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# SENSORY INTERACTION THEORY: REVISION OF THE CRANIOFACIAL REGION

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## Abstract

**Purpose:** The objective of this study was to review the literature to find scientific evidence about the mechanisms involved in orofacial sensory interaction, including trigeminal and special sensory modalities.

**Views:** Conscious sensory perception depends on peripheral external and internal stimuli, which are integrated and processed in central neural centres in order to promote the sensory experience through learning and memory. In the orofacial region, besides somatosensory inputs, there are special sensory modalities (gustation, olfaction, vision and audition) that interact with trigeminal ascendant inputs in a way that makes this area of the body unique. Moreover, the trigeminal nerve may have an important role due to the complex functions of this region, including breathing, feeding and detecting threats. In recent decades the development of equipment accurate enough to detect sensory thresholds has produced a wide range of evidence about orofacial interaction, which allows for the possible development of a unified underlying theory on this issue.

**Conclusions:** The trigeminal system seems to mediate olfactory and gustative sensations in cortical associative centres, and sensory peripheral neural inputs are modulated by physiological and pathological conditions. Future experimental studies should seek to clarify the mechanisms involved in this interaction, and the role of pathological states in abnormalities of sensory thresholds and perception.

**Key words:** sensory integration, interaction, orofacial pain, QST, craniofacial region.

## INTRODUCTION

The investigation of sensory perception has been a field of scientific interest since the end of the 19th century. Although there are separated sensory modalities, there is also an integrated sensory system that is at least a part of the background of conscious perception, which began to be scientifically demonstrated in the second half of the 20th century. The Gate Control Theory of Melzack and Wall (1965) [1] provided clear evidence that different somatosensory stimuli (mediated by nerve fibres of small or large diameter) interact. The main observation was the suppression of pain sensation by tactile and other non-painful inputs. Melzack expanded this theory in 1999 [2] with the concept of the neuromatrix, a complex neural network. This concept posited a more complex neural interaction in the central nervous system which involved somatosensory, limbic and thalamocortical components, dependent on a time-space stimuli relation. Beyond the interaction of somatosensory inputs, Melzack argued, there is integration with special sensory modalities which have a role in the neural processing of perception [2].

Evidence-based studies of this interaction began to be published, especially on the orofacial area, and found that simple perception at the oral cavity integrates somatosensory, gustative and olfactory inputs. Gustative complaints have been reported by patients with trigeminal pain [3-7], and taste studies have shown the association between taste and smell [8, 9]. The temperature of chemical substances seems to impact olfactory and gustative thresholds [10-14], and there is an integration of somatosensory and special sensory modalities in the craniofacial region [15-17]. This review states a unified theory for

craniofacial sensory interaction, which plays an important role in the vital functions of the conscious perception of the environment.

## The dynamic process of sensory perception in the craniofacial area

The trigeminal system is the largest and most complex somatosensory system in the human body. There is an intense convergence in it of inputs from the oral and nasal mucosa, cornea, facial skin, lips, teeth, nose, dura mater, tongue, deep tissues and part of the auditory canal, which are processed in the central nervous system along with adjacent somatosensory inputs mediated by other cranial nerves (VII, IX, X) [18-21]. Its complexity is closely related to the evolutionary importance of this body area in survival and interaction with the environment and other beings [22]. Its functions include breathing, chewing, talking and swallowing, which depend on exteroceptive (e.g. vision, odours, oral sensations that coordinate chewing and swallowing with breathing) and interoceptive sensory inputs (e.g. levels of glucose, $O_2$, $CO_2$ in the blood flow) [18, 21].

Conscious and non-conscious efferent responses, such as salivation, muscular activity facial mimic, mastication and even hand movements to lead the food to the mouth [23], depend on the sensory system. This last one may be the reason for the proximity of the inferior third of the face and the hand in cortical representation of each side, and these responses might be impaired when the sensory system presents dysfunctions [24]. Moreover, not only does saliva depend on sensory interaction, it also facilitates sensory perception in the mouth [25, 26]. Taste is a complex interaction between gustative thresholds and temperature, odorants and texture of the food [17]; thus, any abnormality in this system could affect perception as a whole [16, 24, 27].

It is important to highlight the dynamic influence that sensory perception may present in the contexts of the internal or external environments. High levels of glycated haemoglobin have been associated with facial hypoalgesia in patients with diabetes mellitus [28], and there is an influence of the circadian cycle on sensory perception, depending on hormones and mediators [29, 30].

Women have lower sensory thresholds than men [31] due to hormonal modulation by oestrogen and progesterone [32, 33], neural mechanisms [34, 35] and psychosocial aspects [36, 37]. The genetic influence of the X chromosome is not well-defined and future studies are necessary, including in children before the sex maturation. On the other hand, ageing is related to a decrease of sensory perception [31, 38-41]; possible mechanisms include the decline of immune responses and regulation of neurogenesis [42], the use of medication, chronic processes, variation in the density and distribution of receptors and ionic channels and the composition of saliva and nasal mucus [43].

Cortical maps of sensory representation are dynamic and can change not only with time but also during an activity [44]. The receptive fields seem to be formed according to the simultaneous activation of the ascendant paths amplified in central areas by the circuitries of retransmission or the inhibitory neurons associated with them [45]. Thus, associated with the convergence of information there is a paradoxically divergent pattern [46, 47]. The descendent modulatory circuits permit the passage of some inputs to the detriment to others, and these are the pathophysiological mechanisms that underlie conscious sensory perception [48, 49]. It is also possible to observe the inhibition of pain sensations by the stimulation of periaqueductal grey substance or motor cortical areas [50].

## Clinical and experimental evidence of sensory interaction

In recent decades, quantitative sensory testing protocols had been developed to elucidate the mechanisms involved in orofacial pain conditions [51-54]. Sensory abnormalities appear most often after trauma or in neuropathic conditions [6, 7, 24, 55-61]. The association between trigeminal abnormalities and altered taste perception has been shown [4, 62, 63], and supports orofacial sensory interaction. It is known that an increase in temperature may help in the detection of taste [64].

The unilateral stimulation of the tongue with sodium chlorate in patients with an injury in the contralateral chorda timpani nerve generated bilateral nuclear activation at the brainstem [65]. Gustative impairment after trigeminal surgery indicates the existence of central and peripheral sensorial interaction, as supported by animal studies [21, 66]. Injury to the lingual nerve, which has both trigeminal nerve and facial nerve fibres, leads to the faster regeneration of large fibres to the detriment of the smaller ones (pain, temperature and gustation), and corresponds to the symptoms of pain and dysgeusia in patients [67]. On the other hand, it has also been observed that olfactory threshold decrease impairs the trigeminal function at the nasal mucosa [15].

Despite the clear association of abnormal sensitivity with neuropathy, other orofacial conditions that are not neuropathic also present sensorial changes due to secondary hyperalgesia and central sensitization [18]; for example, temporomandibular disorders that have musculoskeletal mechanisms causing hyperalgesia and sensitization [68, 69]. Research on patients with persistent idiopathic facial pain has generated controversial results [6, 70, 71], and the possible explanations are a diagnosis of exclusion and that there are methodological differences in patients' recruitment for the studies. This suggested that, according to the aetiology of the pain,

the sensory loss pattern is variable. It is also important to consider that there are many drugs that are used for chronic pain control and that alter sensory thresholds, for example carbamazepine, often taken by the patients during the studies [63, 72].

The generalized pain of fibromyalgia is associated with several sensorial abnormalities, including taste and smell disorders [73], and facial palsy primarily involving the VII nerve is associated with secondary somatosensory differences in the trigeminal area [74]. Although the interaction between somatosensory, gustative and olfactory inputs has been widely accepted, and despite the hypothesis of chemosensory (gustation and olfaction) interaction with vision [47], only recently has it been demonstrated, in several studies, that there is interaction among somatosensation, gustation, olfaction, audition and vision [16, 75, 76]. Patients with trigeminal neuralgia who underwent a compression of the trigeminal ganglion as treatment experienced auditory and vision complaints [59], and odours can help in the determination of the location of a sound [77].

## The special modalities: vision, audition, gustation and olfaction

The chemical senses, represented by gustation and olfaction, are highly integrated and comprise the taste sensation along with somatosensory information from the oral and nasal mucosa mediated by the trigeminal nerve [8, 9]. Different chemical neurons are specific for different chemical substances, but a single neuron can recognize a wide range of chemicals due to multiple signalling cascades [78, 79]. Chemical transduction depends on the recognition of the molecular structure according to the dilution of the component in saliva or nasal mucus [9, 79, 80].

Anosmia and hyposmia are common in the general population [15, 81] and can be associated with various conditions such as tumours, infections, nephropathies, epilepsy and neurodegenerative diseases [79, 82]. Women have lower olfactory thresholds and these abnormalities increase with ageing [81, 83]. Both anosmia and hyposmia have also been associated with neurodegenerative diseases (Parkinson's, Alzheimer's disease) as predictors [81, 84].

Ageusia and hypogeusia, characterized by loss of taste sensation, can be associated with several pain conditions at the oral cavity [4, 7, 8, 78, 85]. The electrical activity of gustation is processed at the geniculate (VII), petrosus (IX) and/or nodosus (X) ganglions and the gustative area of the solitary tract at the brainstem [86-88]. Factors such as appetite, blood concentrations of glucose and insulin may interfere in gustative perception [89, 90]. The need for the distribution of substances at the oral cavity in order to favour the detection of taste may be a clue as to the implications of trigeminal inputs for taste detection [79].

## Craniofacial sensory interaction

Sensory receptors are connected to a highly flexible circuitry, capable of discriminating between several types of continuously flowing information from the environment. They generate precise responses determined by anatomic circuits that are potentiated according to the exposition to sensory stimuli, stored as memories [91, 92]. Consistency of perception depends on sensory integration according to the size of receptive fields of neurons, the correct inhibition of undesired stimuli and the convergence of data on cortical areas of association, which are more functional than topographic [21, 46, 93]. To understand craniofacial perception, it is essential to comprehend its multisensorial functions [94]. A large proportion of gustative and olfactory sensations are perceived during mastication [8, 95], and somatosensory participation helps in the determination of the location of taste at the tongue, even if there are olfactory inputs associated [96]. Taste has a somatosensory component itself that includes the texture and temperature of food, and spicy (pain and heat), menthol (cold) and carbonated (small pain fibres) sensations [12, 21, 78]. Saliva has an important role and its absence and reduction can interfere in oral sensations [25]. Its quality is also important and an imbalance in its components – such as peptides, glycoprotein, lipids, enzymes and histamine – can alter taste detection [97].

Several animal studies have elucidated the mechanisms involved in craniofacial sensorial interaction. The neurectomy of chorda timpani causes an increase of salty thresholds in rodents [98] and the neurectomy of the glossopharyngeal nerve increases the bitter taste threshold [99-102]. When the neurectomy of both is performed simultaneously, even if one of them regenerates, there is no normalization of these sensations, showing the interdependence between them for gustation [103]. After the neurectomy of chorda timpani, trigeminal and glossopharyngeal nerves, the level of sensory loss is higher when the lesion is closer to the peripheral tissues [104]. In the last decade it has been demonstrated that the *subnucleous oralis* of the trigeminal complex can also mediate gustative inputs [105]. The perception of taste is a mixture the activity of excitatory (glutamatergic) and inhibitory (gabaergic A) synapses at the brainstem and thalamus involving the trigeminal, facial, glossopharyngeal and vagus afferences [106]. Actually, a large part of gustative processing occurs at the brainstem due to the convergence of inputs conducted by the chorda timpani and glossopharyngeal afferents [107]. In frogs, depending on the chemical gustative stimuli at the tongue, there is an increase or reduction of antidromic activity, though the alteration of membrane potential with electrical stimuli cannot show these findings. This evidence

supports peripheral mechanisms in the interaction between gustative and somatosensory afferences [108].

The rostral nucleus of the solitary tract is the first centre of gustative processing and modulation, followed by the parabrachial nucleus. There is evidence for the involvement of delta-opioid receptors in this process [109]. The circuitry of gustative sensation at the tongue involves known gustative areas (the central rostral nucleus of the solitary tract, synapses with geniculate axons, projections to the parabrachial nucleus at the pons), but also the lateral part of the rostral nucleus of the solitary tract, which also receives trigeminal afferents [110], and the ventral area of the solitary tract and reticular formation, responsible for the interaction with oral motor reflexes, and important for mastication and swallowing [21, 111-113]. The evidence indicates that there is also visceral modulation and the influence of previous gustative experiences by descendent pathways from the anterior cortex. The electrical stimulation of the central nucleus of the amygdala modulates the intensity of the type of gustative input that is transmitted by the parabrachial nucleus [114]. Following gustative stimulation by a sweet substance there is activation of chemoreceptors at the nasal epithelium mediated by trigeminal paths [115]. It is evident that neurons from the solitary tract not only protrude but also receive axons from the parabrachial nucleus and that both communicate to the contralateral side [116].

The parabrachial nucleus connects to the gustative cortex via the parvicellular part of the ventroposteromedial nucleus of the thalamus, which sends back inhibitory projections that modulate gustative sensations [117]. Axons from the hippocampus project not only to the thalamus and hypothalamus but also to the limbic system and to the visual, auditory, somatosensory, olfactory and gustative cortexes. They may be responsible for long-term potentiation (LTP) resulting in the sensory abnormalities observed in clinical studies [118].

During eating, each sensory neuron is apparently specific to each stimulus; however, in the central nervous system the groups of neurons from analogous sensations determine its magnitude, which becomes complex due to the convergence of different modalities on these centres. Animal studies have shown that any taste mixtures lead to ambiguous responses [119], and that the highly concentrated taste modality is the only one that is usually clearly identified in these mixtures. Some neurons even respond better to the mixture than to the taste modality isolated because they are bombarded with action potentials and thus can amplify the highly concentrated taste in that mixture [120]. It is known that sweet and bitter tastes use segregated circuitries in the CNS but have peripheral modulation. Even with this segregated circuitry, the projections of each taste modality reach areas of association that are completely superposed for salty, sour, bitter and sweet [9, 121].

The pattern of cortical activation depends on the emotional characteristic of the taste modality (pleasant or unpleasant), even in flavours designed to activate cortical areas [121]. The model mostly used as an example for the gustative interaction is the inhibition of the sweet taste when bitter is present. This happens because the cationic channel TRPM5, involved in the transmission of sweetness, is inhibited by some bitter substances as such quinine due to an acceleration of channel closing [122]. This modulation is completely peripheral. The taste buds are not uniformly distributed, but depend on the nerve (X, IX or VII), which also can impair the perception of flavour [123]. Central analgesia by breastfeeding is mediated by the activation by sugars of the gustative paths that activate pain-suppressing areas such as the periaqueductal grey substance and the nucleus raphe magnus [124].

A simple injury to the trigeminal fibres has been shown in animal studies to alter taste detection and supports the need of trigeminal integrity for gustative sensitivity [125].

The trigeminal system is also closely connected with the olfactory system [15, 126], and peripheral adaptive mechanisms seem to reduce trigeminal responsiveness in anosmia and hyposmia [15]. This interaction occurs in the direct activation of the trigeminal fibres at the nasal mucosa by the same odorants [127].

## CONCLUSIONS

The trigeminal system seems to mediate olfactory and gustative sensations in cortical associative centres, which implicates somatosensory inputs in the determination of the location of the stimulus, besides other characteristics. This role may be weakened in the occurrence of chronic conditions such as craniofacial pain, resulting in a sensorial imbalance, and dysfunction of orofacial perception. Despite the wide range of evidence so far accumulated, there is a lack of studies investigating the integration between vision and audition with the chemosenses (gustation and olfaction) and somatosensory inputs, which are promising lines of research for the future. Animal models for the investigation of cortical maps of isolated and associated sensorial modalities in healthy or pathological conditions will clarify the still-obscure mechanisms that underlie these observations.

## Conflict of interest

Absent.

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