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REVIEW

Neural Circuits

Neurostomatology: neologism or a paradigm change? A perspective evaluation

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Abstract

The stomatognathic system (SS) has gained higher visibility over the last decades due to emerging primary records evaluating its complex relationships with the central nervous system (CNS). Multiple anatomical and functional functions can be correlated with the SS, including its critical role in craniofacial development, sensory perception, and motor coordination. Despite its central role in neurosensory integration, its relationship with the central nervous system (CNS) remains underexplored in the neurological sciences. The present study aimed to revisit the major (but commonly unexplored) principles of jaw functional orthopedics (JFO) and evidence emerging academic foundation that supports the reframing of the SS within a generalized taxonomy of neural regulation and plasticity. We assessed whether the suggested terminology "neurostomatology" adequately reflects true conceptual scientific advancements or should be considered as a mere neologism. This study used principles of integrative synthesis of the literature, including evidence from multiple fields and medical specialties. Therefore, we collated information related to embryology, neural crest migration, cranial nerve distribution, neurotrophins signaling, bone mechanotransduction, and CNS-SS feedback loops. In addition, we emphasized our analysis and descriptive summarization on experimental and clinical results correlating mastication, neuroplasticity, and hippocampal function. The SS is derived from neural crest cells and is formed by a dense network of afferent and efferent neural pathways and connections, exhibiting a highly developed proprioceptive sensitivity property. The functional stimulation of the SS, especially related to the mastication activation, has been demonstrated to impact hippocampal activity, besides modulating neurotrophins expression and shaping bone architecture through cellular signaling networks. The collated evidence highlights SS as an active modulator of neural development, maintenance, and adaptation. Based on the various publications aforementioned, the authors conclude that the term "neurostomatology" is not solely a neologism, but depicts an existing paradigm shift in comprehending of stomatognathic system physiology. This expanded evaluation of literature and historical features related to the theme reinforces the fundamentals of JFO.

jaw functional orthopedics; mechanotransduction; stomatognathic system; stomatology

INTRODUCTION

The intricate and complex relationship between the stomatognathic system (SS) and the central nervous system (CNS) has been a central focus for all those dedicated to studying and justifying the practices adopted by jaw functional orthopedics (JFO). Neuro-occlusal rehabilitation, a therapy pioneered by Pedro Planas and his followers, emphasized the direct interface of the mouth-brain axis (1). However, many criticisms contrary to what was recommended by Pedro Planas, over time, led to discrediting his clinical observations. As Wilma Alexandre Simões stressed, monotony is not a characteristic of science, and time is responsible for transforming current certainties into either truths or fallacies (2). Recently, a publication from Zhejiang University, containing 261 references, provided a comprehensive review of the interface between SS and CNS (3). As suggested by Wu et al. (3), the nervous system and the SS (including structures such as the teeth, jaws, muscles of mastication, and temporomandibular joints) are interconnected and influence each other in development and disease (4). This interaction, sometimes referred to as the "brain-oral

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axis" correlates to the understanding that neurological conditions can affect oral health, and oral health issues can impact the nervous system (3). In another associate publication proposed by Wang et al. (5), the proposition of the term "neurostomatology" has taken place, primarily defined as an interdisciplinary field that explores the relationship between the nervous system and the SS (6). Notably, the terminology bridges neurology and dentistry, recognizing the significant impact neurological conditions can have on oral health and vice versa. This emerging field is important for understanding the complex interactions between the brain and the mouth, leading to better diagnosis and treatment of a range of oral and neurological conditions. Considering the relevance of this renewed insight on mouth-brain integration, the objective of this work is to highlight this vision by focusing on the foundation of the JFO approach. Through the subsequent topics presented in this article, we intend to determine whether the proposed name is merely a neologism or a real concept that challenges existing paradigms.

JAW FUNCTIONAL ORTHOPEDICS IS DIFFERENT FROM OTHER FORMS OF FUNCTIONAL ORTHOPEDICS

Jaw functional orthopedics (JFO) differs when compared with functional orthopedics of other parts of the body. The SS has unique and sui generis characteristics. For example, its embryological origin differs from the other part of the body (7–10). Bones and muscles of SS originate from ectomesenchymal cells of the neural crest, whereas bone and muscles of other parts of the body derive from the mesoderm. In addition, the innervation of SS structures is particularly specialized. Most cranial nerves are directly related to the SS, and when considering indirect relationships, all cranial nerves are involved with each other (7–10). Likewise, we must include some spinal nerves in this detailed analysis of connections (11) (Fig. 1). Cervical and trigeminal nerves share a convergence mechanism, where inputs from both nerve systems can influence and be influenced by each other in the brainstem and spinal cord, particularly in the upper cervical region. This interaction can lead to a strong connection between the two systems (12) (Fig. 1). Thus, the functional relevance of this area is undeniable. Furthermore, the somesthetic sensitivity of the SS ranks second in receptor density, surpassed only by the hands. Both have a large representation in the cortex, with the mouth located more anteriorly (toward the front of the brain) than the hand. This organization reflects the importance of these two body parts in sensory input and motor control. Furthermore, the somesthetic sensitivity of the SS ranks second in receptor density, surpassed only by the hands (Fig. 2) (13). JFO approaches highlight the need to look beyond the tooth. The primary focus of functional orthopedic therapy is the enhancement of mouth functions. Through the adequate execution of functions, the craniofacial shape is naturally sculpted (13).

EMBRYOLOGY OF STOMATOGNATHIC SYSTEM

To thoroughly understand the function-growth interface and craniofacial development, it is necessary to begin with embryology, as everything starts with the fertilization of the egg (oocytes). It is essential to follow this entire ontogenetic trajectory to better understand the peculiarities related to the craniofacial region. The first point to remember is that the embryological origin of the musculoskeletal structures in this region is completely different from that of the rest of the body, which influences the ability to perceive stimuli and respond to them in a completely differentiated way. The SS originates from the neural crest. The cells originating from the neural crest are divided into four groups: the cranial group, cardiac group, vagal group, and trunk group. Therefore, when we talk about craniofacial growth, we are referring to a specific group of neural crest cells that migrate to the cranial region and express genes distinct from the other groups (14, 15). It is extremely important to understand that genetic studies are highly advanced, and scientific

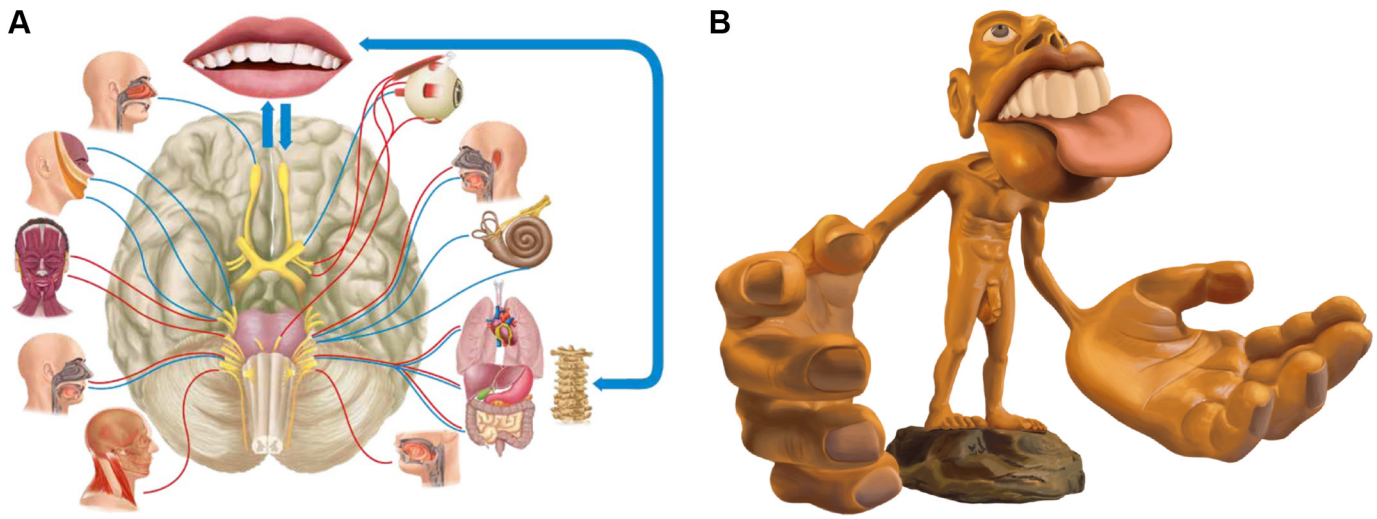


Figure 1. *A*: the relevance of the stomatognathic system (SS) in relation to the cranial and spinal nerves. In some way, the trigeminal system influences and/or is influenced by the other 11 cranial nerves and spinal nerves (figure from author's archives). *B*: Penfield homunculus modified by the authors. The SS (including teeth) is the second region of the body with highest density of sensitive receptors (9).

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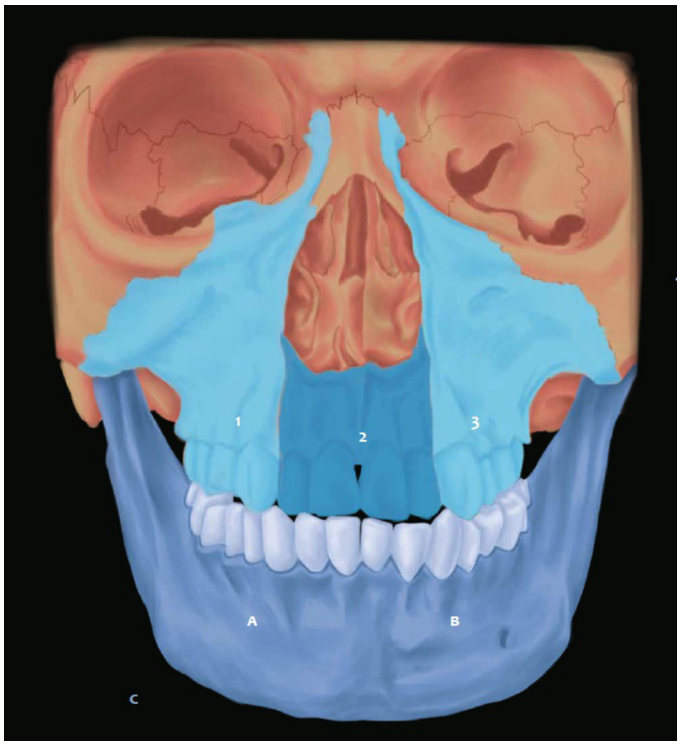


Figure 2. *C.* Origin of maxilla and mandible. They have a common origin in the first gill arch, but the maxilla has its central region originated from the frontonasal process that derived from the forebrain. Therefore, the maxilla has 3 differentiated sites of embryological origin (1–3), whereas the mandible has 2 differentiated sites of embryological origin (*A* and *B*). This will reflect on peculiar characteristics of innervation and consequently different responses to stimuli, generating 3 response fields in the maxilla and 2 in the mandible (image from author's archives).

knowledge has shown that gene expression is modulated by epigenetic factors from the intrauterine environment. Moreover, in addition to this modulation, there can be genetic variation known as "polymorphisms," meaning that the same gene can give rise to different phenotypes even without any specific epigenetic factor (16, 17). These findings allow us to understand that there is no absolute predeterminism in craniofacial growth. There is a basic genetic foundation, but it is essentially influenced by external factors, both intrauterine and extrauterine, which collectively modulate gene expression. This modulation can be influenced by functional activity, thereby determining the final shape of the craniofacial complex (18–20).

Returning to the focus on cell migration, the cranial neural crest cells give rise to the muscles, bones, and cartilages of the viscerocranium, most of the dermis of the face and neck, and the teeth (except for the enamel, which originates from the ectoderm). Therefore, except for enamel, the entire SS originates from the neural crest, giving it its distinctive characteristics inherent to its noble neural origin. For this reason, the type of musculoskeletal tissue response of the SS cannot be generalized to other areas of the body that originate from the mesoderm (middle layer of the trilaminar disk that gave rise to the embryo) (21). Despite the interface between the two regions, they exhibit completely different stimulus and response mechanisms due to their distinct embryological origin (22).

Initially, neural crest cells will migrate directly to the upper part of the stomodeum, and in the middle region of the stomodeum, they induce the differentiation of nearby cells, leading to the formation of branchial arches, which are critical in the development of the craniofacial region (7). Each branchial arch contains a cartilage, a vessel, and a nerve, and all the structures derived from that branchial arch are related to these three components, meaning that they are innervated by the corresponding nerve, vascularized by the associated vascular branch, and supported by the cartilage (at least for a period). Specifically, in the first branchial arch, the cartilage that supports is called "Merkel's cartilage." It initially functions as a primitive mandible, allowing the opening and closing of the embryonic mouth, enabling oral functions to begin at a very early intrauterine stage. By 6 wk of intrauterine life, alongside Merkel's cartilage, we perceive the condensation of mesenchymal cells, derived from the neural crest, due to the induction of differentiation into osteoblasts, marking the onset of mandible formation. The mandible forms laterally to Merkel's cartilage. That is, the mandible does not originate through endochondral ossification of Merkel's cartilage but through intramembranous ossification adjacent to it (23). At 7 wk of intrauterine life, this ossification process has already started, and by the time the mandible is fully formed, Meckel's cartilage will have involuted, with only small sites persisting in the coronoid process and the mental symphysis. The final parts of the cartilage, articulated with the skull, facilitate the opening and closing of the embryonic mouth, acting similarly to a joint found in primitive animals, namely "square bone joint." This joint functions like a hinge, allowing the primitive jaw to open and close. Concurrently, the maturation of the neural system is happening. In mammals, this final part is called as "incudomalleolar joint." The "incus" refers to an anvil, whereas the "malleus" associates with a hammer. Thus, it is already clear that this final part, comprising these two components, did not involute but instead gave rise to the first two ossicles of the ear, the malleus and the incus (24). The "incudomalleolar" joint remained and was incorporated into the formation of the middle ear, joining the "stapes," which ultimately originates from the second branchial arch. It is important to remember that trigeminal fibers will be commanding the malleus muscle and that the facial fibers will be commanding the stapes muscle (25). The perichondrium of Merkel's cartilage also does not involute but instead transforms into two important ligaments: the sphenomandibular ligament and the malleomandibular ligament, which extends from the malleus, passes through the petrotympanic fissure, and connects behind the articular disk within the temporomandibular joint cavity (26). When considering this embryological complexity, we can appreciate how intricately the structures of the ear and mouth are interconnected. By the 11- or 12th-wk intrauterine life, functions such as opening, closing, swallowing, and suction are already in progress. At this point, functions are being established in the intrauterine environment, and with each movement repetition, gene expression is stimulated, which, in turn, shapes the craniofacial structure (27).

We must not forget that for these functions to be performed, the first branchial arch differentiates into one

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branch that forms the lateral parts of the maxilla and another that forms the mandible. The central part of the maxilla originates from the forebrain, which differentiates into the frontonasal process. Subsequently, these three parts fuse to form the maxilla. Due to their embryonic origins, nerve branches in each of the five segments are different (28) (Fig. 2).

NEUROPLASTICITY AND JFO

If we are trying to understand the role of functions in growth and development, we must refocus on the nerve-muscle-bone interface. And within this interface, we cannot overlook the role of neurotrophins. To understand their importance in this relationship, we need to start with a brief historical overview of neurology. The brothers Santiago Ramón Cajal and Pedro Ramón Cajal were highly influential in the early 19th century in the study of nervous tissue, and today they are regarded as the "fathers" of neurology. They began studying nervous tissue using rudimentary microscopes, often using the frog optic nerve due to its large size, which made it easier to visualize. They made the first clinical report of the possibility of reconnection between two stumps of a cut nerve fiber, although at the time, they could not explain why it was happening (29). Many years later, Viktor Hamburger, a German researcher, conducted experiments with chicken embryos. At a very early stage of the embryo, he cut the wing stumps (where the wings joined the body) of an embryo and implanted them on the other side or in another embryo. Dr. Hamburger's objective was to observe whether the transplanted wing would function, but to his surprise, over time, the wing became functional! Perplexed by these findings, he found that the wing had become innervated by fibers extending from the spinal cord of the embryo (30). This unexpected result intrigued him a lot. He discussed these findings with Rita Levi-Montalcini, who was studying muscle tumors at the same time. She discovered that the muscle cells secreted a substance that attracted dendrites, which was posteriorly named neurotrophins or neural growth factor (NGF). For this discovery, she was awarded the Nobel Prize in Medicine. Over the years, they dedicated themselves to deepening the topic (31, 32), gathering information and realizing that the implanted wing in Hamburger's experiment was secreting neurotrophins, which caused the sensory and motor nerve fibers in the embryo's periphery to remain active, despite involuting as they usually would during embryogenesis. Through their work life, they discovered that every embryo has many more nerve fibers reaching the periphery than are present at birth. During the embryonic process, there is an involution of several nerve cells that have been generated, emitted their axons to the periphery, but had no longer function. In the case of the transplanted wings, when the fibers that reached the periphery were given a function, through the release of neurotrophins by the muscles of these wings, these nerve fibers remained. They did not involute. The other fibers that did not receive neurotrophins because the wing was excised involuted (33). The work of Dr. Rita Levi-Montalcini and Dr. Viktor Hamburger generated the foundation for understanding that muscle cells release factors that stimulate innervation (34). As innervation increases, organ functionality improves, which, in turn, releases more neurotrophins, enhancing the function even further. This phenomenon is fundamental in justifying functional orthopedic actions and principles. By inducing postural changes that activate muscle groups, neurotrophins are released, improving innervation and function.

What about the CNS? Do neurotrophins act there as well? Yes, but we are not yet at an advanced stage of therapeutic use of neurotrophins in the CNS because they do not cross the blood-brain barrier, and their administration needs to be in loco. There are several experimental proposals for routes of administration, but they are still in the early stages (35). However, another stimulation form present in the CNS has recently been described. Stem cells, particularly within some areas of the hippocampus, can transform into neurons when stimulated, promoting regeneration and improved function. Specifically, these stem cells are located in the dentate gyrus of the hippocampus (36). The hippocampus is responsible for functions such as reasoning, cognition, and learning, and has a direct relation to the limbic system (recognized as the emotions control center). Chewing is known to be a hippocampal stimulator. Therefore, efficient and powerful chewing is critical for brain health (37). Chewing under stressful conditions suppresses hippocampal hyperactivity and mitigates cognitive deficits induced by chronic stress (38). Having said that, the interface of brain-controlled mouth functions and craniofacial growth and development is of utmost importance. When functional orthopedic interventions generate sensory inputs, the CNS generates motor outputs that act on peripheral nervous system, improving muscle function and leading to the increased release of neurotrophins. There is a more extensive dendritic tree of motor neurons, enhancing muscle function progressively. Step by step, the muscle works harder and undergoes hyperplasia or hypertrophy, increasing the number of sarcomeres. This process causes tendons, fascia, and ligaments also to undergo hyperplasia and secrete more matrix, leading to bone growth (39). Furthermore, optimizing mouth functions, essentially on mastication, significantly improves hippocampal activity, with a significant impact on the individual's health-related outcomes and quality of life (40).

BONE CELLULAR CONNECTION NETWORK AND NEUROTRANSMITTERS

Bone tissue formation is entirely dependent on mechanical stimulus, since the moment of embryonic cell differentiation, which is why muscles precede bones in embryogenesis. When a pluripotent stem cell differentiates into an osteoprogenitor cell and then into a preosteoblast, it assumes highly proliferative and secretory characteristics (41). The preosteoblast matures into an osteoblast, which produces everything needed for self-regulation and the regulation of osteoclastic function. Once the osteoblast has secreted enough matrix (collagen and other proteins) and phosphorylated it (through alkaline phosphatase enzymatic action) (42), matrix mineralization begins. This mineralized matrix surrounds the osteoblast, which then changes into an osteocyte (41). However, during this process of matrix proliferation and secretion, bone cells emit long cytoplasmic extensions that interconnect, thus forming the complex cellular connection network (CNN). Many authors call it the bone tissue dendritic network (43). The CCN has an important role in the transmission of the mechanotransduced signals. Bone cells can

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perceive minimal mechanical disturbances, and this process generates an intracellular calcium wave that modifies gene transcription. Although two membrane receptors involved in this process have been described, it is important to stress the existence of others. Recently, another calcium channel called Piezo1 has been identified and associated with a critical role in gene transcription alteration in bone cells (44). Whatever the calcium channel is involved, the change in gene expression induced by the increased intracellular calcium only has a biological effect if the signal is amplified across a large number of cells. Only through this amplifying process can the region experience increased or decreased osteogenesis, depending on the stimulus received (45). The mechanisms by which this intracellular calcium wave propagates have been studied extensively over the years. Moss first described one such mechanism in the late 1990s, which involves a GAP junction. Bone cells connect through a protein called Connexin 43, which functions like a valve, opening and closing the passage between cells (46). This protein allows the calcium to flow from one cell to another, triggering the biochemical cascade even in cells that were not mechanically stimulated a priori. This amplifies the region's response to the stimulus. In 1998, Skerry's team (47) began studying another mechanism of calcium signaling in bone tissue, which ended up generating the model proposed by Mason, published in 2004. This mechanism is similar to neuronal action potentials, with glutamate as the major neurotransmitter (48). A feature mediated by glutamate in the CNS is the desensitization phenomenon, which also occurs in the CCN. Constant stimuli tend to decrease membrane sensitivity in bone cells, which is why intermittent stimuli are much more effective in generating osteogenesis (49–52).

TOOTH SENSITIVITY

Where is tooth sensitivity located? Is there sensitivity in the enamel region? At first glance, we might answer no, because there are no nerve endings in the enamel. However, as the tooth is a rigid structure connected to extremely sensitive soft structures, even a slight mechanical disturbance in the enamel can be perceived with exquisite detail by the periodontal ligament (53, 54) and the pulp (55). The discriminative ability of the tooth is so great that we can sectorize the dental crown (53, 54).

The division of the dental crown into thirds, vertically, follows the pattern of tooth formation columns that create the mamelon (56). Differentiated receptive fields are present both vestibularly and lingually. Horizontally, we can divide the crown into cervical, middle, and incisal thirds. This permits us to didactically establish nine receptive fields on the tooth crowns. These receptive fields refer to sensations perceived by the pulp and, mainly, the periodontal ligament. In the dental pulp, we have a series of nerve ramifications that penetrate the dentin canaliculi, terminating at the amelodentinal junction. No nerve branches extend into the enamel (57). Therefore, touching the enamel surface does not make direct contact with any nerve endings. Nonetheless, the touch on the crown propagates through the laws of physics (which can be quantified with finite element studies) (58), and can be perceived, as mentioned, by the nerve endings of the pulp and periodontium. It is important to note that we are not discussing nociceptors, but rather proprioceptors, which have been neglected in previous studies that focused primarily on pulp and periodontal pain sensitivity (55). To sum up, when the tooth enamel is touched, it does not directly perceive the stimulus, but the physical dissipation of the touch across the tooth surface is sensed by the nerve receptors in the pulp and, more finely, by those receptors around the root of the tooth in the periodontal ligament. The periodontal ligament has a hydraulic system that is highly sensitive to any mechanical disturbance, containing axonal specializations that generate afferent signals to the CNS (59). Periodontal receptors, which are an important part of proprioceptive reflexes, are similar to those found elsewhere in the body but assume their own morphology and physiology, due to the need for fine control of mandibular movements. There are nerve endings in the periodontal ligament that make spontaneous discharges to the CNS, 24 h a day, informing the mandible's spatial location of the brain. There are encapsulated receptors capable of finely regulating masticatory force and spiral receptors that react to relax the elevator muscles in response to sudden, excessive load (60, 61). These three types of periodontal receptors enable the enamel with the possibility to finely locate any mechanical stimulus applied to the crown. Again, nociceptors are not involved in this process. It is important to emphasize that the participation of the periodontal ligament in the perception capacity of the tooth is much more relevant than the dental pulp. Even endodontically treated teeth maintain their ability to contribute to fine motor control of mandibular movements (62). On the other hand, teeth with no periodontal ligament (ankylosed) have a degeneration of their ability to perceive the mechanical signal, starting to function instead through a process known as osteoperception. This is particularly similar to the perception of dental implants and is infinitely less discriminative when compared with a tooth with an intact periodontal ligament (63–65).

DISCUSSION

In this review, we explored a wide range of elements—spanning from embryological origins to mechanotransduction signaling pathways and CNS-associated plasticity—which offered the reader strong and converging evidence that the SS functions within a dynamic and complex neural framework that goes far beyond usual dental or orthopedic principles. The proposed discussion around "neurostomatology," therefore, should not be considered as a mere linguistic novelty but as a needed and technically justified conceptual/scientific evolution.

To note, the neural crest-derived embryogenesis of the SS apparatus, with its differential genetic mechanisms of regulation and epigenetic responsiveness, promotes several major foundational differentiations from distinct anatomical systems (14, 21). The unique innervation (through cranial and cervical nerves) and associated greatly specialized proprioceptive structures further highlight its neurological importance (66). In addition, the evident interaction between oral functions (mostly mastication) and upper CNS centers (i.e., hippocampus) shows bidirectional regulation, producing both local motor functions and cognitive, memory-related, and stress responses (67, 68). These correlations create a

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solid neurofunctional link that justifies a reclassification of the SS within a directly related neurobiological taxonomy (39). Finally, the association of neurotrophin-modulated pathways and the demonstration of systemic responses to functional orthopedic mediations strengthen the idea that the SS is a highly neuroresponsive system qualified to trigger long-range neuromodulatory and plastic effects (11, 33).

Therefore, based on the combination of the aforementioned factors, the evidence collated in this review supports the proposition that "neurostomatology" encapsulates a true paradigm shift, calling for a new, transdisciplinary-based framework, involving not only neurology specialists but also dental experts, craniofacial orthopedics, and neuroscientists.

CONCLUSIONS

Taking into account the aforementioned topics and discussions, it is easy to understand the unique characteristics of the formation, growth, and development of the SS, as well as its intricate relationship with the CNS. The stereognosis and high density of proprioceptors, mechanoreceptors, and nociceptors enable the SS to function as a highly sensitive and discriminative organ. Its vast network of afferent and efferent pathways, connected to the CNS through important tracts, allows us to conclude that the adoption of the term "neurostomatology" is not just a neologism, but in fact brings with it an important paradigm shift in the understanding of the interface between the CNS and the SS based on the associated relevance in establishing the correct functioning of the organism. The adoption of this term demonstrates the recognition of the science that studying the SS goes far beyond focusing solely on the oral region; it requires expanding our understanding to include the complex neural connections involved in its physiology.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.V. and P.V. prepared figures; R.V., I.J.B.d.N., and P.V. drafted manuscript; R.V., I.J.B.d.N., and P.V. edited and revised manuscript; R.V., I.J.B.d.N., and P.V. approved final version of manuscript.

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