Tara Renton

Obi Egbuniwe

# Pain Part 2a: Trigeminal Anatomy Related to Pain

**Abstract:** In order to understand the underlying principles of orofacial pain it is important to understand the corresponding anatomy and mechanisms. Paper 1 of this series explains the central nervous and peripheral nervous systems relating to pain.

The trigeminal nerve is the 'great protector' of the most important region of our body. It is the largest sensory nerve of the body and over half of the sensory cortex is responsive to any stimulation within this system. This nerve is the main sensory system of the branchial arches and underpins the protection of the brain, sight, smell, airway, hearing and taste, underpinning our very existence. The brain reaction to pain within the trigeminal system has a significant and larger reaction to the threat of, and actual, pain compared with other sensory nerves. We are physiologically wired to run when threatened with pain in the trigeminal region and it is a 'miracle' that patients volunteer to sit in a dental chair and undergo dental treatment.

**Clinical Relevance:** This paper aims to provide the dental and medical teams with a review of the trigeminal anatomy of pain and the principles of pain assessment.

**Dent Update 2015; 42: 238–244**

## The trigeminal system

The trigeminal nerve supplies general sensory supply to the face, scalp and mouth (Figure 1). A vast proportion of the sensory cortex represents the trigeminal input (over 50%).[1]

The trigeminal nerve, or 5th cranial nerve, was first described by Galen (200 AD) as being two separate pairs of cranial nerves, owing to its large peripheral branches. It was not until the Italian anatomist and physician Fallopius (1523–1562) discovered that these branches merged as one, that the 5th cranial nerve was created. In 1732, the Danish anatomist Jacques-Bénigne Winslow (1669–1760) ascribed the name 'nerf trijumeau', referring to the three peripheral branches of this nerve, and the name 'trigeminal nerve' was born meaning 'three twins'. The trigeminal nerve is the largest of the cranial nerves and the largest sensory nerve. It is a mixed sensory nerve made up of both sensory and motor axons, and it plays a particularly important role in sensations of the face and head regions.

The unique nature of the trigeminal nerve is related to several factors:

- The head facial area is made up of a variety of unique tissues such as the meninges, cornea, nasal sinuses, oral mucosa and tooth pulp, that require specialized sensory innervations.[2]
- There is constant neural activity input related to orofacial function.
- 50% of the sensory cerebral cortex area is dedicated to the processing of orofacial sensation (Figure 1), and therefore the impact of trigeminal nerve injury may be significantly larger than in other areas of the body.[2]
- Damage to this sensory nerve can result in numbness (anaesthesia), tingling altered sensation (paraesthesia), pain or a combination of the three in 50–70% of cases.[3]
- Pain is common in sensory nerve injuries and, due to the orofacial region being affected, results in significant functional problems including: eating, speaking, kissing, drinking, applying make-up and shaving, in fact just about every social function that we take for granted.[4]
- The resultant psychological disability of chronic altered sensation or pain includes changes in self-perception, reduced quality of life, social disabilities and handicap. Many patients often find it hard to cope with pain in the trigeminal system.[5]

**Tara Renton,** BDS, MDSc, PhD, FARCDS(OMS), FDS, RCS, FHEA, Professor, Department of Oral Surgery and **Obi Egbuniwe,** BDS, MSc, PhD, AFHEA, Honorary Clinical Researcher, Department of Oral Surgery, King's College London Dental Institute, King's College Hospital London, Bessemer Road, London SE5 9RS, UK.

## The trigeminal nerve or 5th cranial nerve

The trigeminal or 5th cranial nerve is divided into three divisions (Figure 2):

- The ophthalmic division (V1);
- The maxillary division (V2); and
- The mandibular division (V3).

There are three sensory and one motor nuclei. The sensory nuclei (Figure 3) are arranged in a column which spans from the midbrain through the pons and medulla and into the upper cervical cord. The axons of these nuclei cross to the opposite side, ascending in the spinothalamic tract, to relay in the thalamic nuclei; from there, they end in the cerebral cortex. The sensory nucleus of CN V is connected to other motor nuclei of the pons and medulla. In addition, the descending sensory spinal tract receives somatic sensory fibres from other cranial nerves VII, IX and X.

1. Mesencephalic nucleus: proprioceptive fibres for muscles of the face, orbit, mastication, tongue. The proprioceptive fibres of V arise from the muscles of mastication and the extra-ocular muscles. They terminate in the mesencephalic nucleus. This nucleus has connections to the motor nucleus of V.
2. The main sensory nucleus: located in the upper pons, lateral to the motor nucleus, is responsible for touch sensation for all three trigeminal divisions. The main sensory nucleus receives its afferents (as the sensory root) from the semilunar ganglion through the lateral part of the pons ventral surface. Its axons cross to the other side, ascending to the thalamic nuclei to relay in the postcentral cerebral cortex. The descending sensory fibres from the semilunar ganglion course through the pons and medulla in the spinal tract of V to end in the nuclei of this tract (as far as the second cervical segment).

The sensory nucleus, located in the pons, is quite extensive. It receives ordinary sensations from the main three branches of the trigeminal. The ophthalmic division is in the lower part of the nucleus, and the mandibular branch is in the upper part.

The large rostral head is the main sensory nucleus. The caudal tapered part is the spinal tract, which is continuous with substantia gelatinosa of Rolando in the spinal cord. The spinal tract is the sensory nucleus, primarily for pain and temperature. The main sensory nucleus serves mostly for discrimination sense.

3. The spinal nucleus in the lower pons to the upper cervical cord is responsible for pain and temperature; additionally it receives afferent fibres from both the glossopharyngeal nerve and vagus nerve.
4. The motor nucleus is located in the upper pons and innervates the muscles of mastication, as well as mylohyoid and tensor palati. The motor nucleus is ventromedial to the sensory nucleus. It lies near the lateral angle of the fourth ventricle in the rostral part of the pons. The mesencephalic nucleus is in the midbrain and receives proprioceptive fibres from all muscles of mastication.

The motor nucleus of V receives cortical fibres for voluntary control of the four muscles of mastication (masseter, temporalis, medial pterygoid, lateral pterygoid and the other four muscles are the tensor veli palatini, the mylohyoid, the anterior belly of the digastrics and the tensor tympani). These fibres are mostly crossed. It also receives input from the mesencephalic and sensory nuclei. The axons emerge anteriorly to the sensory root from the lateral surface of the pons. This motor root joins the semilunar ganglion together with the sensory root.

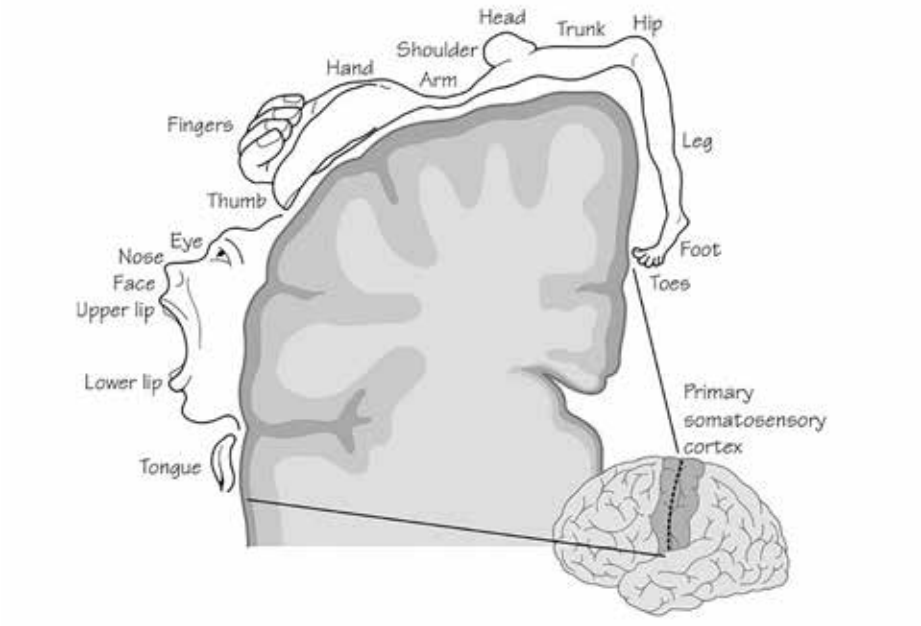


**Figure 1.** The sensory 'Homunculus' illustrating the large area of the somatosensory cortex that represents trigeminal nerve input.

#### Extracranial component

The trigeminal nerve exits at the mid pons into the prepontine cistern and passes anteriorly to the Meckel cave where its fibres relay forming Gasserian ganglion.

The semilunar (Gasserian or trigeminal) ganglion is the great sensory ganglion of CN V. It contains the sensory cell bodies of the three branches of the trigeminal nerve (the ophthalmic, mandibular and maxillary divisions). The ophthalmic and maxillary nerves are purely sensory. The mandibular nerve has sensory and motor functions.

The Gasserian ganglion lies in a depression on the petrous apex, within a dural fold called the Meckel cave. The sensory roots of the three branches of CN V are received anteriorly. They then pass from the posterior aspect of the ganglion to the pons. The motor root passes under the ganglion to join the sensory division of the mandibular nerve and exits the skull through foramen ovale. The carotid plexus contributes sympathetic fibres to the Gasserian ganglion.

The extracranial part V then divides into three main branches (Figure 2):

1. Ophthalmic division (V1)(Figure 4a): While passing at the lateral wall of the cavernous sinus inferior to the trochlear nerve, then through the superior orbital fissure, the ophthalmic nerve divides into the frontal, lacrimal and nasociliary nerves. The frontal nerve divides into the supraorbital and supratrochlear nerves. Nasociliary nerve branches include a communicating branch to the ciliary ganglion, short and long ciliary nerves, the posterior and anterior ethmoidal nerves (the latter divides into internal and external nasal branches) and the infratrochlear nerve (Figure 4a, b).
2. Maxillary division (V2): This passes in the lateral wall of the cavernous sinus then through the foramen rotundum to exit the skull. Then it crosses the pterygopalatine fossa and enters the orbit through the inferior orbital fissure and the infraorbital canal. It emerges through the infraorbital foramen to become the infraorbital nerve. Hence the orbital blow out fracture is associated with a loss of sensation over the maxilla (Figure 4a, b).
3. Mandibular division (V3): This passes through the foramen ovale and gives motor supply to the muscles of mastication and sensory supply to the auriculotemporal region, lower face, mouth and dentition.

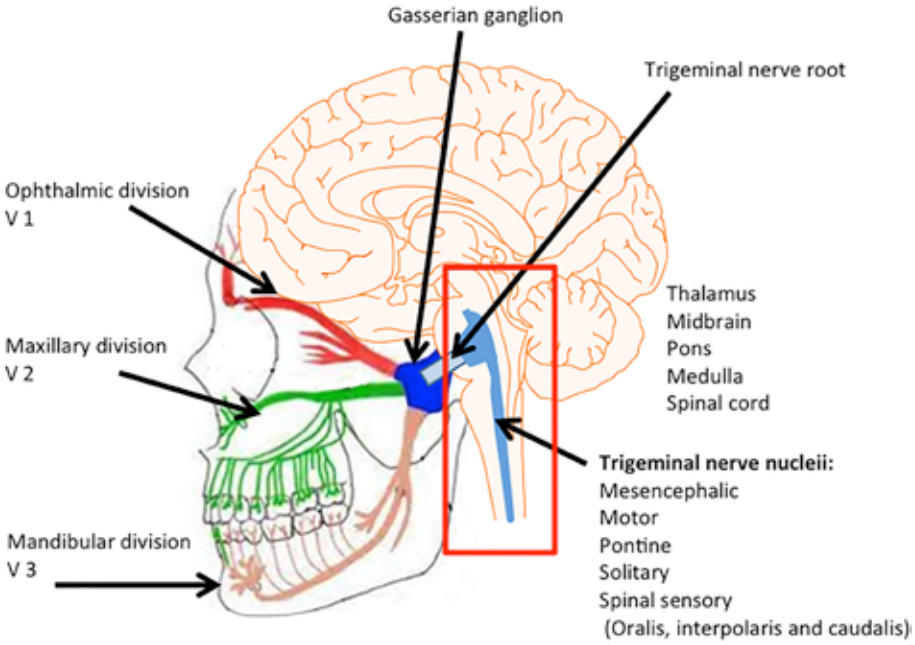


**Figure 2.** Central neural pathways relevant to the trigeminal system.

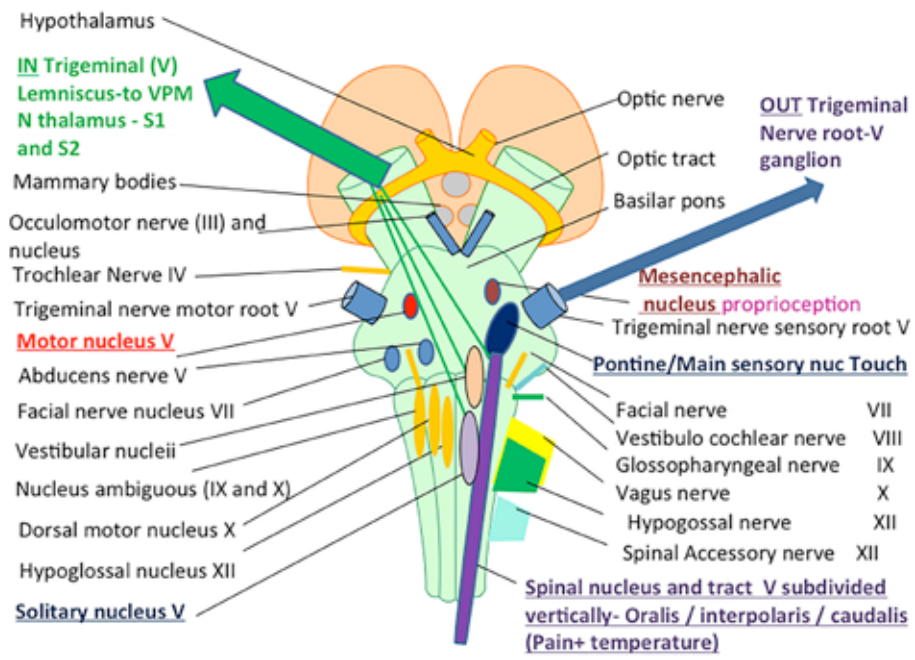


**Figure 3.** Central neural pathways relevant to the trigeminal system: midbrain V nucleii functions and their related other cranial nerve nucleii. VPM - ventral posteromedial nucleus in the thalamus which conveys fibres to the post central gyrus in the sensory cortex.

## Pain transmission

Pain signals originating in the orofacial region are carried through the trigeminal (Gasserian) ganglion on to the trigeminal spinal tract where they then synapse within the subnucleus caudalis (Figure 3).[6] The subnucleus caudalis (SC), which exhibits functional and morphologic similarities to the spinal cord dorsal horn, relays the signals to the thalamus where they synapse again and move on to higher cortical centres.[6] Nociceptive neurons of the subnucleus caudalis converge from the tooth pulp, temporomandiblular joints and muscles of mastication, oral cavity and facial skin. This access of multiple afferent inputs onto a neuron is known as *convergence*. Convergence is believed to be one of the reasons responsible for the extensive degree of pain referral seen within the orofacial region. While trigeminal system pain has not been studied nearly as extensively as spinal cord mediated pain, it is believed that the mechanisms of pain modulation and conduction pathways are very similar.[7,8]

The central axons of the trigeminal nerve terminate in the trigeminal brainstem complex, which ranges from the midbrain to the medulla where it merges seamlessly with the upper cervical spinal cord. The trigeminal brainstem complex is in fact made up of several separate nuclei, including the principal, spinal, paratrigeminal, mesencephalic and supratrigeminal

nucleus (Figure 2).[6-8]

The mesencephalic nucleus is mainly involved in proprioception of the face, and is unique in that it represents the only structure in the CNS to contain cell bodies of primary afferents. All other primary afferent cell bodies are contained in ganglia outside the blood brain barrier. As the paratrigeminal, mesencephalic and supratrigeminal nuclei are mostly involved in integration of motor and sensory signals, proprioception and motor reflexes; they will not be discussed further.[6-8]

The principal and spinal nuclei of the trigeminal brainstem complex are oriented rostro-caudally to one another, and receive most of the sensory inputs from the trigeminal nerve. As the central axons of the trigeminal nerve enter the brainstem from the ganglia through the sensory root lateral to the pons, they divide and send short ascending axons up to the principal nucleus and long descending axons down to the spinal nucleus. Axons ending in the principal nucleus carry tactile or light pressure information, while axons that descend to the spinal nucleus carry temperature and pain information.[8]

The subnucleus caudalis represents the major nociceptive input for the facial area. A Swedish physician Carl Sjöqvist, in 1938, showed that surgically lesioning the trigeminal tract at the level of the medulla (correlating with the subnucleus caudalis) relieved the symptoms of patients suffering from chronic pain in the facial area while leaving other sensory functions intact. The subnucleus caudalis is directly adjacent to the cervical spinal cord, and its organization is comparable to the spinal dorsal horn. Projection neurons from the trigeminal brainstem subnucleus caudalis project to the thalamus and parabrachial nucleus via the posterolateral or anterolateral pathways, similar to the dorsal horn. They also project to the periaqueductal grey, dorsal reticular nucleus, the amygdaloid complex, the septal nuclei, and the hypothalamus.[9,10]

The peripheral axons of the trigeminal nerve are divided into three distinct branches that innervate non-overlapping dermatomes of the head and face (Figure 4a). The ophthalmic nerve innervates the head, upper eyelid and cornea, the maxillary nerve innervates the lower eyelid, nose, upper lip and upper teeth, and gingiva, and the mandibular branch innervates the temporal mandibular joint, lower lip, gingiva and tongue. Only the mandibular branch carries motor neurons that originate from the separate trigeminal motor ganglia, and mediate mastication and the jaw-opening reflex.

The three branches of the trigeminal nerve converge in the trigeminal ganglion (also named Gasserian or semilunar), where the cell bodies of the sensory axons are found. The trigeminal ganglion is located in the middle cranial fossa (Meckel's Cave) at the base of the skull, and the cell bodies are organized somatotopically, a feature unique to the trigeminal ganglion. Remember the skin over the lower parotid region is supplied with general sensory supply by C2 and C3 cervical sensory nerves (Figure 4a).

## Neuropathic mechanism of chronic pain

Recent research has significantly broadened our knowledge into neuroplastic changes that are involved in chronic pain.[9,10] Future research will focus on the question of whether novel neuroimaging techniques can be used in the individual chronic pain patient as a biomarker that would allow for an objective diagnosis of different pain conditions and for the prediction of individual responses to specific therapies.[1]

Both peripheral and central sensitization may result in increased nociceptive input to the brain and also changes the processing of nociceptive information within the brain. In addition, chronic nociceptive input from the periphery or from lesions within the central nervous system may result in cortical reorganization and maladaptive neuroplasticity within somatosensory and motor systems. There is also increasing evidence for pain-induced changes in large-scale neuronal network connectivity and, in patients with chronic pain, resultant structural brain changes result.[11-13]

Thus overall the emerging evidence is that, in chronic pain, the endogenous pain-modulatory system may function aberrantly, presenting a distinct disease of the peripheral and central nervous systems.

## Peripheral mechanisms

Over the last five years there has been significant progress in understanding the mechanisms involved in trigeminal acute and neuropathic pain. The complexity of the peripheral nervous system and related adaptable systems capable of mediating many of the abnormal pain sensations are becoming recognized mechanisms and are common between spinal and trigeminal neuropathic pain. The unique anatomical and physiological characteristics of the trigeminal nervous system leads to some specific maladaptations that are particular to trigeminal neuropathic pain.

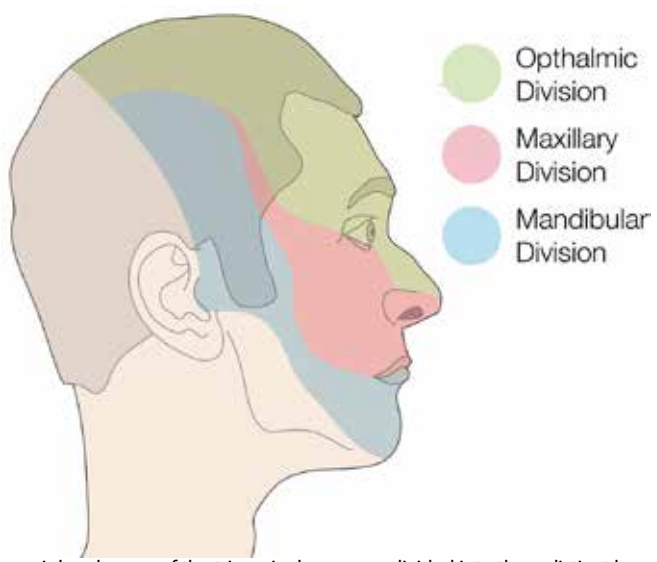


**Figure 4. (a)** The peripheral axons of the trigeminal nerve are divided into three distinct branches that innervate non-overlapping dermatomes of the head and face. (Courtesy of Andrew Mason, University of Dundee.)

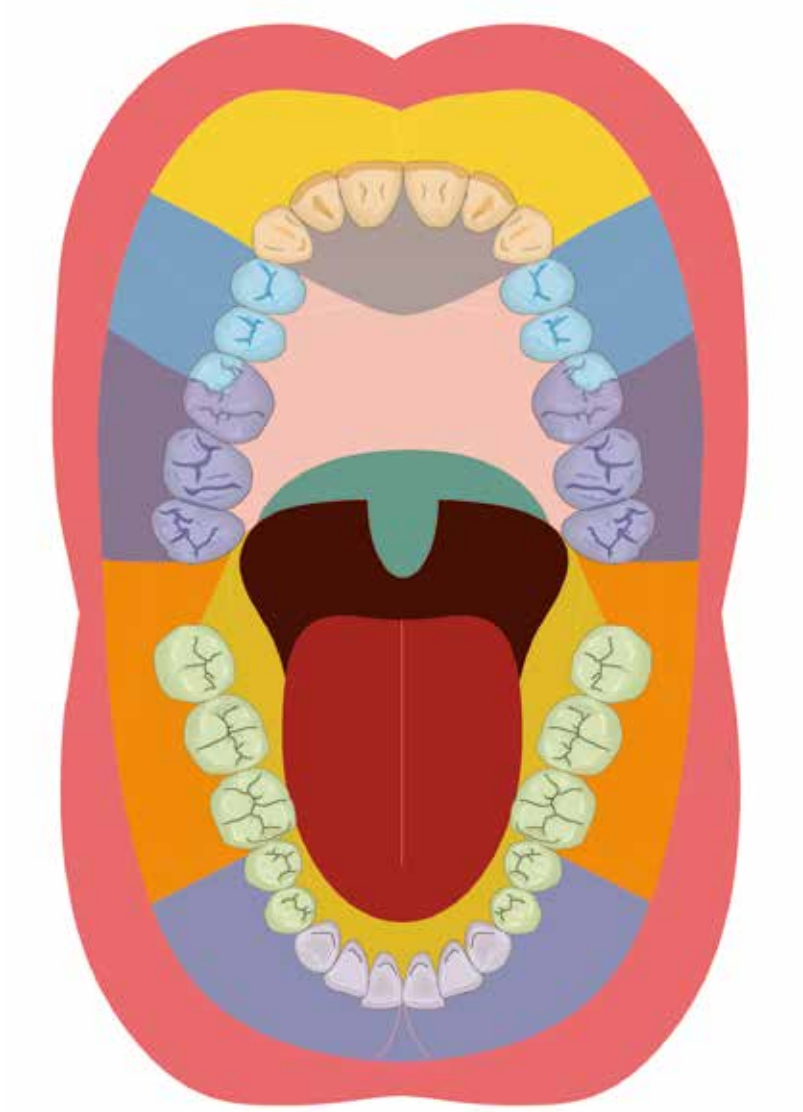

**Figure 4. (b)** Intra-oral dermatomes with key (see below). (Courtesy of Andrew Mason, University of Dundee.)

**Maxillary division all branches of V2**

- Anterior superior alveolar nerve(s)
- Lesser palatine nerve
- Greater palatine nerve(s)
- Middle superior alveolar nerve(s)
- Posterior superior alveolar nerve(s)

**Mandibulary division all branches of V3**

- Inferior alveolar nerve
- Mental nerve (branch of inferior alveolar include supply to lower lips)
- Lingual nerve
- Glossopharyngeal nerve (IX) Also supplies post third of tongue
- Long Buccal nerve(s)

## Autonomic sensitivity

The role of the autonomic nervous system in neuropathic pain is becoming more evident. Silas Weir-Mitchell is credited for making the first observations of abnormal sympathetic activity in patients with a traumatic nerve injury. The adjunctive autonomic signs include excessive sweating, oedema, erythema and abnormal hair and nail growth. In many patients, inhibiting sympathetic activity, through sympathectomy or sympathetic blocks, largely relieve the painful symptoms. Injection of norepinephrine into patients treated with a sympathetic block reignited the painful sensations, confirming the sympathetic role. Administration of guanethedine, a pharmacological intervention that depletes norepinephrine from sympathetic terminals, was shown to relieve the painful symptoms in an animal model of rheumatoid arthritis.[14-16]

Within the orofacial region, sensory and sympathetic fibre innervation is relatively segregated. Most of the sympathetic fibres that innervate the facial area originate from the superior cervical ganglia (SCG), as demonstrated by the fact that bilateral ablation of the SCG results in complete loss of sympathetic fibres in the lower lip skin. Recently, reports of significant sympathetic sprouting into the upper dermis of the skin, an area where they are normally absent, following nerve injury, also correlated well with the pain behaviour of the animal.[17] This may be a fundamental mechanism driving many chronic orofacial pain conditions.

Similar to sympathetic fibres, parasympathetic fibres have been shown to sprout into the upper dermis following nerve lesion, where they are found in close relationship. While the parasympathetic fibres do not release norepinephrine like their sympathetic counterparts, they do release acetylcholine (Ach), ATP, enkephalin, VIP and NPY, which could potentially activate surrounding macrophages, mast cells and keratinocytes, as well as directly activating primary afferents, which express nicotinic, muscarinic and purinergic receptors.[17] Parasympathetic fibres have also been shown to express the SP receptor, NK1, providing evidence for a bidirectional communication pattern by which sensory afferents may affect parasympathetic activity. Overall, the presence of parasympathetic fibres innervating blood vessels of the trigeminal system and their apparent apposition to sensory fibres under neuropathic conditions

suggest parasympathetic activity in the facial skin may represent a unique mechanism involved in trigeminal neuropathic pain.[18]

## Summary

Orofacial pain may be due to various conditions affecting numerous structures local to or distant from the oral cavity including: the meninges, cornea, oral/nasal/sinus mucosa, dentition, musculature, salivary glands and temporomandibular joint.

Without a basic understanding of the sensory supply to the region it is impossible to investigate and diagnose pain conditions successfully.

The region's unique neurophysiologic characteristics, which are different from the spinal nociceptive system, can present diagnostic challenges to clinicians specializing in this area. The region's sensory supply is from both spinal (C2 and 3) and cranial nerves (III, V, VII [nervous intermedius], IX, X), the latter providing both sensory and autonomic supply. The main sensory supply to the orofacial region is from the trigeminal nerve and its large representation in the sensory cortex means that pain in the orofacial region can have significant biopsychosocial impacts: interruption of daily social function such as eating, drinking, speaking, kissing, applying make-up, shaving and sleeping and, in some cases, can compromise a patient's self-identity.[4]

Overall, our respect for the complexity of pain has increased with recent innovative imaging, genetic and psychological methodologies. The role of the endogenous analgesic systems seem to be of great potential, however, the manipulation of these systems may rekindle memories of a clockwork orange!

## References


1. Omori S, Isose S, Otsuru N, Nishihara M, Kuwabara S, Inui K, Kakigi R. Somatotopic representation of pain in the primary somatosensory cortex (S1) in humans. *Clin Neurophysiol* 2013; **124**(7): 1422–1430. doi: 10.1016/j.clinph.2013.01.006. Epub 2013 Feb 12.
2. Sanders RD. The trigeminal (V) and facial (VII) cranial nerves. *Psychiatry* (*Edgmont*) 2010; **7**(1): 13–16. Epub 2010 Jan.
3. Renton T, Yilmaz Z. Profiling of patients presenting with posttraumatic neuropathy of the trigeminal nerve. *J Orofac Pain* 2011; **25**(4): 333–344.
4. Forssell H, Jääskeläinen S, List T, Svensson P, Baad-Hansen L. An update on pathophysiological mechanisms related to idiopathic oro-facial pain conditions with implications for management. *J Oral Rehabil* 2015; **42**(4): 300–322. doi: 10.1111/joor.12256. Epub 2014 Dec 8.
5. Locker D, Grushka M. The impact of dental and facial pain. *J Dent Res* 1987; **66**: 1414–1417.
6. Arends JJ, Dubbeldam JL. The subnuclei and primary afferents of the descending trigeminal system in the mallard (*Anas platyrhynchos* L). *Neuroscience* 1984 Nov; **13**(3): 781–795.
7. Fujiyoshi T, He YF, Xiao C, Ichikawa H. Trigeminal primary projection to the rat brain stem sensory trigeminal nuclear complex and surrounding structures revealed by anterograde transport of cholera toxin B subunit-conjugated and Bandeiraea simplicifolia isolectin B4-conjugated horseradish peroxidase. *Neurosci Res* 1997 Aug; **28**(4): 361–371.
8. Upadhyay J, Knudsen J, Anderson J, Becerra L, Borsook D. Non invasive mapping of human trigeminal brainstem pathways. *Magn Reson Med* 2008 Nov; **60**(5): 1037–1046. doi: 10.1002/mrm.21682.
9. Oka A, Yamamoto M, Takeda R, Ohara H, Sato F, Akhter F, Haque T, Kato T, Sessle BJ, Takada K, Yoshida A. Jaw-opening and -closing premotoneurons in the nucleus of the solitary tract making contacts with laryngeal and pharyngeal afferent terminals in rats. *Brain Res* 2013 Dec 2; **1540**: 48–63. doi: 10.1016/j.brainres.2013.10.009. Epub 2013 Oct 12.
11. Greenwood LF, Sessle BJ. Inputs to trigeminal brain stem neurones from facial, oral, tooth pulp and pharyngolaryngeal tissues: II. Role of trigeminal nucleus caudalis in modulating responses to innocuous and noxious stimuli. *Brain Res* 1976 Nov 26; **117**(2): 227–238.
12. Jaggi AS, Singh N. Role of different brain areas in peripheral nerve injury-induced neuropathic pain. *Brain Res* 2011 Mar 24; **1381**: 187–201. doi: 10.1016/j.brainres.2011.01.002. Epub 2011 Jan 14. Review.
13. Seifert F, Maihöfner C. Functional and structural imaging of pain-induced neuroplasticity. *Curr Opin Anaesthesiol* 2011 Oct; **24**(5): 515–523. doi: 10.1097/ACO.0b013e32834a1079. Review.
14. Benarroch EE. Pain-autonomic interactions. *Neurol Sci* 2006 May; **27**(Suppl 2): S130–133. Review.
15. Osikowicz M, Ribeiro-da-Silva A. Consequences of the ablation of non peptidergic afferents in an animal model of trigeminal neuropathic pain. *Pain* 2012; **153**(6): 1311–1319. doi: 10.1016/j.pain.2012.03.023. Epub 2012 Apr 21.
16. Drummond PD. Sensory-autonomic interactions in health and disease. *Handb Clin Neurol* 2013; **117**: 309–319. doi: 10.1016/B978-0-444-53491-0.00024-9. Review.
17. Eftekhari S, Warfvinge K, Blixt FW, Edvinsson L. Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. *J Pain* 2013; **14**(11): 1289–1303. doi: 10.1016/j.jpain.2013.03.010. Epub 2013 Aug 17.
18. de Sousa Buck H, Caous CA, Lindsey CJ. Projections of the paratrigeminal nucleus to the ambiguus, rostroventrolateral and lateral reticular nuclei, and the solitary tract. *Auton Neurosci* 2001 Mar 23; **87**(2–3): 187–200.