The Evolution of Neuroscience as a Research Field Relevant to Dentistry

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Abstract

The field of neuroscience did not exist as such when the *Journal of Dental Research* was founded 100 y ago. It has emerged as an important scientific field relevant to dentistry in view of the many neurally based functions manifested in the orofacial area (e.g., pain, taste, chewing, swallowing, salivation). This article reviews many of the novel insights that have been gained through neuroscience research into the neural basis of these functions and their clinical relevance to the diagnosis and management of pain and sensorimotor disorders. These include the neural pathways and brain circuitry underlying each of these functions and the role of nonneural as well as neural processes and their "plasticity" in modulating these functions and allowing for adaptation to tissue injury and pain and for learning or rehabilitation of orofacial functions.

Keywords: brain function, mastication, multisensory perception, nervous system, neuroscience/neurobiology, orofacial pain/TMD

Introduction

When the *Journal of Dental Research* (*JDR*) was founded 100 y ago, the gross anatomy of the brain and nerves, including the trigeminal nerve and other cranial nerves, had been described, and some insights into brain function were gained through observations of behavior and functional defects after brain injury or disease. Experiments in animals also provided some insights into the excitability of muscle nerves (i.e., the reflex basis of many motor functions) and the conditioning influences on sensory and motor functions (e.g., salivation). Nonetheless, there was limited knowledge of the processes that underlie neurally based functions in general, let alone those of the face, jaws, and mouth.

Over subsequent decades, neuroscience has emerged as a scientific field that has particular relevance to dentistry. This field has grown substantially, especially over the past 5 decades, as reflected in the marked increase in published papers (Table 1) and some landmark discoveries over this period (Table 2). A major driver has been advances in technologies relevant to scientific investigation (e.g., electrophysiology), improved histologic approaches and the use of electron microscopy, and, more recently, technologies such as immunohistochemistry, molecular biology, and brain imaging. Application of these advances has led to new insights into the structure, connectivity, and functioning of central nervous system (CNS) areas involved in orofacial functions and disorders, as well as other functions having an influence on orofacial behaviors (e.g., consciousness, sleep, cognition, emotion, stress, memory). Another factor driving orofacial neuroscience was the establishment in the 1970s of societies with a focus on neuroscience per se (e.g., Society for Neuroscience), special interest groups with an orofacial neuroscience focus within established scientific organizations (e.g., the IADR), and organizations and educational programs with an interest in orofacial clinical conditions having a neural basis. Many of these functions and disorders are unique to this part of the body (e.g., dental pain, taste, chewing, biting, swallowing, and salivation). Given space limitations, this review focuses on neuroscientific research advances related to these functions relevant to dentistry.

Pain

At the time that the *JDR* was established 100 y ago, some orofacial pain conditions were already recognized (e.g., trigeminal neuralgia, headaches, and toothaches); some approaches to control orofacial pain already existed (e.g., nonsteroidal anti-inflammatory drugs, opiates, local anesthetics); and dentists had led the way 75 y earlier in the use of general anesthesia. Although the specificity theory of sensations espoused in the 19th century attributed pain to activation of primary afferents and neurons and pathways in the CNS that responded exclusively to noxious stimulation of body tissues, there was limited knowledge of nociceptive processes; indeed, theories were proposed over the next 30 y that challenged this concept of specificity. Nonetheless, the spinothalamic pathway and its analog in the trigeminal system had been partly defined by neuroanatomic studies and, as supported by clinical observations, were

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Table 1. Neuroscience Publications.

Year	No. of Publications	
	Neuroscience[a]	Neuroscience Related to Dentistry[b]
Before 1949	14,024	157
1949 to 1958	74,175	782
1959 to 1968	127,375	2,959
1969 to 1978	201,046	6,813
1979 to 1988	266,076	9,338
1989 to 1998	374,880	14,376
1999 to 2008	579,340	22,164
2009 to 2018	836,475	35,004

The data listed reflect only the number of articles indexed in PubMed.
[a]*Neuroscience* refers to all neuroscience articles. MeSH terms used: (((((((((“Neurosciences”[Mesh]) OR “Cognitive Neuroscience”[Mesh]) OR “Neuroanatomy”[Mesh]) OR “Neurobiology”[Mesh]) OR “Neurochemistry”[Mesh]) OR “Neuroendocrinology”[Mesh]) OR “Neuropathology”[Mesh]) OR “Neuropharmacology”[Mesh]) OR “Neurophysiology”[Mesh]) OR “Nervous System Diseases”[Mesh]. Keywords used: Neuroscience OR Neuroanatom* OR Neurobiolog* OR neurobiochemical OR Neurochemistry OR Neuroendocrinology OR Neuropathology OR Neuropharmacolog* OR Neurophysiology.
[b]*Neuroscience related to dentistry* includes articles published in dental journals and articles published in nondental journals that have dentistry-related terms either as MeSH terms or as keywords in title and abstract. MeSH terms used: “dentistry”[Mesh]. Keywords used: Dental OR Dentist* OR oral OR Periodont* OR Endodontics OR Tooth OR Teeth OR Mouth OR Orthodont* OR Prosthodontics OR Prosthesis OR odont* OR craniofacial OR maxillofacial OR temporomandibular.

Table 2. Examples of Landmark Discoveries and Concepts over the Past 50 y in Relation to Orofacial Neuroscience.

- Presentation of the gate control theory of pain.
- Conceptualization of the multidimensionality and biopsychosocial aspects of pain and their application to improved diagnosis and management of orofacial pain conditions.
- Discovery of trigeminal nociceptive afferents and their modulation by processes within orofacial tissues, including processes involved in peripheral sensitization and orofacial pain control.
- Discovery of nociceptive neurons in the brain and their modulation by intrinsic CNS circuits and endogenous mediators, including processes involved in orofacial pain control.
- Discovery of the plasticity of the nociceptive neurons, including processes involved in trigeminal central sensitization and its role in acute and chronic orofacial pain conditions.
- Definition of the central pattern generators for chewing and swallowing.
- Elucidation of CNS sensorimotor circuits and discovery of the plasticity of sensorimotor cortex and other CNS regions in relation to orofacial sensorimotor control, learning, and adaptation to injury and other changes in orofacial tissues.
- Elaboration of new technologies, such as those based on brain imaging and molecular biology, and their application for elucidating the neural basis of orofacial functions.
- Delineation of peripheral processes and CNS circuits underlying touch, temperature, taste, and salivation, including the discovery of a fifth taste, umami.
- Discovery of the role of nonneural cells (e.g., immune, glia) in peripheral and CNS processes involved in orofacial pain and sensorimotor functions.

CNS, central nervous system.

considered the major pain pathways ascending to higher levels of the CNS. Neuroanatomic and clinical observations had also provided some evidence that the spinal dorsal horn (and its trigeminal analog, subnucleus caudalis [Vc]) acted as the first CNS relay site in these pathways. In the next 2 decades, there was further support, notably by Sjoqvist (1939), showing that surgical interruption of the ascending pathways originating from the Vc could relieve the excruciating pain of trigeminal neuralgia, which Blom (1962) showed a few years later could be managed pharmacologically by carbamazepine.

A major breakthrough in understanding pain came with the gate control theory of pain (Melzack and Wall 1965), pointing out the multidimensional character of pain (sensory discriminative, cognitive, affective, motivational) and the modulatory influences on nociceptive transmission in the CNS of other sensory inputs and the descending influences emanating from higher CNS centers involved in cognition, emotion, attention, memory, and so on. The theory was the spark for an upsurge of research into pain that, when coupled with the emerging field of neuroscience (see Introduction), catalyzed research endeavors aimed at improving the understanding and management of orofacial pain. It is also noteworthy that, around this time and indeed beyond for several decades, the tooth pulp was viewed as a “pure” source of nociceptive inputs to the CNS, since pain was the common sensation clinically elicited by dental stimuli and the pulp was reported to be innervated only by small-diameter afferents (A delta and C fiber), which elsewhere in the body were associated with signaling pain. Based on this premise, several studies examined behavioral responses, CNS activity, and the jaw-opening reflex evoked by pulp stimulation, and it was not until several years later that findings were produced that challenged this concept of pain being the only sensation evoked from tooth pulp and dentine (Dubner et al. 1978; Sessle 1987, 2000).

Also, around this time were related studies addressing the long-held question of whether and how dentine, as well as tooth pulp, was innervated to account for dentinal sensitivity. This question was resolved from the late 1960s and beyond through the use of electrophysiologic recordings and improved or new histologic techniques showing that small-diameter afferents indeed innervated dentinal tubules as well as pulp, although it was apparent that larger-diameter afferents (A beta) also supplied the pulp (Matthews 1970; Greenwood et al. 1972; Narhi and Antila 1973; Byers 1984; Narhi 1985). Another long-held question related to how the afferent endings were activated. The mechanism of activation was shown to include a hydrodynamic process whereby afferent endings in the dentinal tubules or pulp proper were mechanically activated indirectly by dentinal stimuli (Brännström et al. 1969). The subsequent investigations also showed a differential activation of A-delta afferents and C-fiber afferents in dentine versus pulp proper and that the odontoblast may act as an intermediary in the transduction process (Dubner et al. 1978; Sessle 1987; Magloire et al. 2010). The curious property of these afferents to respond to dentinal stimuli that elsewhere in the body are not painful (e.g., tactile, thermal) has been recently noted, suggesting that pulp afferent endings function as “algoneurons” and emphasizing this unique pain-related feature of the tooth pulp (Fried et al. 2011).

Starting in the late 1970s, electrophysiologic recordings from functionally identified A-delta and C-fiber nociceptive afferents innervating the facial skin were also made, classifying them as heat nociceptors, high-threshold mechanoreceptors, and polymodal receptors (Sumino et al. 1973; Beitel et al. 1977). Subsequently, the patch-clamp recording method and immunohistochemistry were developed and used for identifying various chemical mediators and their receptors on the endings of trigeminal afferents and their cell bodies in the trigeminal ganglion (TG; Lazarov 2002; Tsuboi et al. 2004). For example, several transient receptor potential (TRP) channel subtypes have in the past 20 y been discovered in TG neurons innervating the tooth pulp, facial skin, oral mucosa, temporomandibular joint, tongue, and meninges and implicated in primary afferent processing related to various orofacial noxious as well as nonnoxious stimuli (Kobayashi et al. 2005; Liu et al. 2007; Batbold et al. 2017). Furthermore, it has been found that noxious stimuli and also nerve injury or inflammation cause release of numerous chemical mediators from tissue cells, nerve endings, or blood vessels (e.g., substance P, CGRP, OLAMS, glutamate, prostaglandins)—for example, as shown in pulp perfusion studies of human tooth pulp (Hargreaves and Ruparel 2016). ATP, NGF, BDNF, and mediators released from immune cells can also modulate their excitability, the latter contributing to processes by which the nociceptive and immune systems may interact. Electrophysiologic recording studies showed that these mediators can activate nociceptive afferent endings and their cell bodies in the TG or enhance their excitability (so-called peripheral sensitization; Cairns et al. 2001; Tsuboi et al. 2004; Kitagawa et al. 2006; Iwata et al. 2017). These findings have clinical relevance, since peripheral sensitization processes explain why an injured or inflamed tissue is very sensitive and why some peripherally acting drugs can be effective analgesics; nonsteroidal anti-inflammatory drugs, for example, suppress prostaglandin production by functioning as cox-2 inhibitors in the arachidonic acid cascade (Buer 2014), and their potent analgesic effect on pain associated with peripheral inflammation is commonly utilized in dentistry. Interestingly, opioid receptors are expressed on peripheral afferent endings and represent therapeutic targets for analgesic effects without side effects typical of opioid drug actions in the CNS (Sessle 2011; Hargreaves and Ruparel 2016; Francois and Scherrer 2018). Also, sex differences found in some of these processes in humans as well as laboratory animals suggest that peripheral physiologically based sex differences may contribute to well-known sex differences in pain sensitivity.

From the 1970s onward, these studies on peripheral mechanisms of orofacial pain were complemented by a variety of studies evaluating trigeminal nociceptive pathways and neuronal networks in the CNS. They employed immunohistochemistry, electrophysiologic recordings, and improved neuroanatomic tracing techniques (e.g., HRP, c-fos), with pharmacologic and behavioral measures to document trigeminal nociceptive pathways (Iwata et al. 1992; Iwata, Takahashi, et al. 1998; Kawabata et al. 2004; Chichorro et al. 2017; Fig. 1). They also revealed a role for several chemical mediators (e.g., substance P, CGRP, glutamate, 5-HT, enkephalins) in facilitating or modifying nociceptive transmission within the trigeminal brainstem sensory nuclear complex (TBSNC), including its Vc. The single-cell recording studies also delineated in anesthetized animals the functional properties of TBNSC nociceptive neurons receiving afferent inputs from the orofacial region (Price et al. 1976; Sessle et al. 1981; Iwata et al. 1999; Iwata et al. 2001; Saito et al. 2008). Their many structural as well as functional similarities of those in the Vc, with spinal dorsal horn nociceptive neurons, has led to the Vc often being termed the *medullary dorsal horn*. Nociceptive neurons were also discovered in other components of the TBSNC (although their precise role in orofacial pain remains unclear) and in higher levels of the trigeminal CNS pathways (e.g., nucleus ventralis posteromedialis thalamic nucleus, somatosensory cortex, insula; Raboisson et al. 1989; Iwata et al. 2005; Chichorro et al. 2017).

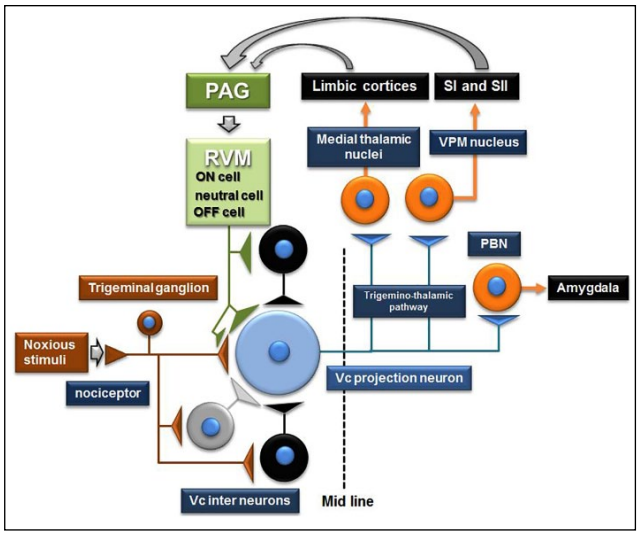

Figure 1. Ascending and descending pathways in the trigeminal nociceptive system in the CNS. PAG, periaqueductal gray; PBN, parabrachial nucleus; RVM, rostroventromedial medulla; Vc, subnucleus caudalis; VPM, ventralis posteromedialis.

Descending modulatory influences on trigeminal nociceptive transmission were shown in the 1970s and 1980s from CNS sites, including the sensorimotor cortex, periaqueductal gray, and rostroventromedial medulla (Yokota and Hashimoto 1976; Sessle et al. 1981). Dubner's group and others demonstrated in awake behaving monkeys the relationship between Vc or cortical neuronal activity and nocifensive behavior related to the sensory-discriminative aspect of orofacial pain and the modulating effect of the behavioral state (e.g., attention) via descending influences from higher brain centers (Bushnell et al. 1984; Iwata, Tsuboi, and Sumino 1998; Iwata et al. 2005). Neuroanatomic and immunohistochemical studies revealed projections from several higher brain centers to the Vc, releasing various chemical mediators (e.g., enkephalins, 5-HT, norepinephrine) that act through their respective receptors expressed on neurons to modulate Vc neuronal activity. Several centrally acting analgesic drugs have subsequently been shown to act directly on these receptor processes in Vc nociceptive neurons or indirectly via

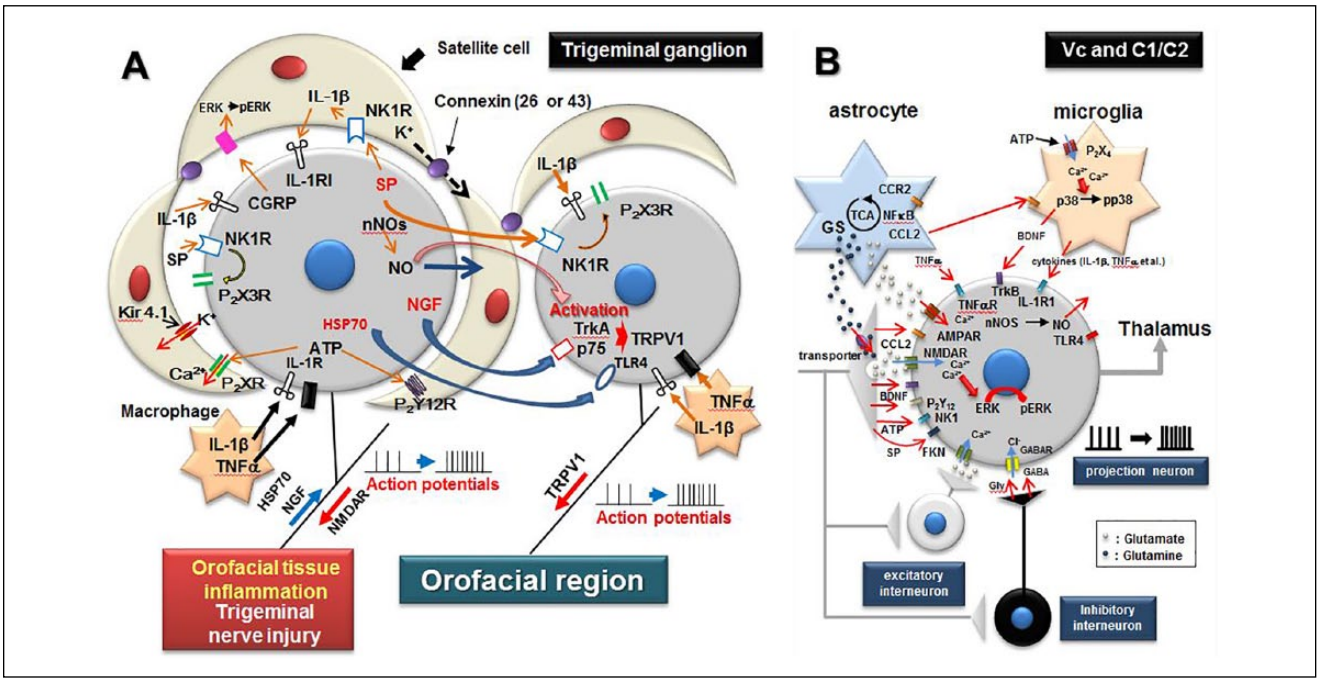

Figure 2. Peripheral mechanisms of orofacial pain. (**A**) After trigeminal nerve injury or orofacial inflammation, the primary afferent neurons become hyperexcitable, resulting in satellite glial cell activation and macrophage accumulation. Hyperactivated trigeminal ganglion neurons, activated satellite glial cells, and macrophages communicate with one another via various molecules, neuropeptides, and chemokines, as well as nerve growth factor, ATP, and nitric oxide. Neuron, satellite glial cell, and macrophage communication causes further enhancement of trigeminal ganglion neuronal activity. (**B**) Input and output mechanisms of noxious information in the nociceptive neurons of the trigeminal spinal subnucleus caudalis (Vc) and upper cervical spinal cord (C1/C2) under normal and pathologic conditions. Vc neurons become hyperactive after trigeminal nerve injury and orofacial inflammation. After hyperactivation of Vc and C1/C2 nociceptive neurons, microglial cells and astrocytes are activated. Neuron–glial cell communication via various molecules is the important mechanism causing hyperexcitation of Vc and C1/C2 nociceptive neurons.

descending modulatory projections (Fig. 1). For example, opioid drugs act through μ, δ, and κ opioid receptors expressed on the nociceptive neurons or periaqueductal gray neurons. Many other therapeutic approaches and strategies to manage pain operate through these descending influences (e.g., distraction, cognitive behavioral therapy, acupuncture, deep brain or motor cortex stimulation). Moreover, sex differences subsequently shown in some neuronal properties and modulating influences likely contribute to the well-documented sex differences in many chronic orofacial pain states (Okamoto et al. 2005).

The studies in the 1970s and 1980s of trigeminal nociceptive processes principally used acute pain models, but many studies over the past 3 decades have focused instead on mechanisms of orofacial chronic or pathologic pain (Imbe et al. 2001; Sessle 2011; Iwata et al. 2017). Particularly noteworthy are findings from Iwata's group and others that nerve injury or inflammation induces high-frequency discharges in trigeminal afferents and that TG neurons become hyperactive as a result. Various molecules, such as neuropeptides and ATP and glutamate receptors (NMDAR and AMPAR), are produced in hyperactive TG neurons and conveyed to their peripheral and central axon terminals. Satellite glial cell activation and macrophage accumulation also occur in the TG following trigeminal nerve injury or orofacial inflammation (Chiang et al. 2011; Katagiri et al. 2012). A variety of cytokines and chemokines are produced in these nonneural cells and released from them within the TG, resulting in enhancement of TG neuronal activity (see detailed mechanisms in Fig. 2A). Interestingly, receptors for these molecules are upregulated in uninjured as well as injured TG neurons (Chiang et al. 2011; Iwata et al. 2017), likely because gap junctions (Cx 26 and 43) are also activated and promote the spreading of satellite glial cell activation within the TG. This glial cell–neuron communication affects the excitability of uninjured TG neurons and contributes to the induction of pain hypersensitivity in the uninjured orofacial tissues—so-called extraterritorial or ectopic hyperalgesia (Kaji et al. 2016; Komiya et al. 2018).

With regard to central mechanisms contributing to chronic orofacial pain, it should first be noted that studies in the 1980s and 1990s revealed that deafferentation of the tooth pulp (e.g., through root canal therapy) or facial whiskers could produce neuroplastic changes in somatosensory neurons of the TBSNC (Westrum et al. 1976; Gobel 1978; Hu et al. 1986; Hu and Sessle 1989; Jacquin et al. 1989). In the case of nociceptive neurons, the hyperactivity occurring in the primary afferent neurons following orofacial inflammation or nerve injury was shown to produce a barrage of action potentials conducted into the CNS, causing the release of glutamate and other chemical mediators that induce neuroplastic changes manifested as a sustained increased excitability of Vc and C1/C2 nociceptive neurons, accompanied by pain behavior (Fig. 2B). This hyperexcitability ("central sensitization") involves NMDAR and

other neuronal receptor mechanisms as well as phosphorylation of extracellular signal–regulated kinase that is strongly enhanced following noxious stimulation (Kobayashi et al. 2011; Ren and Dubner 2011; Suzuki et al. 2013; Nakaya et al. 2016).

Central sensitization following trigeminal nerve injury or orofacial inflammation is expressed in nociceptive neurons in the Vc and higher brain centers (e.g., VPM thalamus) as increased spontaneous activity, enhanced evoked responses to mechanical and heat stimuli, expanded receptive field size, and decreased activation threshold. These neuroplastic changes—coupled with the extensive convergence of sensory inputs to the Vc and C1/C2 documented from nontrigeminal (e.g., cervical, other cranial nerves) as well as trigeminal afferents supplying diverse tissues (e.g., facial skin, tooth pulp, temporomandibular joint, masticatory muscle, meninges)—are considered to be fundamental CNS mechanisms contributing to the spread and referral of pain, allodynia (pain produced by normally innocuous stimuli), and hyperalgesia (hypersensitivity to noxious stimuli) that characterize many acute and chronic pain states (e.g., toothaches, headaches, temporomandibular disorder). Clinically relevant from these findings are that drugs shown to help relieve some chronic orofacial pain states (e.g., opiates, gabapentinoids) are effective because they target the processes producing or sustaining central sensitization. The findings also bear on local anesthesia, which has long been a standard of practice in dentistry for relieving pain. It is effective because it not only prevents intraoperative pain by blocking nociceptive afferent inputs from the operative site but also can help in preventing an acute pain state transitioning into a chronic pain state by blocking these inputs that could subsequently trigger the development and maintenance of trigeminal central sensitization.

Recent studies have also revealed that trigeminal central sensitization is dependent on the functional integrity of nonneural cells—namely, microglia and astroglia in the Vc and C1/C2. These cells are activated following trigeminal nerve injury or orofacial inflammation and release several cytokines and chemokines that modulate central sensitization in the Vc and C1/C2 (Chiang et al. 2011). Thus, another promising target for the development of new approaches for orofacial pain relief might be nonneural cells. As well as these glial-dependent neuroplastic changes in the ascending nociceptive pathways originating from the Vc and adjacent CNS sites, changes in descending modulatory pathways from higher brain centers have also been recently shown to be involved in these orofacial pathologic pain mechanisms (Ren and Dubner 2011; Chichorro et al. 2017; Saito et al. 2017; Okada et al. 2019). These glial and descending influences underscore the complexity of pain mechanisms and the many factors that can influence diagnosis and management of chronic orofacial pain states.

Touch and Temperature Sensations and Taste

Touch and Temperature. Up to the 1920s, the high sensory discriminability of the orofacial region as compared with most other body regions was generally acknowledged, but it was not until improved neuroanatomic techniques and electrophysiologic methods were introduced that much greater insights were gained of the neural basis of orofacial touch and temperature sensations. These insights, coupled with those gained from advancements in psychophysical (e.g., quantitative sensory testing) and other behavioral measures, documented the high innervation density and exquisite sensitivity of the orofacial region in humans and laboratory animals (Dubner et al. 1978; Matos et al. 2011). These features indeed provided an impetus to use orofacial tissues to study somatosensory mechanisms. As a result, several functionally distinct subtypes of mechanoreceptors and thermoreceptors were identified, and for some, a morphologically distinct receptor was delineated (Poulos and Lende 1970; Beitel and Dubner 1976a; 1976b; Rice et al. 1986). Some of the ion channels and membrane receptors (e.g., TRP) and signaling processes noted above in relation to pain have since been shown to have a role in thermo- and mechanotransduction and encoding.

Through their A-beta, A-delta, and C-fiber afferent inputs into the CNS, these somatosensory receptors provide the brain with information about the quality, location, intensity, velocity, or duration of each type of stimulus. These include mechanoreceptors in periodontal tissues, studies of which defined their morphologic and physiologic properties in humans as well as laboratory animals—showing, for example, that periodontal mechanoreceptors encode the location, magnitude, duration, velocity, and even direction of an occlusal force applied to teeth and that some periodontal mechanoreceptors have morphologic features contributing to these encoding properties (Hannam and Farnsworth 1977; Trulsson et al. 1992; Trulsson 2006). Correlated psychophysical studies showed that this sensory information is crucial for the CNS neural substrate underlying the tactile sensitivity of the teeth and the regulation of mastication, speech, and other orofacial sensorimotor behaviors.

The exquisite tactile and thermal sensitivity of the orofacial region has been shown to be a reflection of not only its high innervation density and the encoding properties of the orofacial receptors and their afferent inputs into the brain but also the extensive representation in the brain of this part of the body and the properties of the neurons in the CNS that receive and process orofacial somatosensory information. For example, pioneering electrophysiologic mapping experiments in awake human subjects in Montreal by Penfield and Boldrey (1937) revealed that the cerebral cortex has a topographic arrangement of the somatosensory (and motor) representations of the body ("homunculus") wherein there is a disproportionate representation of the orofacial region as compared with nearly every other body part. Subsequent studies using more refined electrophysiologic approaches in laboratory animals confirmed the extensive orofacial somatosensory representation and provided novel findings in the somatosensory cortex and VPM thalamus of the response properties of single neurons activated by discreet mechanical or thermal stimulation of the face or other parts of the body (Rose and Mountcastle 1952), consistent with neuroanatomic findings of trigeminal and spinal pathways to the cerebral cortex and their relays in the brainstem and thalamus (Dubner et al. 1978). Subsequently, the TBSNC was a focus, and its nuclear and subnuclear organization of the TBSNC, its inputs from several cranial and cervical nerves,

and its projections to other brainstem and higher brain areas were defined. The response properties of its neurons, those in the thalamus and somatosensory cortex, and their exquisite sensitivity to mechanical, cold, or warm stimulation of localized parts of the face or mouth were also documented (Darian-Smith 1966; Dostrovsky and Hellon 1978; Tsuboi et al. 1993; Lin and Sessle 1994; Yamamoto 2008). The mechanosensitive neurons were also shown to be modulated by afferent inputs originating from outside the orofacial mechanoreceptive field of the neurons (so-called afferent or surround inhibition) and by intrinsic CNS circuits involving local (e.g., brainstem) and higher brain centers (Darian-Smith and Yokota 1966; Sessle and Dubner 1971). These modulatory influences were shown to operate in humans, reinforcing the view that they allow for refined spatial and temporal localization of orofacial stimuli and "gating out" of tactile or other sensory inputs not pertinent to the individual at that point of time.

A related but more recent finding is the neuroplasticity of the orofacial somatosensory processes in the CNS, as exemplified by findings that deafferentation of the facial whiskers in rodents can lead to neuroplastic changes at each level of the trigeminal system in the CNS (Fox 2002; Avivi-Arber and Sessle 2018). Thus, as noted in the Pain section related to pain, the trigeminal somatosensory pathways are not hardwired but can be modified by peripheral alterations (e.g., injury) and changes in CNS-based functions (e.g., attention, emotion).

Taste. It was generally considered by the 1920s that there were 4 basic taste modalities or qualities (sweet, sour, salt, and bitter) and that the tongue was the "organ" of taste because it had structures (taste buds) thought responsible for this special chemical sense. Over the next 50 y, enhanced knowledge was gained of the CNS pathways receiving and relaying taste signals carried into the brainstem by primary afferents of the facial and glossopharyngeal nerves supplying taste buds on, respectively, the anterior and posterior tongue; it was further revealed that there were taste buds on the palate, pharynx, and epiglottic larynx. The activity patterns of these so-called gustatory afferents were defined in laboratory animals and complemented by psychophysical investigations in humans and behavioral studies in laboratory animals. Electrophysiologic recordings up to the 1970s found little evidence that the gustatory afferents and the neurons in the taste relays in the CNS were specifically sensitive to just a single taste modality but that indeed they could be activated by chemical solutions of ≥2 taste modalities. This was not in keeping with the specificity theory of sensations and so led to a concept that our ability to distinguish and discriminate among the different basic taste modalities resulted from differential patterning of neural signals in the gustatory afferents and neurons in the CNS taste relays evoked by each modality of taste stimuli (Dubner et al. 1978; Yamamoto 2006).

From the 1970s onward, the application of advanced techniques has provided further elucidation of the ultrastructure of the cellular elements of taste buds, receptor transduction and signaling processes, and the CNS pathways relaying taste-related information to higher levels of the brain (Dubner et al. 1978; Matsumoto et al. 2013; Han et al. 2019). One cellular element in taste buds appears to act as a taste receptor cell in taste buds and generates nerve impulses via its close contact with the endings of gustatory afferents terminating at the base of the taste bud. G protein–coupled receptors and channel-type receptors are the candidate receptors for the different basic tastes. Interestingly, some chemosensory TRP receptors found on the tongue and other oral tissues may account for the spicy character of some food stuffs, such as peppers.

The nerve impulses generated in the gustatory afferent terminals are relayed through the brainstem (e.g., solitary tract nucleus) and thalamus to the cortical gustatory area (Nomura et al. 1979; Yamamoto 2008; Matsumoto 2013). Most gustatory afferents and taste-responsive neurons in the CNS taste relays have been shown to respond optimally to 1 taste modality (Ogawa et al. 1968; Yamamoto 2008). Electrophysiologic recordings and the use of recently introduced methodologies involving optical imaging, molecular biology, and brain imaging suggest, depending on the quality of taste, a topographic/chemotopic arrangement of the taste-responsive neurons in each of these taste relays (Yamamoto 2008; Han et al. 2019).

While these taste relays are important in the sensory-discriminative aspect of taste, taste-related information is processed in the brain's limbic system in relation to the affective (emotional) pleasurable aspect of taste, in the hypothalamus (which contains the so-called feeding center and satiety center) in relation to the regulation of feeding, and in parts of the cortex and nucleus accumbens (forming components of the brain's reward system) in relation to reinforcing or modifying taste behavior (Castro and Berridge 2014; Han et al. 2019). Recent studies reinforced an earlier view that chemical mediators outside the brain, in the oral cavity itself, play a role in influencing taste. Although not fully understood, several polypeptides and proteins in saliva play an important role, as do other factors, such as salivary flow rate, buffering capacity, and ionic composition (Kolkka-Palomaa et al. 2015; Martin et al. 2018).

The past 40 y have seen further psychophysical studies testing threshold and suprathreshold features of tastes. A fifth taste ("umami") involving taste receptors responding to glutamic acid has been discovered, and fatty acids have recently been suggested as another taste (Yamamoto 1984, 2008; Han et al. 2019). The tongue has been shown to not be the sole organ of taste, but taste receptors on the palatal mucosa and pharyngeal mucosa can contribute, although there are differences among individuals; the palatal taste buds nonetheless need to be kept in mind clinically since they are susceptible to encroachment by full maxillary dentures. Furthermore, taste changes may occur in certain metabolic diseases and systemic disorders (e.g., Sjögren's disease) and pain conditions (e.g., burning mouth syndrome; Mott et al. 1993; Kolkka-Palomaa et al. 2015).

Finally, one of the outcomes of taste research over the past 100 y is the evidence that taste is crucial in determining and influencing food and fluid preferences and aversions, as well as playing an important role in nutritive, electrolyte, and energy balance (Han et al. 2019). Some tastes are innately determined and so can be difficult to modify. An example relevant to dentistry is our "sweet tooth" and the difficulty that dentistry and public health agencies have had in changing people's habits

and preferences, resulting in other approaches to mitigate the cariogenic potential of sweet foods and drinks (e.g., advocacy of personal oral health care, fluoridation). Nonetheless, our innate preference for sweet and aversion to sour and bitter can be influenced through learning and experience, as exemplified by many people's pleasurable experiences in drinking red wine, coffee, or beer. The ability to modify people's taste preferences and aversions has long been recognized by the food industry and is still well practiced (e.g., through advertisements in the media).

Chewing, Swallowing, and Related Sensorimotor Functions and Dysfunctions

By the 1920s, little was known of the neural mechanisms driving and controlling chewing, swallowing, and related orofacial sensorimotor activities. Nonetheless, the gross anatomy of the muscles and cranial nerve nuclei innervating them had generally been delineated, and some definition of related CNS circuits had been obtained by neuroanatomists and neurophysiologists, such as Cajal and Sherrington.

After 1920, technological advances allowed for monitoring brain activity (e.g., electroencephalography) and orofacial muscle activity (e.g., electromyography) during chewing, swallowing, speech, and related sensorimotor activities, in concert with devices for monitoring associated movements of the jaw, lips, or tongue in humans—showing, for example, different patterns associated with the particular craniofacial skeletal features and dentitional state of the individual (Moyers 1950; Moller 1966; Ahlgren 1967). Related studies during this mid-19th-century period in laboratory animals by Szentagothai (1949) and others used improved neuroanatomic methodologies to delineate some of the underlying CNS neural circuitry, and the subsequent use of histochemical and refined electrophysiologic methods allowed for the characterization of different muscle fiber types and activity patterns of single motor units in orofacial muscles (Dubner et al. 1978).

Subsequent investigations of trigeminal primary afferents, CNS neurons, and muscles in laboratory animals provided for further definition of the peripheral processes as well as the CNS mechanisms underlying orofacial sensorimotor behaviors (Nakamura et al. 1967; Jerge 1968; Kidokoro et al. 1968; Takata and Kawamura 1970). This period leading up to the 1970s saw the pioneering findings by Doty et al. (1967) and Dellow and Lund (1971) of central pattern generators (CPGs) in the brainstem that acted as a "chewing center" and a "swallow center" to provide the rhythmic or patterned motor activities characteristic of chewing and swallowing. The swallowing center was documented to be dependent on sensory inputs (e.g., from the oropharynx and larynx) for activating this CPG, whereas the chewing center was shown to be capable of functioning independently of sensory inputs. Nonetheless, subsequent research in humans, as well as animals, found that this CPG normally did utilize orofacial sensory inputs (e.g., from periodontal mechanoreceptors) to help refine and control the cyclic patterns characteristic of chewing movements (Dubner et al. 1978; Sessle 2006). The complex sensorimotor behavior of speech also utilizes orofacial sensory inputs for producing or refining speech patterns.

Other studies in this period documented afferent inputs and descending projections from higher brain centers (e.g., sensorimotor cortex) and their chemical mediators that influence the expression and control of jaw reflexes and the numerous other reflexes evoked by orofacial stimuli (Nakamura and Wu 1970; Chase et al. 1973; Olsson and Landgren 1980; Fig. 3). These findings have subsequently been complemented by studies in awake behaving animals (Lund and Lamarre 1974; Murray and Sessle 1992; Lin and Sessle 1994; Yamamura et al. 2002; Arce-McShane et al. 2014) showing the importance of descending projections to the brainstem from the sensorimotor cortex (e.g., Yoshida et al. 2009) in initiating or modulating orofacial sensorimotor behaviors, such as chewing, swallowing, biting, and tongue protrusion. In addition, some of the mechanisms and circuits by which chewing and swallowing operate as components of the feeding system have been further defined (also see Taste section), as have the neuronal properties of the CPGs, their chemical mediators, and the interneuronal and motoneuron pools with which they interact (Nakamura et al. 2004; Morquette et al. 2012). The recent advent of approaches such as brain imaging, biochemical analyses, and transcranial magnetic stimulation has allowed for additional insights into the sensorimotor patterns and underlying mechanisms that characterize chewing, swallowing, speech, and other oral sensorimotor functions and the many influences on them, such as pain, bite force, dental occlusal alterations, immune factors, stress, and dysfunctional states including temporomandibular disorder and sleep disorders (Trulsson et al. 2012; Lavigne and Sessle 2016; Kumar et al. 2018).

Of related clinical relevance is the recent documentation of the neuroplasticity of the orofacial sensorimotor system. Neuroplasticity of the orofacial region of the sensorimotor cortex and other CNS areas has been shown to be critical in learning and memorizing orofacial sensorimotor skills and in adaptation to changes in the orofacial region brought about by aging, injury, pain, and even loss of teeth and oral rehabilitative procedures such as implants (Avivi-Arber et al. 2011; Arce-McShane et al. 2014; Kumar et al. 2017; Avivi-Arber and Sessle 2018; Sessle 2019). The findings have clinical implications since plasticity can be tapped for learning, improving, or rehabilitating the orofacial sensorimotor skills of patients and their adapting to pain, loss of teeth, or other alterations in the face, mouth, or jaws.

This review would not be complete without some mention of the evolution of neuroscientific insights into another orofacial sensorimotor function—namely, salivation. By the 1920s, Pavlov had shown that salivation in dogs is accelerated by various conditioning stimuli (Schoenfeld 1976). Subsequently, salivation has been shown to be controlled by the brainstem superior and inferior salivatory nuclei. Parasympathetic innervation of the salivary glands is more prominent than sympathetic innervation, and whereas sympathetic stimulation (adrenergic activation) produces protein-rich saliva, parasympathetic stimulation (cholinergic activation) produces large quantities of saliva. Likewise, administration of the cholinergic

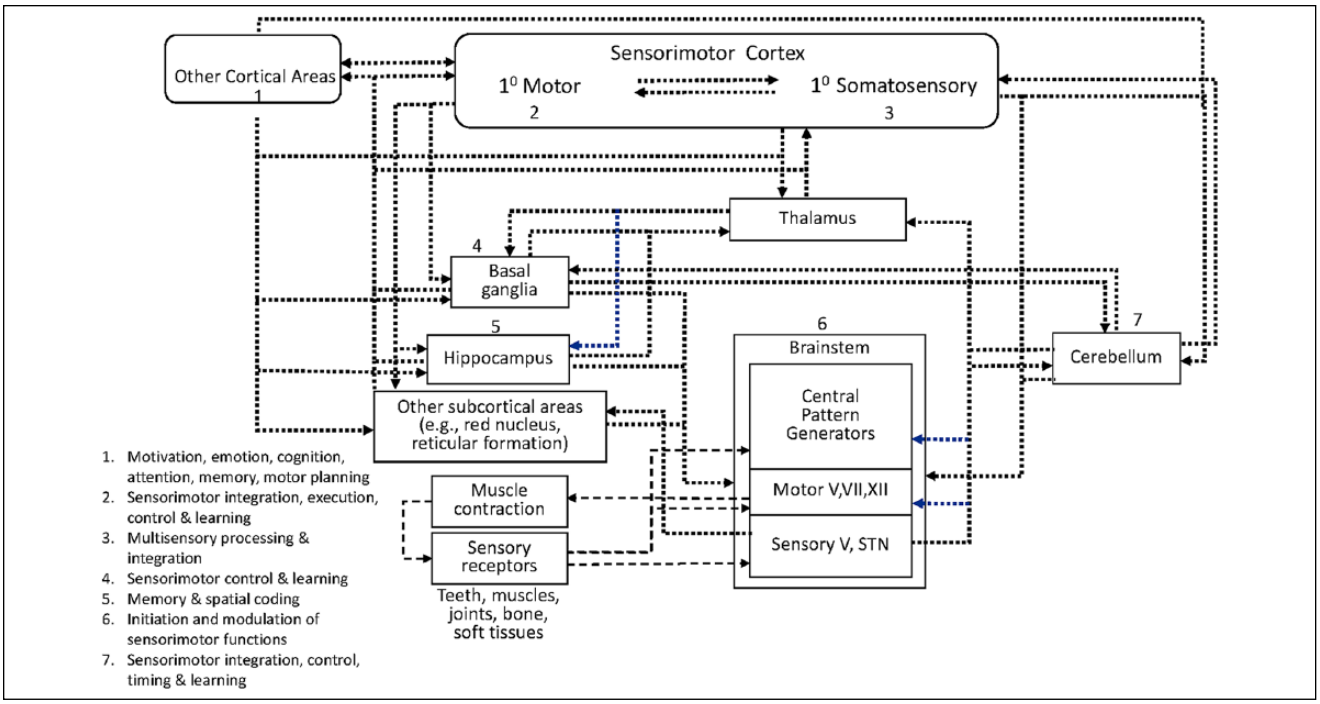

Figure 3. Major afferent inputs to and between sites in the central nervous system and efferent projections between central nervous system sites and to orofacial muscles. NTS, solitary tract nucleus; sensory V, trigeminal brainstem sensory nuclear complex; V, VII, XII, motor nuclei of the trigeminal, facial, and hypoglossal nerves. Reproduced with permission from Sessle (2019).

receptor agonist pilocarpine facilitates salivation, but noradrenalin administration attenuates it. Furthermore, stimuli such as taste and mechanical or thermal stimulation of oral mucosa or teeth induce saliva secretion (Satoh-Kuriwada et al. 2018). Higher CNS areas also can influence salivation; for example, electrical stimulation of the lateral hypothalamus has a facilitatory effect on preganglionic parasympathetic fibers responding to these stimuli (Proctor 2016). Most recently, many studies have focused on salivary gland regeneration and related molecular mechanisms; this research holds promise for the development of new therapies to treat patients suffering from dry mouth (Tanaka et al. 2018).

One final comment about the outcome of research into the orofacial sensorimotor system is that while the system shares many similarities with the sensorimotor system controlling muscle activities and movements in the neck, trunk, and limbs, several important fundamental differences exist between the systems (Avivi-Arber and Sessle 2018); thus, findings in one system cannot be assumed to apply to the other.

Conclusions and Future Perspectives

At the time that the *JDR* was established 100 y ago, little was known of the neural processes that contribute to orofacial functions. The rapid emergence of neuroscience as a scientific field relevant to dentistry has been the impetus for many studies, providing novel insights into the neural basis of orofacial functions. Consequently, we now have a much better understanding of pain and taste and sensorimotor functions, such as chewing, swallowing, and salivation, and this has proved important in improving diagnosis and management of pain and sensorimotor disorders. Given the expanded interest in this field and further technological advances undoubtedly to be made in molecular biology, genetics, artificial intelligence, and so on, the future holds much promise for further insights into mechanisms underlying these functions and disorders that will undoubtedly have clinical application in diagnosis and management in dentistry.

Author Contributions

K. Iwata, B.J. Sessle, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised manuscript. Both authors gave final approval and agree to be accountable for all aspects of the work.

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