The deconstruction of chronic orofacial pain and a hiding inhibition pathway of orofacial pain: the trigeminal proprioceptive mesencephalic periaqueductal gray pathway

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ABSTRACT

Chronic orofacial pain has a significant negative impact that influences individuals' quality of life and our society. The prevalence is around 11.2% to 33.2% and remains high in females. Currently, there are two main diagnostic classification systems that are used internationally for chronic pain: the International Classification of Diseases, 11th Revision (ICD-11), which was published by the World Health Organization (WHO) in 2018, and the International Classification of Orofacial Pain, which was published by the International Association for the Study of Pain (IASP) in 2020. Deficits in ascending and descending pain modulation pathways may be involved in the chronic pain pathophysiology. A newly described "trigeminal proprioceptive mesencephalic periaqueductal gray pathway" is considered to be the mechanism of action of occlusal appliance in managing orofacial pain. The genetic basis of chronic orofacial pain is not yet fully understood, but a genetic susceptibility involving multiple genes among the peripheral nerves, brainstem and higher brain regions to regulate and suppress the transmission of pain signals, thereby modulating the perception of pain, is likely.

Pain is defined as "*an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*", and this definition was recommended by the Subcommittee on Taxonomy and adopted by the International Association for the Study of Pain (IASP) Council in 1979,[1] but was expanded by following contextual points in 2020:[2]

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- A person's report of an experience as pain should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological wellbeing.
- Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

The common feature of chronic pain is sensitisation of the neural pathways, and this could involve peripheral and/or central sensitisation. Three main mechanisms of chronic pain were described: nociceptive, neuropathic and nociplastic (Table 1).[3] By the IASP definition, nociceptive pain is a response to real or potential tissue-damaging stimuli that activates a neural pathway; neuropathic pain is caused by a lesion or disease of the somatosensory nervous system; and nociplastic pain is a type of pain that develops from the improper processing of pain signals without any obvious signs of tissue injury or distinct somatosensory system dysfunction.[4]

The term "orofacial pain" describes the pain that arises from the oral cavity, face and neck.[5] The term "chronic orofacial pain" refers to a group of painful regional disorders or conditions that have a persistent, unremitting pattern for 3 months or longer. Although there is no clear delineation of when the acute pain becomes chronic, the International Classification of Diseases and the International Classification of Orofacial Pain (ICOP) suggests any pain persisting beyond the expected healing time (more than 3 months and on at least 15 days per month) is pathological.[6,7]

The prevalence of orofacial pain has been

reported between 11.2% and 33.2%.[8–12] Females have a higher prevalence of chronic orofacial pain than males—it is reported to be twice as high in adult females compared to adult males.[8,13] Regarding race and ethnicity, study results are mixed, with some suggesting that white females showed the highest incidence, whereas others suggest there were no racial differences.[14–16] For example, a study of Jewish and Arab–Israeli patients found no differences.[17] Another study showed higher incidence in African Americans than in Asians.[18] Financial factors, cultural differences and a lack of access to care may be some of the reasons for racial disparities. [19] Indigenous peoples, according to studies, display fewer obvious pain behaviours and are reluctant to talk about the causes of their suffering, maybe because pain that weakens a person is seen as a sign of weakness.[20] In New Zealand, the pronounced under-attendance of Pacific and Asian races is evidence of ethnic differences in access to chronic pain care.[21,22] The most frequently reported orofacial pains were temporomandibular disorder (TMD), burning mouth syndrome, persistent idiopathic dentoalveolar pain (atypical odontalgia) and persistent idiopathic facial pain (atypical facial pain).[8,23] The peak age ranges vary from among different types of orofacial pain. For example, the peak age incidence for TMD is from 20 to 40 years of age.[24] Burning mouth syndrome is from around 50 to 70 years of age.[25] Persistent idiopathic dentoalveolar pain is from around 35 to 63.[26]

Classification

There are two main diagnostic classification systems that are currently used internationally for chronic pain. The International Classification of Diseases, 11th Revision (ICD-11), published by the World Health Organization in 2018, includes codes and classifications for a wide range of diseases and conditions across all medical specialities.[27]

The ICD-11 divides chronic primary pain into five subgroups: 1) chronic primary visceral pain, 2) chronic widespread pain, 3) chronic primary musculoskeletal pain, 4) chronic primary headache or orofacial pain, and 5) complex regional pain. Chronic primary orofacial pain and chronic primary TMD pains are coded within chronic primary headache or orofacial pain under this classification. However, chronic migraine, burning mouth syndrome, chronic tension-type headache, chronic cluster headache and hemicrania continua are coded within other categories. The phrase "chronic primary pain" was selected and is intended to be agnostic with regard to aetiology. It also tries to avoid the antiquated distinction between "physical" and "psychological" factors, as well as terminology that is vague or imprecise, (for example, "nonspecific").[28] Apart from chronic primary pain, the ICD-11 also indicates other chronic pain categories, such as chronic cancer-related pain, chronic post-surgical or post-traumatic pain, chronic secondary musculoskeletal pain, chronic secondary visceral pain, chronic neuropathic pain, chronic secondary headache or orofacial pain, other specified chronic pain and chronic pain (unspecified).

The ICOP, 1st edition, was developed by the IASP in 2020.[7] It is a specialised classification system specifically focussed on orofacial pain conditions, which provides a framework for the diagnosis and classification of orofacial pain disorders. It provides detailed descriptions, diagnostic criteria and classification guidelines for various types of orofacial pain disorders. It classified orofacial pain into seven groups: 1) orofacial pain attributed to disorders of dentoalveolar and anatomically related structures, 2) myofascial orofacial pain, 3) temporomandibular joint (TMJ) pain, 4) orofacial pain attributed to lesion or disease of the cranial nerves, 5) orofacial pain resembling presentations of primary headaches, 6) idiopathic orofacial pain, and 7) psychosocial assessment of patients with orofacial pain. However, "chronic pain" was described within some of the subtypes.

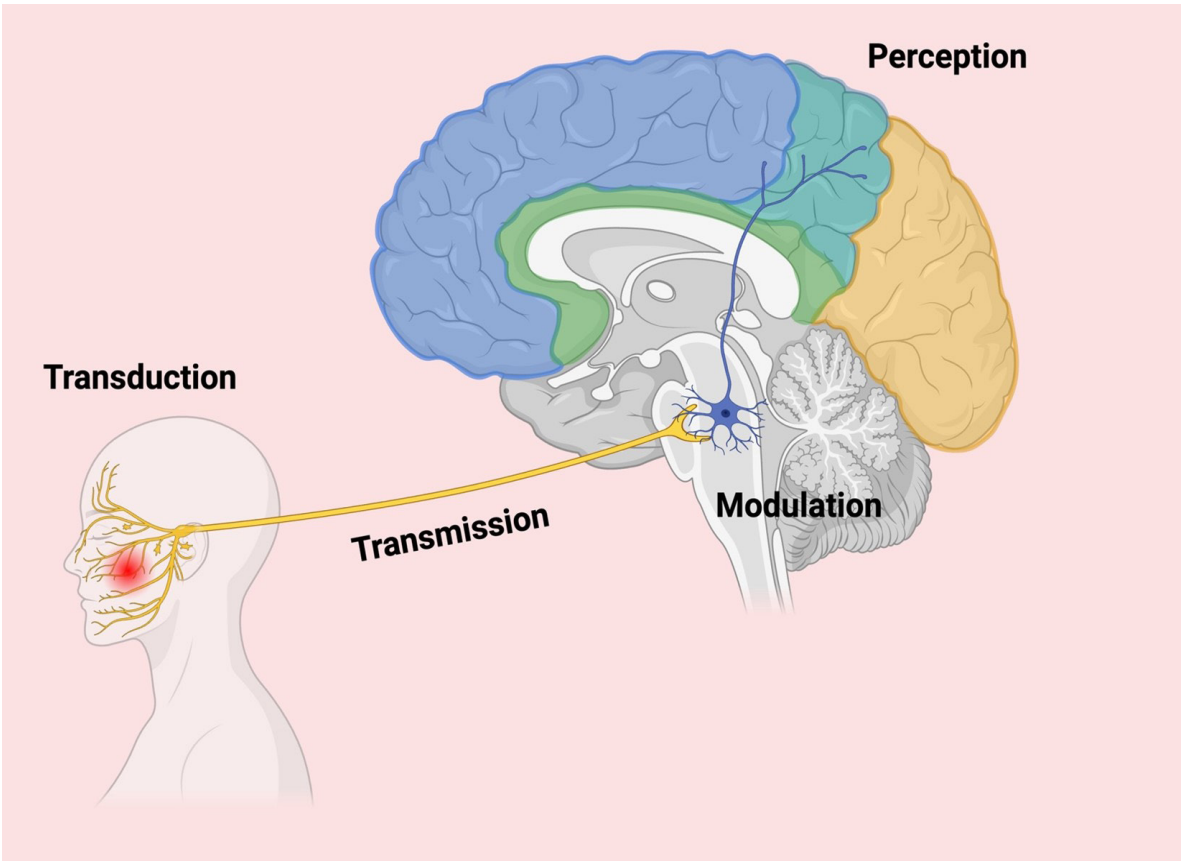
Orofacial pain pathway

In general, there are four major pain processes, which include transduction, transmission, modulation and perception (Figure 1).[29] The orofacial pain pathways might include primary afferent neurons, trigeminal ganglion, brainstem nociceptive neurons and higher brain function that controls orofacial nociception.[30] The trigeminal nerve is a sensory nerve that innervates the orofacial region. Although C, A-delta and A-beta fibres are the most common names for sensory nerve fibres (neurones), there are others, and to varying degrees they can respond to chemical, thermal and mechanical energy.[31] In general, there are three major classes of nociceptors: Aδ mechanosensitive nociceptors, Aδ mechanothermal nociceptors and polymodal nociceptors (C-fibres). The peripheral nociceptors are activated by the chemical factors from damaged tissue, such reactive oxygen species, protons, kinins, prostanoids, adenosine triphosphate, serotonin, histamine, and neurogenic

Table 1: Three main mechanisms of chronic pain.

	Nociceptive pain	Neuropathic pain	Nociplastic pain
Causes	Actual or potential tissue damage	Diseases or damage of the nervous system	Dysregulation of nociceptive process. No evidence of tissue or nerve damage
Examples	Toothache, infection, mucosal ulcers and trauma	Trigeminal neuralgia, post-herpetic neuralgia and diabetic neuropathy	Fibromyalgia, irritable bowel syndrome, chronic lower back pain and temporomandibular disorder
Signs and symptoms	Well-localised pain, with infrequent or no sensory deficits	Electrical-like, lancinating pain and follow dermatomal distribution. Sensory deficits (numbness and tingling) are common. Neurological weakness may present if motor nerve is affected	Diffused, widespread aching and not confined to an anatomical structure. Often associates with psychological stress
Medical management	NSAIDs, paracetamol, opioids and peripheral management	Tricyclic antidepressants, carbamazepine, gabapentinoids, SNRI and lidocaine	Tricyclic antidepressants, gabapentinoids and SNRI

Figure 1: The pathway of pain perception (created with BioRender.com).



substances, and inflammation mediators from the immunocytes, such as cytokines (IL-1beta, IL-6, IL-8, tumour necrosis factors), neurotrophins and neuropeptides, after receiving repetitive noxious stimuli from infection and inflammation.[32] This process is called **transduction**—when the chemical, thermal and/or mechanical energy is changed into electrical signals.[29] The key element in the **transmission** of nociceptive signals is the action potential.[33] The first order neuron transmits the pain signals to the trigeminal ganglia (similar to dorsal root ganglia). The pain signals then transmit to the second order neurons in the trigeminal nucleus (main sensory nucleus and spinal trigeminal nucleus) at the brainstem. The second order neurons decussate at the brainstem. The ventral post-eromedial nucleus of the contralateral thalamus is where the second order neurones' axons end (trigeminothalamic tract). The third order neuron in the thalamus then connects to the sensory cortex. Pain perception occurs at this level and could be influenced by transmission, modulation and cognitive evaluation.[34] **Modulation** is the process by which the normally functioning nervous system adjusts to changes in and around the body.[35]

Pain perception, regulation and inhibition

Based on the previous study (positron emission tomography and functional magnetic resonance imaging), six areas of the brain have been identified, and are thought to contribute to the acute pain process.[36] They are the primary somatosensory cortex, secondary somatosensory cortex, anterior cingulated cortex (ACC), insula, prefrontal cortices (PFC) and thalamus (see Table 2 and Figure 2). However, chronic pain is a complex sensory and emotional experience that includes biological, psychological and social factors. In our brain, emotions are thought to be regulated by the frontal cortex, amygdala, ACC, insula and several interconnected structures.[37] Chronic pain often engages these brain areas for cognitive and emotional processes, suggesting that this component of pain may have a distinguishing characteristic between chronic and acute pain.[38] For example, research showed that insula and PFC connectivity was increased in chronic pain studies.[39,40] Since the insula and PFC are both engaged in emotion, motivation and pain modulation, this suggests that the processing of pain may have an impact on the pain perception.[41] Changes in these centres are thought to be associated with the chronification of pain.[42] A recent study also suggested that an activated cingulate cortex (emotional and cognitive processing) insula pathway could induce and maintain nociceptive hypersensitivity in the absence of peripheral noxious stimuli. This pathway may facilitate the transition from acute to chronic pain.[43] An imaging study has demonstrated that amplification of the thalamic, insular and secondary somatosensory cortex responses has been linked to abnormal pain that is elicited by allodynia. In addition, several pathways such as ACC–amygdala, ACC–thalamus–amygdala and ACC–periaqueductal gray–rostromedial ventral medulla–spinal dorsal horn that are associated with ACC might be activated in chronic pain conditions.[44–46] These suggest that ACC plays an important role in the initiation, development and maintenance of chronic pain. In the orofacial region, several studies have found increased PFC, ACC and insula activities in chronic pain conditions.[47–50]

Table 2: Pain areas of activity in the brain.

Brain region	Activity
Primary somatosensory cortex	Sensory discrimination—determines where pain message is coming from[34,51]
Secondary somatosensory cortex	Pain intensity-related activation [52,53]
Anterior cingulated cortex (ACC)	Integration of sensory, executive, attentional, emotional and motivational components of pain and pain intensity[54,55]
Insula	Pain perception, modulation and contribution of chronification[56,57]
Prefrontal cortex (PFC)	Pain processing, modulation, induction of pain chronification[58–60]
Thalamus	Receiving, processing and transmitting to various parts of the cortex [61,62]

Figure 2: Ascending pain pathway (created with BioRender.com).

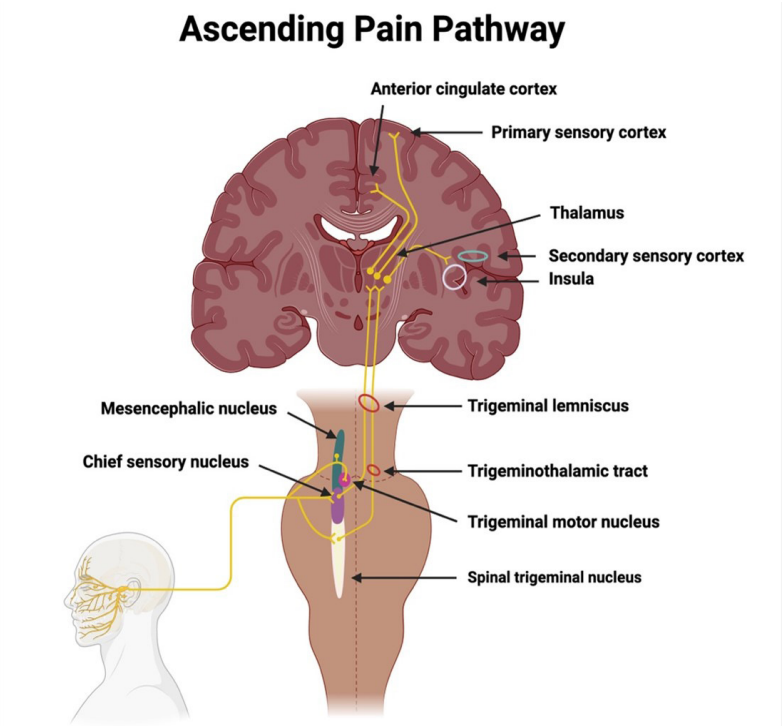


Figure 3: Descending pain pathway (created with BioRender.com).

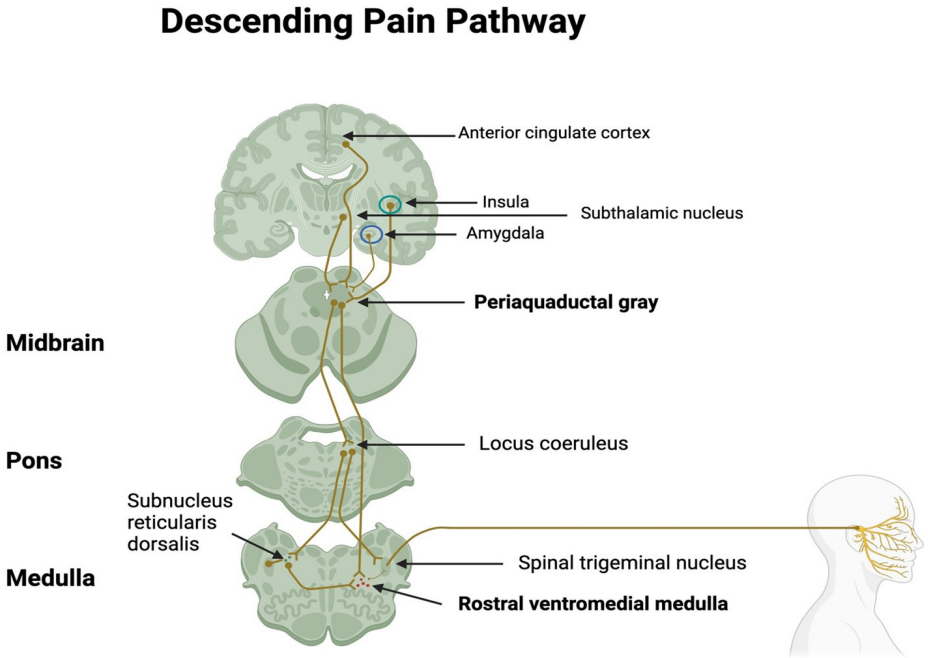
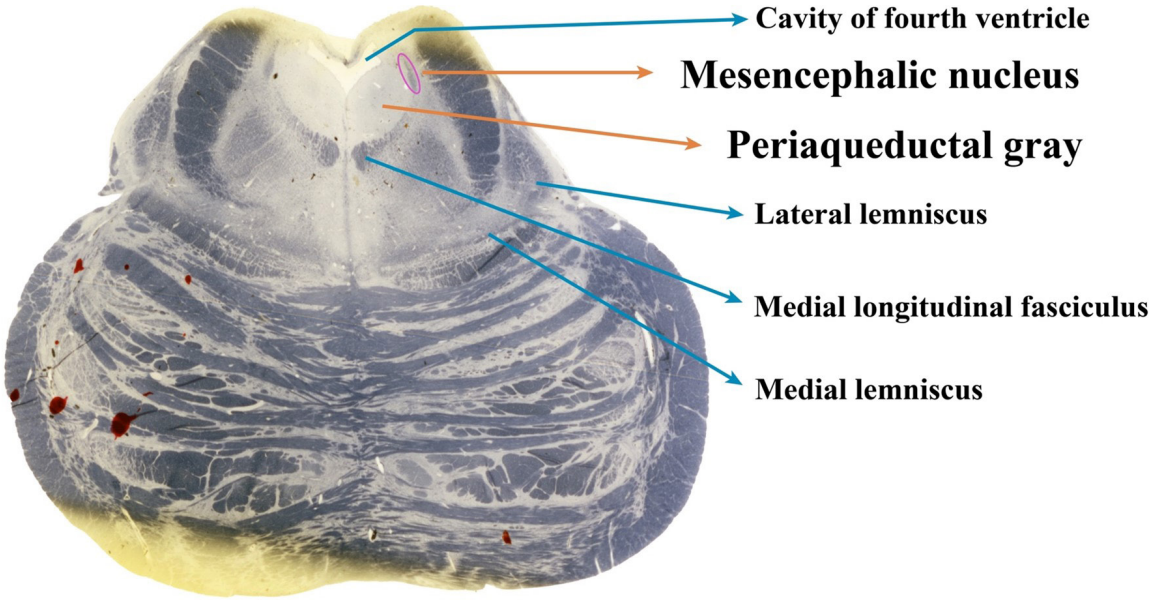


Figure 4: The closed association between mesencephalic nucleus and periaqueductal gray at the level of upper pons (from W D Trotter Anatomy Museum, University of Otago).



The pain inhibition pathway refers to the complex network of structures and processes in the body that modulate or suppress the transmission of pain signals (Figure 3). In general, there are four main components that involved pain inhibition, such as the "gate control theory" at the peripheral nervous system,[63] the presence of inhibitory interneurons at the spinal cord,[64] the pain descending pathway (periaqueductal gray and rostroventromedial medulla)[65] and pain modulation centres in the brainstem and brain such as the thalamus, amygdala and PFC.[58,66] In addition, several brainstem regions, such as periaqueductal gray matter, rostral ventromedial medulla, locus coeruleus and subnucleus reticularis dorsalis, are considered as key structures that modulate pain.[67–69] It is thought that the inhibitory and facilitatory systems of descending pain work together to maintain a baseline condition of sensory processing.[70] Several studies have shown that dysfunction of the periaqueductal gray–rostroventromedial medulla–dorsal horn/spinal trigeminal nerve pathways may lead to a pronociceptive state, eventually facilitating neurotransmission and promoting pain.[71,72] In addition, the pain inhibition pathway is associated with the emotional centres such as amygdala, insula and PFC in the brain.[73] Studies using functional MRIs have shown an increased activity in the emotion regions of the brain such as PFC, insula and cingulate, but decreased activity in the descending inhibition pathway at the brainstem in chronic pain patients.[74–77]

Dysfunction of inhibition pathway could comprise both an aberrant pain response to a non-noxious stimulus at the injury site or surrounding areas and a heightened pain response to a noxious stimulus at the injury site or surrounding regions, referred to as primary and secondary allodynia. These have been demonstrated in several chronic pain conditions such as fibromyalgia, irritable bowel syndrome, chronic lower back pain and TMD.[78–82] Moreover, the inhibition pathway might be involved with the "placebo-related" changes seen in pain management.[83] This may also relate to meditation and positivity, which have a positive effect on pain improvement, whereas catastrophising has a negative effect.[84] The epidemiological studies provided evidence of sex differences in

pain perception. An animal study suggested this could be due to the greater activation of periaqueductal gray–rostroventromedial medulla pathway in males than females.[85] However, human studies investigating sex differences in pain inhibition pathways have shown mixed results. It depends on both the experimental methodology and the modes of measurement of the effect.[86] Furthermore, chronic pain often coexists with sleep disorders, which worsen the pain. Pain perception is often affected by many forms of sleep disturbance, but it is unclear if these effects are the same for males and females.[87] Dysfunction of inhibition pathway, therefore, may lead to the development of chronic pain, thereby accompanied by cognitive deficits and aversive emotional states.

The hiding inhibition pathway of orofacial pain: the trigeminal proprioceptive mesencephalic periaqueductal gray pathway

The trigeminal nerve, also known as cranial nerve V or CN V, includes sensory and motor functions. Three branches of the nerve—the combined sensory and motor mandibular nerve (V3), the sensory maxillary nerve (V2) and the sensory ophthalmic nerve (V1)—supply the face. The sensory, also known as afferent neurones transmit of general somatic information from the face, such as pain, temperature, vibration, fine and crude touch and proprioception to the brainstem in contrast to the motor or efferent neurones, project information from the brainstem to the tensor veli palatini, tensor tympani, anterior belly of the digastric, mylohyoid and muscles of mastication, such as masseter, temporalis, lateral and medial pterygoids.[88] The trigeminal nerve is associated with three sensory nuclei (mesencephalic nucleus, the chief/principal sensory nucleus and spinal trigeminal nucleus) and one motor nucleus (trigeminal motor nucleus). The sensory fibres from V1, V2 and V3 travel via axons from pseudounipolar neurones to their cell bodies in the trigeminal ganglion. The afferent neurons then decussate at the brainstem to join the trigeminal lemniscus. The secondary neuron joins the tertiary neuron at the thalamus.

However, most of the proprioceptive afferents for the orofacial region in the trigeminal nerve are slightly different, as they have their cell bodies located in the mesencephalic trigeminal nucleus. The mesencephalic nucleus is involved with proprioception of the teeth, palate, TM, and muscles of mastication; that is, detecting of the position and controlling force and pressure of the muscles and joints.[89] The mesencephalic nucleus is situated on the anterolateral aspect of the periaqueductal gray and ascends to the height of the inferior colliculus[88] (Figure 4). Studies suggested that periaqueductal gray received input/nerve fibres from mesencephalic nucleus.[90, 91]

The occlusal appliance therapy as one of pain management modalities has been used in a number of orofacial pain conditions, such as TMD and tension-type headache.[92,93] However, the mechanism of action of occlusal appliance used for the successful treatment of orofacial pain remains unclear and controversial. There are a few concepts, which explain how occlusal appliance could help, including prevention in maximal intercuspal position,[94] even distribution of forces,[95] stabilisation of periodontal ligament proprioception,[96] relief of jaw muscle tension,[97] guidance for muscle relaxation,[98] reposition of the jaw[99] and impact on vertical dimension of occlusion.[100] Most of the mechanism appears to be associated with the activating/changing of the trigeminal mesencephalic response. As the mesencephalic nucleus is highly associated with the pain inhibition centre (periaqueductal gray), we propose that occlusal appliance improves orofacial pain by activating/facilitating the periaqueductal gray via the mesencephalic nucleus, known as **the trigeminal proprioceptive mesencephalic periaqueductal gray pathway** (TPMP). This is a significant discovery as it could direct the future management of orofacial pain. Thus, physical therapy, including occlusal appliance (activation of periaquedual gray) may be as effective as medication and surgery in managing orofacial pain, and it should be used as first line as it has fewer side effects.[101] The activation of TPMP can be confirmed by functional MRI. This may include the investigation of the activity patterns in the TPMP between normal subjects and orofacial pain patients, the association between the ascending pain pathway and TPMP and the possible link between TPMP with the higher pain process centre.

Chronic pain and genetics

Chronic overlapping pain conditions (COPCs) are a group of chronic pains that may include TMD, fibromyalgia, irritable bowel syndrome, vulvodynia, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, chronic

tension-type headache, migraine headache and chronic lower back pain.[102] There is now a considerably wider range of research that could be applied to orofacial pain thanks to the relationship between these prevalent chronic pain syndromes, as shown by the COPC. A genetically pain-susceptible person who may also have susceptibility to a high state of psychological distress may convert to a chronic pain sufferer through an exogenous trigger;[103] this has also been suggested with regard to chronic orofacial pain, such as chronic TMD.[104] This might lead to sensitisation "down-up" from periphery to central pathway.[105] Ongoing pain might then further lead to a "top-down" sensitisation, which would further wind up the pain level.[106] Understanding these mechanisms allows us to better understand the current strategies that have worked.

Research on the topic of genetic variants associated with chronic pain is still in its initial phase. The genetic basis of chronic pain is not yet fully understood. It is also known that genetic variation and changes could make a person more susceptible to becoming a chronic pain sufferer.[103] However, several genes have been identified as potential contributors to the development and modulation of chronic pain. For example, increased expression of SCN9A may affect the perception and intensity in acute pain, and the susceptibility to chronic pain.[107,108] The COMT gene encodes a protein that breaks down norepinephrine, epinephrine and dopamine. Low COMT activity may increase the risk of some of chronic conditions, such as fibromyalgia or chronic widespread pain.[109] OPRM1, a mu opioid receptor gene, together with COMT, has been linked to the initiation of chronic pain.[110] GCh1 is a pain-protective gene (responsible for the production of the neurotransmitters such as serotonin, dopamine and norepinephrine), and it could decrease the level of pain, perhaps by influence on the COMT enzyme activity.[111] TRPV1 (gene for transient receptor potential cation channel) participates in chronic pain through transcriptional and translational regulation, and also the development of nociceptive and depressive behaviours.[112] SLC6A4, ADRB2 and HTR2A may be associated with chronic widespread pain.[103] These genes only make up a small portion of the genetic components that may be involved in the aetiology of chronic pain, which is a complicated and multifaceted disorder.

Conclusion

It is important to understand the neurophysiology of chronic pain in order to diagnose and manage chronic orofacial pain. Modification (nociplasticity) of pain information may take place in several ascending or descending pathways. TPMP may be considered as the mechanism of action of occlusal appliance in managing orofacial pain related to TMD. Factors such as sleep, psychological disease (e.g., anxiety/depression), hormonal and other factors not yet identified might be under the influence of genetics. The interplay between genes is still an active area of research in understanding chronic pain.

COMPETING INTERESTS
The authors have no conflict of interest to declare.

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URL
www.nzmj.org.nz/journal/vol-137-no-1588/the-deconstruction-of-chronic-orofacial-pain-and-a-hiding-inhibition-pathway-of-orofacial-pain-the-trigeminal-proprioceptive-mes

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