early experiments was quite different from the actual clinical conditions. Clinically, there is no possibility that patients can tolerate such a severe occlusal change. Moreover, no previous studies have measured hyperalgesia in masticatory muscle.

We have previously established a rodent model of masticatory muscle hyperalgesia induced by experimental occlusal interference (EOI) by cementing a metal crown on rats' first molars. We demonstrate that EOI induced long-term and bilateral hyperalgesia in masticatory muscle, which was proven by both spontaneous and evoked pain behavioural tests. The EOI-induced mechanical hyperalgesia persists for 4 weeks, starting on day 1, peaking from day 5 to 7 and lasting until day 28 of the experiment. The hyperalgesia on the contralateral side tends to be greater than that on the ipsilateral side, but no significant differences were detected.[53] The EOI model simulates chronic primary myofascial oro-facial pain according to ICOP. It is an animal model quite similar to the clinical situation, with the following characteristics.

*Stimulus quantifiable*

Bonding crowns of different thicknesses can be used to adjust the intensity of the stimulus. Crowns with thickness from 0.2 to 0.6 mm, representing different severities of occlusal interference, were administered in our previous studies. For sham controls, bands that do not interfere with occlusion are bonded to simulate sensory change. The occlusal interference groups with 0.4- and 0.6-mm crowns showed more significant mechanical hyperalgesia than the group with 0.2-mm crowns. However, no significant difference was present between the groups with 0.4- and 0.6-mm crowns. The stimulus-response effects reported here suggest that occlusal interference could be an essential factor causing chronic masticatory muscle pain.[53]

*Stimulus reversible*

The crown cemented to the tooth can be easily removed at any time point, making it possible to study mechanisms in different pain states. We removed crowns at different time points after EOI and obtained some meaningful findings. The hyperalgesia became irreversible after 6 days or longer following EOI placement but could be reversed if the EOI was removed within 6 days of placement.[30,53,54]

*Submodels*

According to the behavioural results obtained with the EOI model and the removal of EOI model, the hyperalgesia can be divided into three stages: an initial stage (post-operative days 0–6) when EOI-induced hyperalgesia becomes established (this stage is reversible); a chronification stage (post-operative days 7–8) when hyperalgesia transitions from acute to chronic; and a maintenance stage (post-operative days 9 and beyond) when hyperalgesia becomes sustained and irreversible. Removal of the EOI in the initial stage results in the reversal of oro-facial hyperalgesia, whereas EOI removal during or after the chronification stage is associated with persistent hyperalgesia.[55,56] Therefore, PEOI (persistent EOI) and REOI (EOI removed on any post-operative day) submodels were established for further exploration of the mechanism. In our recent study, the PEOI, REOI3d and REOI8d models were used to study the mechanisms in different hyperalgesia stages.

## 1.4 | Peripheral and central mechanism of the EOI model

### 1.4.1 | The muscular mechanism in the EOI model

The EOI-induced myofascial oro-facial pain shows features that mimic some characteristics of human chronic primary myofascial pain, which is characterised by pain and tenderness to palpation of the masticatory muscles. One previous study showed that the mechanical nociceptive thresholds measured with larger probes reflect the nociceptive threshold of deep tissues, possibly muscle, while smaller-diameter probes reflect nociceptive thresholds for the skin.[57] The method for evaluation of the mechanical nociceptive threshold of muscle nociceptors in the oro-facial region of rats was first described by us for EOI experiments, allowing transmission of pressure onto the masticatory muscles, thereby avoiding skin stimulation and cutaneous pain as elicited by previous sharp von Frey filaments.[53]

In comparison with the much lower behavioural thresholds evoked by mechanical stimulation of facial cutaneous receptors that were reported with other oro-facial pain models, the range of high mechanical thresholds for evoking the withdrawal behaviour in EOI research is consistent with the activation of receptors in deep tissues such as the masseter.[58,59] Thus, it seems likely that activation of masseter muscle receptors at least contributed to the sensory input evoking the behaviour.

In some early studies, partial histological changes were observed in the masticatory muscles of unilateral bite-raised rats, such as extension of connective tissue, appearance of inflammatory cells in the muscle fibres, existence of muscle fibres with central nuclei and degenerative atrophy of myofibres.[49,50] In our EOI model, PGP9.5 and substance P expressions transiently increased after occlusal alteration, but muscle fibre damage or inflammation was not observed.[60] Moreover, the levels of energy metabolites such as adenosine triphosphate (ATP), inosine monophosphate, phosphocreatine and creatine in masseters are transiently changed after EOI.[28] Trauma has been recognised as a cause of chronic myofascial pain. Therefore, microtrauma related to dental treatment can also be an important factor.[61,62] The muscle microtrauma produced by EOI can induce changes in energy metabolites. The involvements of the metabolites in sensitisation of muscle nociceptive afferents might underlie the muscular mechanisms of myofascial pain.[63,64]

### 1.4.2 | Trigeminal ganglion (TG) mechanism in the EOI model

EOIs can induce expression changes of ion channels and receptors in TG. An early study reports that occlusal trauma upregulates $PN_3$ mRNA and NaN mRNA expression.[65] The gene expression and protein levels of TRPV1 and ASIC3 in bilateral TGs were also upregulated after EOI. The proportion of ASIC3-positive neurons in

the masseter muscle afferent neurons increased after EOI, but the proportion of TRPV1-positive neurons did not increase. TRPV1 and ASIC3 are expressed by more small-sized and small- to medium-sized masseter afferents. These changes peaked on day 7 and then reverted to their original status within 10 days after EOI. Intramuscular injection of the TRPV1 antagonist AMG-9810 partially reversed the mechanical hyperalgesia of the masseter muscle, while no improvement was observed with the ASIC3 antagonist APETX2. AMG-9810 combined with APETX2 showed better efficacy than AMG-9810 alone.[27]

### 1.4.3 | Medulla dorsal horn mechanism in the EOI model

In addition to the peripheral sensitisation processes of TG, higher brain regions such as medulla dorsal horn (MDH), the processing centre of oro-facial signals was intensely studied. Dong et al. showed that both PPTA and c-fos mRNA expressions are elevated in dog's MDH after traumatic occlusion.[66] Our findings suggest that central mechanisms, including sensitisation of trigeminal nociceptive neurons and glial processes involving mitogen-activated protein kinases (MAPKs), play significant roles in producing EOI-induced oro-facial pain. Central sensitisation of functionally identified MDH nociceptive neurons following EOI was documented by extracellular electrophysiological recordings. Astrocytes and microglia also showed activation up to 14 days after EOI. Prolonged upregulation of p38 MAPK and extracellular signal-regulated kinase (ERK) was also noted in MDH, in both neurons and glial cells at time points when rats showed peak mechanical facial hypersensitivity. Intrathecal administration of p38 MAPK and ERK inhibitors to the medulla significantly inhibited EOI-induced hypersensitivity, and the latter produced an even stronger effect on hypersensitivity and neuronal sensitisation.[67]

### 1.4.4 | Anterior cingulate cortex (ACC) mechanism in the EOI model

Chronic pain inevitably involves changes in the higher centres, and many studies have confirmed the role of ACC in this process. The pathological changes in the lower level nuclei of the trigeminal system amplify nociceptive inputs, project ascendingly and further induce plasticity in the higher brain regions. The essential mechanisms account for long-term sustained behavioural sensitivity. Increased medial thalamus (MT) stimulation steadily elicited gradually enhanced local field potential (LTP) amplitudes in the ACC of control and EOI rats. Rats that received EOI for 14 and 21 d exhibited dramatically enhanced LFP in the ACC in response to MT stimulation, in comparison with control rats and rats that received EOI for 7 d. The results suggest that MT-ACC synaptic transmission was potentiated since 14 d after EOI application.[68]

### 1.4.5 | Descending modulation in the EOI model

The RVM neuronal changes exhibited in the spontaneous or evoked activity suggest that adaptive neuroplasticity expressed in ON and OFF cells contributed to the chronification, maintenance and reversal of oro-facial hyperalgesia in the EOI model. EOI induced time-dependent oro-facial mechanical hyperalgesia, and EOI removal in the initial stage but not in the chronification stage can reverse the hyperalgesia in male rats. These may be modulated by adaptive changes in descending inhibitory and facilitatory influences from the RVM. Moreover, activation of astrocytes in the RVM was observed in the maintenance of oro-facial hyperalgesia following EOI removal in the later stage, likely by promoting descending facilitation from the RVM.[69,70]

### 1.4.6 | The psychological state and the EOI model

Tang et al. used this model to study the psychological state of rats. They found that EOI could lead to an increase in serum corticosterone concentration and behavioural changes in rats, suggesting a state of anxiety. Meanwhile, chronic stress combined with EOI could aggravate anxiety. They also detected significant changes in 5-HT and 5-HT2A receptor expressions in the prefrontal cortex, hippocampal CA1 and dentate gyrus areas, which implied that EOI could induce anxiety through the central pathway via the 5-HT system.[71]

## 2 | CONCLUSIONS

In conclusion, this review aimed to summarise the relationship between occlusal disharmony and oro-facial pain from observations in clinical settings to animal studies. Occlusal disharmony can lead to pathological changes, extending from the peripheral tissues to the central nervous system. Occlusal disharmony-related myofascial oro-facial pain is closely related to dental treatment and can seriously affect patients' quality of life. When a patient complains of occlusal problems after dental treatment, it is important to pay more attention to it than to merely make the patient adapt to the abnormality. In the peripheral nociceptive stage, most of the pathological changes are reversible. The disease becomes difficult to manage when it becomes centralised. The peripheral and central mechanisms, the relationship between occlusal disharmony and psychological disorders, and the clinical treatment require special attention and in-depth studies.

**CONFLICT OF INTEREST**

The author declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**PEER REVIEW**

The peer review history for this article is available at https://publons.com/publon/10.1111/joor.13236.

## DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

## ORCID

*Ye Cao* https://orcid.org/0000-0001-7663-1480

## REFERENCES


1. Gauer RL, Semidey MJ. Diagnosis and treatment of temporomandibular disorders. *Am Fam Physician*. 2015;91(6):378-386.
2. Kino K, Sugisaki M, Haketa T, Amemori Y, Miyaoka H. The comparison between pains, difficulties in function, and associating factors of patients in subtypes of temporomandibular disorders. *J Oral Rehabil*. 2005;32(5):315-325.
3. Gesch D, Bernhardt O, Alte D, et al. Prevalence of signs and symptoms of temporomandibular disorders in an urban and rural German population: results of a population-based Study of Health in Pomerania. *Quintessence Int*. 2004;35(2):143-150.
4. Goncalves DA, Dal Fabbro AL, Campos JA, Bigal ME, Speciali JG. Symptoms of temporomandibular disorders in the population: an epidemiological study. *J Orofac Pain*. 2010;24(3):270-278.
5. List T, Jensen RH. Temporomandibular disorders: Old ideas and new concepts. *Cephalalgia*. 2017;37(7):692-704.
6. Graue AM, Jokstad A, Assmus J, Skeie MS. Prevalence among adolescents in Bergen, Western Norway, of temporomandibular disorders according to the DC/TMD criteria and examination protocol. *Acta Odontol Scand*. 2016;74(6):449-455.
7. Nilsson IM, List T, Drangsholt M. Prevalence of temporomandibular pain and subsequent dental treatment in Swedish adolescents. *J Orofac Pain*. 2005;19(2):144-150.
8. Cao Y, Yap AU, Lei J, Zhang MJ, Fu KY. Subtypes of acute and chronic temporomandibular disorders: Their relation to psychological and sleep impairments. *Oral Dis*. 2020.
9. Yap AU, Cao Y, Zhang MJ, Lei J, Fu KY. Temporomandibular disorder severity and diagnostic groups: Their associations with sleep quality and impairments. *Sleep Med*. 2021;80:218-225.
10. Yap AU, Cao Y, Zhang MJ, Lei J, Fu KY. Comparison of emotional disturbance, sleep, and life quality in adult patients with painful temporomandibular disorders of different origins. *Clin Oral Investig*. 2021;25(6):4097–4105.
11. Benoliel R, Svensson P, Evers S, et al. The IASP classification of chronic pain for ICD-11: chronic secondary headache or orofacial pain. *Pain*. 2019;160(1):60-68.
12. International Classification of Orofacial Pain, 1st edition (ICOP). *Cephalalgia*. 2020;40(2):129-221.
13. Benoliel R, Svensson P, Heir GM, et al. Persistent orofacial muscle pain. *Oral Dis*. 2011;17(Suppl 1):23-41.
14. Clark GT. Classification, causation and treatment of masticatory myogenous pain and dysfunction. *Oral Maxillofac Surg Clin North Am*. 2008;20(2):145–157.
15. The Glossary of Prosthodontic Terms: Ninth Edition. *J Prosthet Dent*. 2017;117(5S):e1-e105.
16. Skarmeta NP, Pesce MC, Saldivia J, et al. Changes in understanding of painful temporomandibular disorders: the history of a transformation. *Quintessence Int*. 2019;50(8):662-669.
17. Clark GT, Tsukiyama Y, Baba K, Watanabe T. Sixty-eight years of experimental occlusal interference studies: what have we learned? *J Prosthet Dent*. 1999;82(6):704-713.
18. Seligman DA, Pullinger AG. The role of functional occlusal relationships in temporomandibular disorders: a review. *J Craniomandib Disord*. 1991;5(4):265-279.
19. LeResche L. Assessment of physical and behavioral outcomes of treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1997;83(1):82-86.
20. Le Bell Y, Jamsa T, Korri S, Niemi PM, Alanen P. Effect of artificial occlusal interferences depends on previous experience of temporomandibular disorders. *Acta Odontol Scand*. 2002;60(4):219-222.
21. Le Bell Y, Niemi PM, Jamsa T, Kylmala M, Alanen P. Subjective reactions to intervention with artificial interferences in subjects with and without a history of temporomandibular disorders. *Acta Odontol Scand*. 2006;64(1):59-63. https://doi.org/10.1080/00016350500419867
22. Seligman DA, Pullinger AG. Association of occlusal variables among refined TM patient diagnostic groups. *J Craniomandib Disord*. 1989;3(4):227-236.
23. Wright EF. *Manual of temporomandibular disorders*, 2nd ed. Wiley-Blackwell; 2010.
24. Cao Y, Xie QF, Yang ZH. Electrical pain thresholds of face and finger in patients with chronic masticatory muscle pain. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2009;44(6):373-376.
25. Mitrirattanakul S, Dds P, Jariyasakulroj SD. Dental treatment as perceived etiology of temporomandibular disorders. *Cranio*. 2020;38(2):109-114.
26. Petrie KJ, Jago LA, Devcich DA. The role of illness perceptions in patients with medical conditions. *Curr Opin Psychiatry*. 2007;20(2):163-167.
27. Xu XX, Cao Y, Ding TT, et al. Role of TRPV1 and ASIC3 channels in experimental occlusal interference-induced hyperalgesia in rat masseter muscle. *Eur J Pain*. 2016;20(4):552-563.
28. Xu XX, Cao Y, Fu KY, Xie QF. Changes of productions of energy metabolism in masseter of rats induced by occlusal interference. *Beijing Da Xue Xue Bao Yi Xue Ban*. 2017;49(1):25-30.
29. Harper DE, Schrepf A, Clauw DJ. Pain Mechanisms and Centralized Pain in Temporomandibular Disorders. *J Dent Res*. 2016;95(10):1102-1108.
30. Li X, Cao Y, Xie Q. Characteristics of experimental occlusal interference-induced masticatory mechanical hyperalgesia of rats. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2014;49(10):596-599.
31. Li J, Jiang T, Feng H, et al. The electromyographic activity of masseter and anterior temporalis during orofacial symptoms induced by experimental occlusal highspot. *J Oral Rehabil*. 2008;35(2):79-87.
32. Hara ES, Matsuka Y, Minakuchi H, Clark GT, Kuboki T. Occlusal dysesthesia: a qualitative systematic review of the epidemiology, aetiology and management. *J Oral Rehabil*. 2012;39(8):630-638.
33. Marbach JJ. Phantom bite. *Am J Orthod*. 1976;70(2):190-199.
34. Melis M, Zawawi KH. Occlusal dysesthesia: a topical narrative review. *J Oral Rehabil*. 2015;42(10):779-785.
35. Imhoff B, Ahlers MO, Hugger A, et al. Occlusal dysesthesia-A clinical guideline. *J Oral Rehabil*. 2020;47(5):651–658.
36. Leon-Salazar V, Morrow L, Schiffman EL. Pain and persistent occlusal awareness: what should dentists do? *J Am Dent Assoc*. 2012;143(9):989-991.
37. Ligas BB, Galang MT, BeGole EA, et al. Phantom bite: a survey of US orthodontists. *Orthodontics (Chic.)*. 2011;12(1):38-47.
38. Ambalavanar R, Yallampalli C, Yallampalli U, Dessem D. Injection of adjuvant but not acidic saline into craniofacial muscle evokes nociceptive behaviors and neuropeptide expression. *Neuroscience*. 2007;149(3):650-659.
39. Ro JY, Capra NF, Masri R. Contribution of peripheral N-methyl-D-aspartate receptors to c-fos expression in the trigeminal spinal nucleus following acute masseteric inflammation. *Neuroscience*. 2004;123(1):213-219.
40. Cairns BE, Gambarota G, Svensson P, Arendt-Nielsen L, Berde CB. Glutamate-induced sensitization of rat masseter muscle fibers. *Neuroscience*. 2002;109(2):389-399.
41. Dessem D, Ambalavanar R, Evancho M, et al. Eccentric muscle contraction and stretching evoke mechanical hyperalgesia and modulate CGRP and P2X(3) expression in a functionally relevant manner. *Pain*. 2010;149(2):284-295.

42. Guo W, Wang H, Zou S, et al. Long lasting pain hypersensitivity following ligation of the tendon of the masseter muscle in rats: a model of myogenic orofacial pain. *Mol Pain*. 2010;6:40.
43. Liu XD, Wang JJ, Sun L, et al. Involvement of medullary dorsal horn glial cell activation in mediation of masseter mechanical allodynia induced by experimental tooth movement. *Arch Oral Biol*. 2009;54(12):1143-1150.
44. Waldo CM, Rothblatt JM. Histologic response to tooth movement in the laboratory rat; procedure and preliminary observations. *J Dent Res*. 1954;33(4):481-486.
45. Jing L, Liu XD, Yang HX, et al. ERK potentiates p38 in central sensitization induced by traumatic occlusion. *Neuroscience*. 2017;340:445-454.
46. Zhang HY, Yang HX, Liu Q, et al. Injury responses of Sprague-Dawley rat jaw muscles to an experimental unilateral anterior crossbite prosthesis. *Arch Oral Biol*. 2020;109:104588.
47. Wang YL, Zhang J, Zhang M, et al. Cartilage degradation in temporomandibular joint induced by unilateral anterior crossbite prosthesis. *Oral Dis*. 2014;20(3):301-306.
48. Itoiz ME, Carranza FA, Cabrini RL. Histotopographic Distribution of Alkaline and Acid Phosphatase in Periodontal Tissues of Laboratory Animals. *J Periodontol*. 1964;35(6):470-475.
49. Nishide N, Baba S, Hori N, Nishikawa H. Histological study of rat masseter muscle following experimental occlusal alteration. *J Oral Rehabil*. 2001;28(3):294-298.
50. Akagawa Y, Nikai H, Tsuru H. Histologic changes in rat masticatory muscles subsequent to experimental increase of the occlusal vertical dimension. *J Prosthet Dent*. 1983;50(5):725-732.
51. Chen J, Zhang J, Zhao Y, et al. Hyperalgesia in response to traumatic occlusion and GFAP expression in rat parabrachial [correction of parabranchial] nucleus: modulation with fluorocitrate. *Cell Tissue Res*. 2007;329(2):231-237. https://doi.org/10.1007/s00441-007-0409-3
52. Yu YF, Gu ZY, Fu KY. Central mechanisms of masticatory muscle pain induced by occlusal interference. *Hua Xi Kou Qiang Yi Xue Za Zhi*. 2007;25(6):588-590.
53. Cao Y, Xie QF, Li K, Light AR, Fu KY. Experimental occlusal interference induces long-term masticatory muscle hyperalgesia in rats. *Pain*. 2009;144(3):287-293.
54. Bai SS, Mo SY, Xu XX, et al. Characteristics of orofacial operant test for orofacial pain sensitivity caused by occlusal interference in rats. *Beijing Da Xue Xue Bao Yi Xue Ban*. 2020;52(1):51-57.
55. Liu CR, Xu XX, Ye C, Xie QF. Influence of the occlusal interference time on masticatory muscle mechanical hyperalgesia in rats. *J Peking Univ Health Sci*. 2016;48(1):51-56.
56. Li X, Cao Y, Xie Q. Characteristics of experimental occlusal interference-induced masticatory mechanical hyperalgesia of rats. *Chin J Stomatol*. 2014;49(10):596.
57. Takahashi K, Taguchi T, Itoh K, et al. Influence of surface anesthesia on the pressure pain threshold measured with different-sized probes. *Somatosens Mot Res*. 2005;22(4):299-305.
58. Iwata K, Imai T, Tsuboi Y, et al. Alteration of medullary dorsal horn neuronal activity following inferior alveolar nerve transection in rats. *J Neurophysiol*. 2001;86(6):2868-2877.
59. Guo W, Wang H, Watanabe M, et al. Glial-cytokine-neuronal interactions underlying the mechanisms of persistent pain. *J Neurosci*. 2007;27(22):6006-6018.
60. Cao Y, Li K, Fu KY, Xie QF. Experimental occlusal interference induces the expression of protein gene products and substance P in masseter muscles of rats. *Beijing Da Xue Xue Bao Yi Xue Ban*. 2010;42(1):50-55.
61. Huang GJ, LeResche L, Critchlow CW, Martin MD, Drangsholt MT. Risk factors for diagnostic subgroups of painful temporomandibular disorders (TMD). *J Dent Res*. 2002;81(4):284-288.
62. Fischer DJ, Mueller BA, Critchlow CW, LeResche L. The association of temporomandibular disorder pain with history of head and neck injury in adolescents. *J Orofac Pain*. 2006;20(3):191-198.
63. Sessle BJ. The neural basis of temporomandibular joint and masticatory muscle pain. *J Orofac Pain*. 1999;13(4):238-245.
64. Mense S. Nociception from skeletal muscle in relation to clinical muscle pain. *Pain*. 1993;54(3):241-289.
65. Zhu ML, Liu HC, Hao ZQ, Duan LJ. Expression of PN3 and NaN in trigeminal ganglion during occlusal trauma in rat. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2004;39(5):421-424.
66. Dong Y, Liu HC, Wang XM, Liu DQ, Wu SX. The expression of PPTA and c-fos mRNA in dog caudal spinal trigeminal nucleus induced by traumatic occlusion. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2004;39(5):418-420.
67. Cao Y, Li K, Fu KY, et al. Central sensitization and MAPKs are involved in occlusal interference-induced facial pain in rats. *J Pain*. 2013;14(8):793-807.
68. Xu XX, Cao Y, Mo SY, Liu Y, Xie QF. ACC Plasticity Maintains Masseter Hyperalgesia Caused by Occlusal Interference. *J Dent Res*. 2019;98(5):589-596.
69. Mo SY, Bai SS, Xu XX, et al. Astrocytes in the rostral ventromedial medulla contribute to the maintenance of oro-facial hyperalgesia induced by late removal of dental occlusal interference. *J Oral Rehabil*. 2021.
70. Mo S-Y. *The Mechanisms of Rostral Ventromedial Medulla Modulating Different Outcomes of Experimental Occlusal Interference-induced Orofacial Hyperalgesia in rats*. Peking University; 2021. (Published doctoral dissertation).
71. Tang X, Li J, Jiang T, Han SH, Yao DY. Experimental occlusal disharmony - A promoting factor for anxiety in rats under chronic psychological stress. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;75:165-175.


**How to cite this article:** Cao Y. Occlusal disharmony and chronic oro-facial pain: from clinical observation to animal study. *J Oral Rehabil*. 2022;49:116–124. https://doi.org/10.1111/joor.13236