HHS Public Access

Author manuscript

J Dent Res. Author manuscript; available in PMC 2025 October 28.

Published in final edited form as:

J Dent Res. 2026 February ; 105(2): 195–206. doi:10.1177/00220345251376295.

Bridging Temporomandibular Joint Structure, Function, and Pain: An Integrated Multiscale Perspective

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Abstract

The temporomandibular joint (TMJ) features unique tissue structures that support its complex functional demands. Alterations in these structures are often linked to jaw dysfunction, with pain being one of the most prevalent symptoms. However, the mechanisms underlying TMJ pain and its relationship with structural deterioration or functional impairment remain poorly understood. A comprehensive understanding of the interplay between TMJ structure, function, and pain is essential for uncovering disease mechanisms and developing effective therapies. To date, TMJ research in humans and animal models has been predominantly conducted in separate domains of structure, function, and pain, limiting integrative insights. Clinical studies also show

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AUTHOR CONTRIBUTIONS

P. Chen, J.S. Lee, and H. Yao contributed to the conception, design, and data acquisition, drafted and critically revised the manuscript; M.C. Embree, M.K. Chung, B.A. Winkelstein, and E.J. Granquist contributed to the conception and design, and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

DISCLAIMER

This research was supported in part by the Intramural Research Program of the National Institutes of Health (NIH). The contributions of the NIH author were made as part of her official duties as an NIH federal employee, are in compliance with agency policy requirements, and are considered works of the US government. However, the findings and conclusions presented in this article are those of the authors and do not necessarily reflect the views of the NIH or the US Department of Health and Human Services.

inconsistent correlations among joint structural changes, jaw dysfunctions, and craniofacial pain, complicating diagnosis and treatments. This review aims to bridge these traditionally fragmented areas by synthesizing current knowledge across macroscopic and microscopic scales in both human and animal models. TMJ diseases involve spatially proximate cellular, extracellular, and neural components that undergo multiscale, spatiotemporal changes. These components experience complex mechanical loading during joint movement, triggering mechanical, neural, and immune responses that interact bidirectionally to influence TMJ integrity and pain. In turn, the brain modulates motor output and autonomic function, further impacting joint mechanics and cellular and nociceptive responses. To holistically and quantitatively assess these spatiotemporal dynamic processes, we propose a multiscale and multiphysics framework that integrates joint and tissue biomechanics, biochemical signals, cellular responses, nociception, and psychosocial influences. Realizing this vision requires a transdisciplinary effort and the development and adaptation of advanced methods to study TMJ at unprecedented resolution and details. By unifying structural, functional, and pain-related data, this integrated multiscale approach holds promise for elucidating new mechanisms of TMJ development, disease onset and progression, and pain chronicity. Ultimately, it may guide more effective diagnostics and treatments, including the combined use of physical therapy, neuromodulation, and biologically targeted interventions.

Keywords

temporomandibular joint disorders (TMD); biomechanics; nervous system; extracellular matrix (ECM); cell-matrix interactions; computer simulation

INTRODUCTION

Temporomandibular disorders (TMDs) are a set of diseases involving the temporomandibular joint (TMJ), muscles, and tissues of the jaw, impacting over 11 million U.S. adults (National Academies of Sciences et al. 2020). Many individuals with TMD experience TMJ problems, which are categorized as TMJ disorders. Pain from TMJ (arthralgia), joint structure alterations (e.g., disc displacement, degenerative joint disease), and restricted joint function (e.g., limited opening), frequently co-occur and impair quality of life. However, determining causal relationships among these factors is challenging. For example, pain symptoms are not always associated with the structural changes seen with magnetic resonance imaging (MRI) or cone-beam computed tomography (CBCT), as only 25%–55% of TMD patients show degenerative changes in the TMJ (Chung et al. 2023; Ita et al. 2022). This discordance between joint structure and pain has been a source of confusion and frustration for both patients and clinicians, complicating diagnoses and effective treatments.

The TMJ is one of the most frequently used joints in the body, playing a crucial role in daily activities such as speaking and eating. Its movements uniquely combine both translation and rotation that create a demanding mechanical environment, prompting extensive study of TMJ structure and biomechanics. That research has primarily focused on investigating the catabolic and anabolic activity of joint tissues and their correlation with joint function and disease progression (Nickel et al. 2018). However, despite pain being the primary reason

patients seek medical care for TMJ disorders, it has not been well integrated into these studies. In contrast, TMJ pain research has largely concentrated on the central nervous system and symptomatic outcomes, often overlooking the role of TMJ tissues themselves (Slade et al. 2016). Given that TMJ pain involves both peripheral and central components, this gap further limits our understanding of TMDs. Recent efforts have proposed a more integrated approach, simultaneously examining joint structure and pain (Chung et al. 2023; Sperry et al. 2017). However, the causal relationships between joint structure, function, and pain remain poorly understood, which poses a hurdle for developing a comprehensive management strategy for TMD involving structural repair, functional rehabilitation, and pain management (Fig. 1).

As a whole organ system, each TMJ component is essential for joint function, and injury or disease affecting any part can disrupt jaw movement. TMJ tissues have well-organized structures, such as delicate collagen fiber networks, designed to meet functional demands. However, abnormal loading due to injury or degeneration can lead to macroscale structure changes and microdamage, compromising tissue integrity, reducing mechanical strength, and impairing joint function (Nickel et al. 2018). Furthermore, many TMJ tissues are innervated by pain-sensing nerve fibers capable of detecting mechanical and biochemical changes within joint microenvironment (Perry and Emrick 2024). These nerve fibers generate nociceptive signals, which are transmitted to the central nervous system, where pain is perceived. Additionally, nerves interact with joint tissues by secreting signaling molecules that influence joint structure and function (Chen et al. 2024). Understanding the spatiotemporal interplay between TMJ structure and nociception is crucial for uncovering TMJ disease and chronic pain mechanisms. However, many microscale changes are undetectable using standard clinical imaging modalities, such as MRI or CBCT, limiting the correlation between symptoms and radiographic findings.

This review explores TMJ structure, function, and pain from a multiscale perspective. The goal is to integrate changes across scales to advance understanding of TMJ disorders. This review highlights TMJ structure, function, and innervation in health and disease and explores their crosstalk, including the influence of psychosocial factors. A conceptual framework is presented to illustrate these interactions. Finally, we propose a quantitative structure-function-pain research model and discuss its clinical implications and key knowledge gaps for future studies.

TMJ STRUCTURE AND FUNCTION IN HEALTH AND DISEASES

Despite growing research, the precise timing, location, and triggers for TMJ disease initiation remain poorly defined. This section reviews the macroscale and microscale structural and functional characteristics of the TMJ and examines how they are altered in disease states to facilitate an integrated understanding of TMJ diseases.

Joint structure and function in health

The TMJ comprises mandibular condyle, glenoid fossa, articular disc, retrodiscal tissue, synovial membrane, joint capsule, adjacent ligaments, and associated muscles, each contributing to joint function (Fig. 2A, Fig. 2B, and Table 1). The three-dimensional

(3D) shape and morphology of the TMJ affect joint development and function (Nickel et al. 2018). In adults, intrinsic sex-specific differences in TMJ tissue morphology have been identified, independent of overall skull size (Coombs et al. 2019). Furthermore, the 3D morphology of muscle attachment sites also exhibits sexual dimorphism (She et al. 2021). These morphological differences between sexes influence joint biomechanics and may contribute to variations in TMJ function and susceptibility to dysfunction.

TMJ tissues are porous and viscoelastic, with a biphasic structure comprising a fluid phase of water, solutes, and ions, and a solid extracellular matrix (ECM) phase of collagen, glycosaminoglycans (GAGs), elastin, and resident cells (Table 1). Quantitative data on their precise biochemical composition remain limited. The articular disc and condylar cartilage have been commonly investigated. Studies have demonstrated spatially heterogeneous ECM composition and organization in TMJ tissues of both humans (Wright et al. 2016) and animals (Chandrasekaran et al. 2017; Shi et al. 2013), contributing to their region-specific mechanical behaviors (Fig. 2C). In contrast, relatively few studies have quantitatively investigated retrodiscal tissues, synovial membranes, capsules, and ligaments, highlighting the need for further research into these structurally and functionally important TMJ components.

Joint structure changes in diseases

Alterations in TMJ macro- and microscale structures compromise tissue mechanical properties and can impair joint function (Table 1). Macroscopic structural changes such as bony abnormalities and disc displacement are frequently observed in patients with TMD. Notably, TMD is often associated with smaller mandibles and flatter condyles, leading to increased joint loading and elevated risk (Sun et al. 2024). Preclinical TMJ osteoarthritis models show cartilage degeneration, bone edema, bone loss, deformation of the condyle and disc, and inflammation (Embree et al. 2015).

At the microscopic level, the loss of proteoglycans in condylar cartilage is recognized as a hallmark of TMJ pathology (Embree et al. 2015). Second harmonic generation (SHG) imaging has revealed disorganization of ECM collagen fiber architecture in diseased rabbit TMJ discs (Zhang et al. 2021). Complementary electron microscopy studies have identified ultrastructural collagen alterations, including abnormally thick collagen fibrils, in a rat model (Cui et al. 2019). Additionally, the pericellular matrix has shown increased expression of collagen VI and aggrecan in mechanically overloaded, painful TMJs in rats (Franklin et al. 2022). Beyond ECM alterations, pathological shifts in TMJ cell phenotypes and behaviors have been observed under diseased conditions, disrupting the chondrogenic and osteogenic activities necessary for maintaining joint homeostasis (Ruscitto et al. 2023). However, most studies have assessed these structural changes at advanced stages of joint degeneration, leaving the initiating events of TMJ disease poorly understood. Moreover, while structural and morphological alterations have been the primary focus of most studies in this field, the underlying mechanisms of TMJ-associated pain remain relatively understudied, limiting our understanding of the relationship between tissue degeneration and pain in TMD.

TMJ INNERVATION AND NEURAL PLASTICITY IN DISEASES

The precise origin or source of pain in TMJ diseases remains unclear, but clinical evidence strongly implicates the joint as a primary contributor. This is supported by: (1) clinical diagnosis is often based on pain and dysfunction localized to the TMJ (Schiffman et al. 2014); (2) symptom relief following local interventions like arthrocentesis (Tang et al. 2025); and (3) significant pain reduction after total TMJ replacement in severe cases (Zou et al. 2018). Since pain arises from sensory nerve terminals, TMJ innervation is critical to pain sensation. This section explores the spatiotemporal organization of TMJ innervation at both macro- and microscale levels to better understand its role in joint pain and dysfunction.

Macroscale TMJ innervation pathway

The mandibular nerve from the trigeminal ganglion innervates the lower jaw and TMJ (Fig. 3A). A recent study found that the human TMJ is primarily innervated by the auriculotemporal nerve posteriorly, the masseteric nerve anteriorly, the posterior deep temporal nerve anteromedially, and a TMJ branch originating directly from the mandibular nerve medially and observed subject variations (Fig. 3B) (Kucukguven et al. 2022). Despite ongoing efforts to map the innervation topography of the TMJ and its associated musculature, controversial observations remain in the literature, which warrants further studies to fully elucidate and confirm the macroscopic innervation pathways of individual TMJ tissues. Moreover, data on the macroscopic TMJ innervation topography in animals remains limited. Retrograde tracing studies have shown that, in rats, TMJ innervation comes not only from the trigeminal ganglion but also from autonomic ganglia, including the superior cervical, stellate, otic, and sphenopalatine ganglia, as well as vagal ganglia and dorsal root ganglia at levels C_2–C_5 (Uddman et al. 1998).

Microscale TMJ innervation spatiotemporal profile

Both sensory nerves (calcitonin gene-related peptide (CGRP) and substance P (SP) immunopositive) and autonomic nerves (tyrosine hydroxylase (TH), neuropeptide Y (NPY), and vasoactive intestinal peptide (VIP) immunopositive) have been detected in TMJ tissues except cartilage (Alfaro and Akopian 2025; Alfaro et al. 2025; Kido et al. 2001; Ma et al. 2025; Morani et al. 1994; Shinoda et al. 2003; Tahmasebi-Sarvestani et al. 2001) (Table 1). However, innervation of TMJ ligaments remains poorly studied, and reports on autonomic innervation of the synovial membrane and joint capsule are inconsistent (Kido et al. 2001; Tahmasebi-Sarvestani et al. 2001). The innervation of the TMJ disc is also controversial, largely due to ambiguities in defining the anatomical boundaries of the disc (Kido et al. 1993). Furthermore, the precise quantitative distribution of different nerves in TMJ tissues remains poorly documented. In mouse and rat TMJ tissues, 70%–80% of nerve fibers have been identified as CGRP+ (Alfaro and Akopian 2025; Ueki et al. 2003). A recent RE-JOIN study has also quantified innervation of human retrodiscal tissues from TMD patients (Alfaro et al. 2025). Although CGRP is a well-established marker of sensory nerves, it is also expressed in other populations such as neurons in the nodose ganglia (Uddman et al. 1998), complicating the nerve classification and quantification. Moreover, recent single-cell sequencing studies have uncovered subtypes of trigeminal sensory neurons, as reviewed by Perry et al. (Perry and Emrick 2024), providing additional molecular markers

to further phenotyping TMJ innervation. Studies have started to investigate the subtypes in TMJ tissues (Alfaro and Akopian 2025; Sato et al. 2018). However, their functional roles in TMJ development and disease progression remain to be determined.

The spatiotemporal distribution of nerve fibers within TMJ remains largely unexplored. In the human TMJ disc, nerves are predominantly localized to the peripheral regions, with greater nerve density in the anterior and posterior areas, while the central region remains consistently non-innervated during adolescence and adulthood. Similar patterns have been observed in rats (Kido et al. 1993). Prenatal and postnatal TMJ innervation are summarized in the Appendix. Moreover, distinct spatial distributions of sensory and autonomic nerves were found in the rat TMJ (Kido et al. 2001). However, these studies are primarily based on histological analysis of two-dimensional (2D) tissue sections, providing limited spatial context, lack accuracy in capturing 3D nerve architecture, and cannot resolve neural connectivity between TMJ tissues. To address these limitations, our recent work employed tissue clearing and 3D imaging to map the innervation of the entire mouse TMJ, providing high-resolution visualization of joint-wide innervation and inter-tissue neural connectivity (Fig. 3C).

Microscale TMJ innervation plasticity in diseases and injury

Limited studies have investigated the effects of TMJ diseases or injuries on microscale nerve structural changes in joint tissues, with inconsistent findings (Table 1). In a rat model of TMJ arthritis induced by complete Freund's adjuvant (CFA) intra-articular injection, protein gene product 9.5 + (PGP9.5+) and CGRP+ nerve length and density were significantly increased in the arthritic TMJ disc (Shinoda et al. 2003). This result aligns with the findings of a recent CFA-induced mouse model, which reported increased TMJ innervation in retrodiscal and synovial tissues but no significant changes in bone marrow or disc tissues (Jariyasakulroj et al. 2025). However, in a surgically induced TMJ arthritis sheep model, PGP9.5+ and CGRP+ nerve densities were significantly reduced in the joint capsule of arthritic animals compared to controls (Tahmasebi-Sarvestani et al. 2001). Moreover, a study in growing rats found a significant increase in the number and density of CGRP+ nerve fibers in TMJ discs after six weeks on a liquid diet, a condition that simulates decreased joint loading (Takei et al. 2008). However, a recent unilateral anterior crossbite mouse model designed to induce excessive TMJ loading demonstrated increased innervation at the osteochondral junctions of the TMJ condyle (Ma et al. 2025). Additionally, increased CGRP+ innervation has also been observed in masseter muscles of rats with myositis (Carleson et al. 2004) and in synovial membranes of human patients with internal derangement (Sato et al. 2004). Variability in findings across studies may be attributed to differences in species, disease induction methods, and the specific tissues or regions analyzed. Additionally, discrepancies may arise from differences in the timing of evaluation, whether during the acute or chronic phase of disease.

The mechanism underlying neural remodeling in TMJ remains unclear. Studies in knee joints suggest factors like nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophins, fibroblast growth factor, and glia-derived growth factor promote nerve growth and sprouting, while semaphorin 3C and high concentration NGF can cause

nerve degeneration and retraction (Mathew et al. 2024). Additionally, mechanical loading can induce nerve injury via microtubule disruption (Coppini et al. 2024). Further studies are needed to clarify TMJ neural remodeling mechanism.

More research is needed to differentiate TMJ innervation patterns in acute versus chronic pain conditions. The sexual-specific differences in TMJ innervation and neural remodeling also warrant further investigation. Importantly, it is not only the quantity but also the quality (e.g., receptor expression and intracellular pathways) of the TMJ innervation impacts the pain sensation. Examining the sensitization of the TMJ nerves will be critical to understanding the TMJ pain mechanism. Moreover, most studies are conducted in animals. Given the intrinsic anatomical and physiological difference between animal and human TMJ, it remains to be determined whether similar findings can be translated to humans.

CROSSTALK AMONG NERVES AND JOINT STRUCTURES

Nerves are embedded within TMJ tissues, where they closely interact with the ECM, resident joint cells, and immune cells. Nerves and resident cells are all mechanosensitive and share receptors for neuropeptides/neurotransmitters, cytokines, and growth factors (Grässel and Muschter 2017; Pinho-Ribeiro et al. 2017). As the jaw moves to perform its oral function, each joint tissue is subjected to varying mechanical loadings, inducing ECM responses like tissue deformation, interstitial fluid flow, hydrostatic pressure changes, and the transport of soluble nutrients and signaling molecules (Nickel et al. 2018). These biomechanical stimuli activate resident cells and nerve fibers, initiating a cascade of downstream biological events such as cytokine releasing and nociceptor activation (Grässel and Muschter 2017). Moreover, excessive mechanical loading can cause tissue microdamage and promote ECM turnover. Elevated catabolic activities, often reflected in an imbalance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), contribute to ECM degradation and the generation of bioactive fragments. These ECM fragments can further stimulate nociceptive nerve fibers. Indeed, MMP-1 and MMP-9 in human TMJ tissues is positively correlated with pain (Ita et al. 2022). Activated nerve fibers release neuropeptides/neurotransmitters that modulate joint cell behavior, creating bidirectional communication. Additionally, joint cells and nerves also interact with components of the innate immune system, collectively influencing tissue integrity and pain sensation (Pinho-Ribeiro et al. 2017). Nociceptive signals are relayed to the central nervous system, where pain is perceived. In turn, the brain modulates motor outputs to adjust muscle activity and tune autonomic functions through autonomic nerves, affecting joint mechanics, function, and cellular responses (Cairns 2022; Murray and Sessle 2024). Figure 4 outlines the interactions between joint structure, function, and pain. This section summarizes these interactions in the TMJ, drawing insights from other joints like the knee and spine.

Tissue structure impact on neuronal excitation

The ECM organization of joint tissues plays a critical role in modulating the activation of nerves embedded in these structures. In an in vitro neuron-collagen construct model, the neuron activation was found to correlate with collagen fiber realignment (Zhang et al. 2016). Subsequent studies demonstrated that aligned collagen constructs induced significantly

higher neuronal excitability than randomly organized matrices under loading (Zhang et al. 2018). Computational modeling studies further supported this, showing that mechanical stress and strain distributions on neuronal surfaces vary depending on the surrounding ECM configuration (Zarei et al. 2017). Moreover, ECM organization and composition govern the transport properties of signaling molecules, shaping the local biochemical environment and thereby influencing nociceptive signaling (Chen et al. 2021). In the TMJ, molecular diffusion is highly anisotropic and sensitive to loading conditions (Shi et al. 2013; Wu et al. 2019). Sustained mechanical loading can restrict nutrient transport and cause the accumulation of metabolic byproducts such as lactate, resulting in decreased local pH and tissue acidosis (Nickel et al. 2018; Wu et al. 2019), a biochemical milieu known to sensitize sensory nerves and contribute to joint pain.

Excessive mechanical loading or joint injury leads to ECM breakdown through microdamage or enzymatic degradation, resulting in the generation of bioactive ECM fragments. These include low-molecular-weight hyaluronic acid (LWHA), tenascin C, fibronectin, and aggrecan, as reviewed by Lambert et al. (Lambert et al. 2020). Such ECM fragments can directly activate nociceptive nerves. For instance, LWHA has been shown to induce mechanical hyperalgesia (Ferrari et al. 2016). Similarly, aggrecan fragments (32-mer) have also been found to directly excite nociceptive neurons, mediating knee joint pain (Miller et al. 2018). Beyond their direct effects on nerves, ECM fragments also activate innate immune responses and interact with joint cells, such as chondrocytes and synoviocytes, causing inflammation and release of pro-algesic cytokines and pain mediators, such as nerve growth factors and chemokine (C-C motif) ligand 2 (CCL2), to further sensitize sensory nerves and contribute to joint degeneration (Miller et al. 2019). Moreover, abnormal mechanical loading can directly stimulate joint cells to release pro-algesic signaling molecules, establishing a feed-forward loop that amplifies nociceptive signaling and accelerates tissue degradation (Miller et al. 2019). While the specific contribution of joint structural and molecular changes to nociception has been explored in other joints such as the knee, further investigations are needed to determine whether these findings are conserved in the TMJ or if unique, joint-specific mechanisms are involved in TMJ pain.

Resident cellular and molecular impact on nerves

Resident joint cells and immune cells closely interact with nerve fibers and regulate neural activity through the release of various signaling molecules. These mediators include axon guidance factors (e.g., semaphorin 3A and netrin-1), neurotrophins (e.g., NGF and BDNF), inflammatory cytokines (e.g., interleukin-1β (IL-1β), IL-6, prostaglandin E2, tumor necrosis factor alpha, and histamine), and neuropeptides (e.g., CGRP and SP) (Pinho-Ribeiro et al. 2017). Elevated levels of several of these bioactive factors have been detected in the synovial fluid of TMD patients and are positively correlated with pain severity (Shrivastava et al. 2021). These mediators can activate sensory nerves, modulate their gene expression profiles and secretory activity, promote nerve sensitization, and alter the local chemical microenvironment, thereby contributing to TMJ pain pathophysiology.

Neural impact on joint tissues and cells

Sensory nerves regulate the homeostasis of joint cells, including mesenchymal stem cells, osteoblasts, osteoclasts, chondrocytes, and synoviocytes, as recently reviewed by Chen et al. (Chen et al. 2024). This neural regulation is mainly achieved through cytokines and neuropeptides, such as CGRP and substance P (SP), mediating joint cell metabolism and controlling the synthesis and turnover of ECM proteins. Increased concentration of CGRP and SP in TMJ synovial fluid and tissue has been observed in patients with TMJ arthritis (Sato et al. 2004). A recent study has also shown that intra-articular overexpression of CGRP causes pathological changes in TMJ structure (Brouxhon et al. 2022). Beyond direct effects on joint cells, neuropeptides and other neurotransmitters can also activate the immune cells, initiating secondary pro-inflammatory effects (Yi et al. 2021) and contributing to joint degeneration. Furthermore, emerging evidence suggests that sensory nerves are involved in regulating craniofacial development, such as tooth morphogenesis (Pei et al. 2023), and orthodontic tooth movement (Wang et al. 2025).

Autonomic nerves also modulate joint cell activities. Norepinephrine, released by sympathetic nerve, has been shown to promote osteoclastogenesis and contribute to bone loss during the progression of TMJ osteoarthritis (Jiao et al. 2015). Additionally, norepinephrine can activate sensory nerves and promote axonal growth, contributing to pain in TMJ disease (Ma et al. 2025). Moreover, NPY inhibits mesenchymal progenitor cell differentiation and mature osteoblast activities, thereby reducing bone formation. In contrast, VIP promotes bone formation by decreasing osteoclast formation (Grässel and Muschter 2017). Future studies are warranted to elucidate the role of neural signaling in TMJ development and disease progression.

Interactions with psychosocial factors

While our focus here is primarily on the TMJ itself, it is important to acknowledge that TMJ dysfunction and pain are multifaceted and mediated by both peripheral and central components involving complicated interactions with psychosocial factors (Slade et al. 2016). The central nervous system plasticity, affected by psychosocial factors, can contribute to the development and persistence of pain symptoms. Notably, psychological stress has been linked to TMD-related pain, suggesting a role for autonomic dysregulation in its pathophysiology (Cairns 2022). The interactions between autonomic nerves and TMJ tissues discussed above provide a biological basis for exploring the mechanisms through which psychosocial factors influence TMD. In addition, psychosocial status can alter muscle activities through motor nerves, as comprehensively reviewed by Murray et al. (Murray and Sessle 2024), thereby modulating joint function and affecting joint structure through the pathways illustrated in Figure 4.

DISCUSSION AND OUTLOOKS

This review summarizes current understandings of the structure, function, and pain aspects of TMJ diseases, which have traditionally been studied separately. Establishing the relationships among these aspects is critical, as it can help delineate the disease mechanism, improve disease diagnosis, and develop more effective treatments.

Connecting TMJ structure, function, and pain requires a holistic, multiscale integration of spatiotemporal biomechanical, biochemical, and nociceptive information. This necessitates a transdisciplinary approach encompassing assessments from the body to the cellular level, with the consideration of psychosocial contributions. At the body level, it is critical to capture jaw kinematics and quantify mechanical loads via methods like inverse dynamic modeling (She et al. 2021; Sun et al. 2024) and link these to macroscale anatomy. At the joint level, joint force and dynamics are essential to determine the contact region and spatiotemporal profile of stress and strain in joint tissues (She et al. 2021; Sun et al. 2024). At the tissue level, microscale tissue organization and 3D innervation pattern are crucial for determining local biomechanics, biochemical environment, and nociceptive activation profile (Wu et al. 2019). At the cellular and molecular level, it is necessary to characterize how joint cells and nerve fibers respond to the tissue microenvironment and engage in bidirectional crosstalk, as this influences nociceptive signaling and cellular and tissue responses. Figure 5A outlines a multiscale and multiphysics approach that integrates joint and tissue biomechanics, biochemical factors, cellular responses, and nociception to holistically analyze these spatiotemporal dynamic changes in joint structure, function, and pain. In addition, the psychosocial impact can be incorporated into the framework by monitoring central nervous system activities and connectivity through emerging brain imaging methods, muscle activities during TMJ movement using electromyography, and autonomic function with electrocardiography (Fig. 5B). This integrated approach underscores the importance of collecting multiscale data and reveals new opportunities for research. Figure 5C highlights the model's clinical relevance and identifies key gaps to guide future investigations.

Finally, TMJ diseases are complicated and multifactorial conditions involving an interplay among biomechanical, biological, and psychosocial components. Understanding the relationships between TMJ structure, function, and pain in the context of the biopsychosocial framework presents a promising approach to uncovering the fundamental mechanisms of TMJ disorders and developing comprehensive therapeutic strategies, whether structural, functional, neurological, or behavioral.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This study was supported by the National Institutes of Health (NIH) grants P20GM121342 and R01DE021134 to H.Y.; R34DE033593 and U01DE031512 to H.Y. and J.S.L.; R01DE031477 and R35DE030045 to M.K.C.; R01DE029068 to M.C.E.; and the Musculoskeletal Transplant Foundation grant to P.C.; and support from the Catharine Sharpe Foundation to B.A.W.

We would like to thank Dr. Joann Sullivan from Clemson University for editing and Dr. Shuchun Sun, Jiaxin Chai, Farhad Ahmadi, Jian Chen, and Jichao Zhao from Clemson University for their assistance in drawing the figures. Schematic figures were created on the Biorender website (https://www.biorender.com/).

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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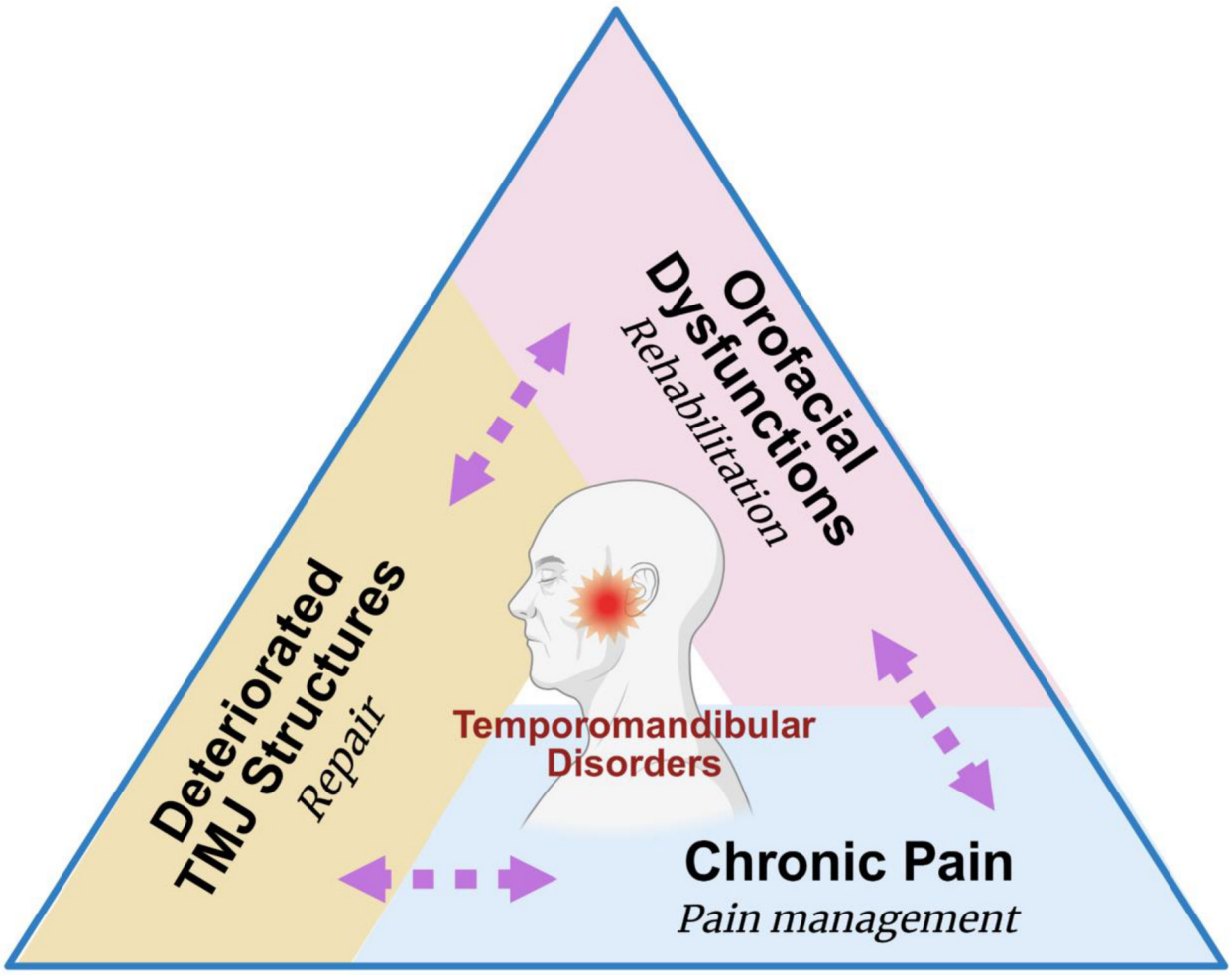

Figure 1. Challenges in the research and care of temporomandibular disorders (TMDs).
The complex relationships between joint structure, function, and pain in TMDs remain poorly understood. This knowledge gap hinders the development of a comprehensive management strategy that effectively integrates structural repair, functional rehabilitation, and pain management.

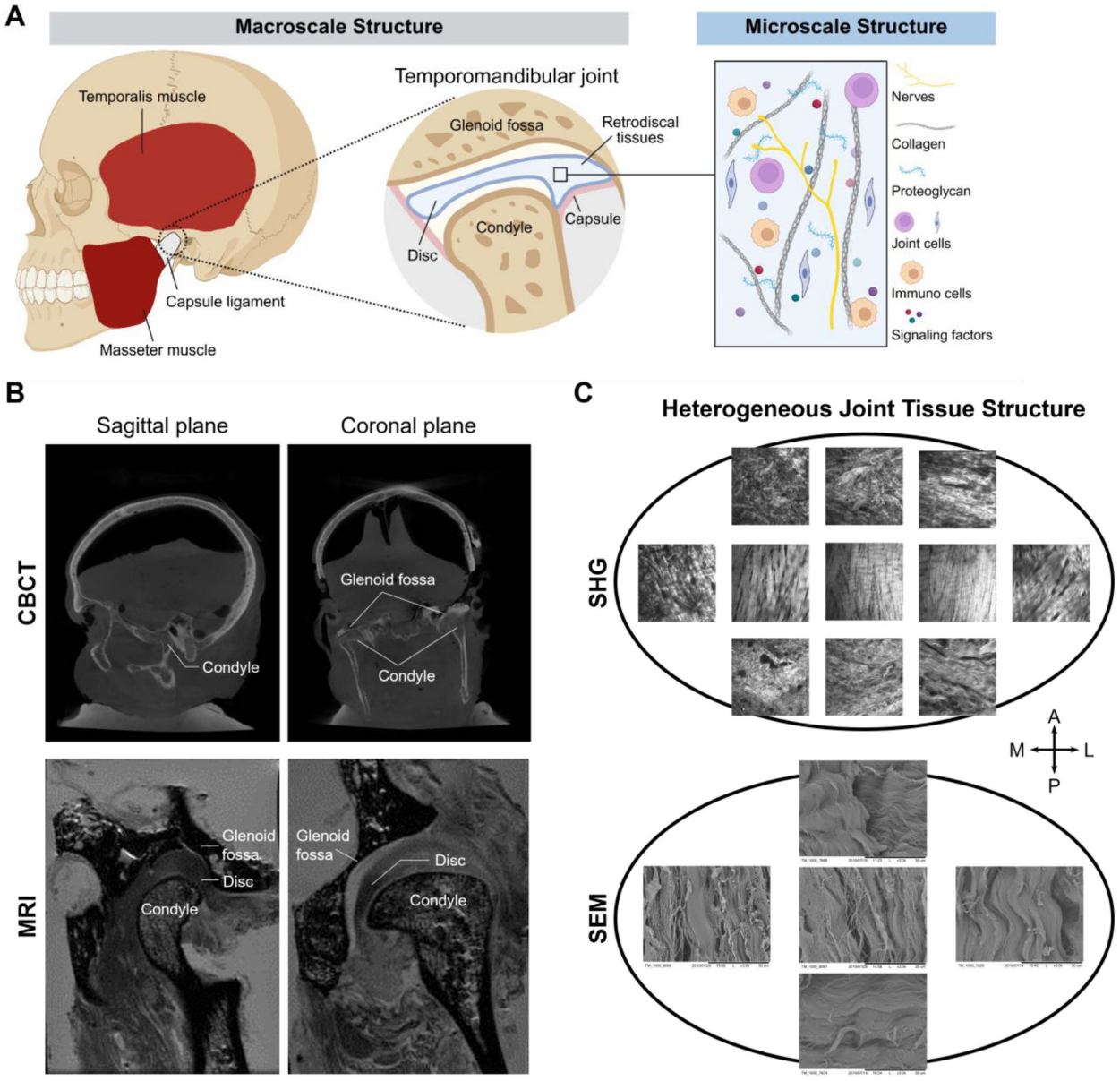

Figure 2. TMJ macroscale and microscale structure.

(**A**) Anatomic structure of human TMJ and the microscale structure of TMJ tissues. (**B**) CBCT (top) and MRI (bottom) images of human TMJ, highlighting key macroscale anatomical features. Figures adapted from the work by Coombs et al. (Coombs et al. 2019). (**C**) Collagen fiber structure imaged with second harmonic generation (SHG) in human (top) and scanning electron microscopy (SEM) in pig (bottom) TMJ disc of healthy subjects, demonstrating the heterogeneous microscale joint tissue structure. Figures adapted from the publications Wright et al. and Shi et al. (Shi et al. 2013; Wright et al. 2016). A, anterior; P, posterior; M, medial; L, lateral.

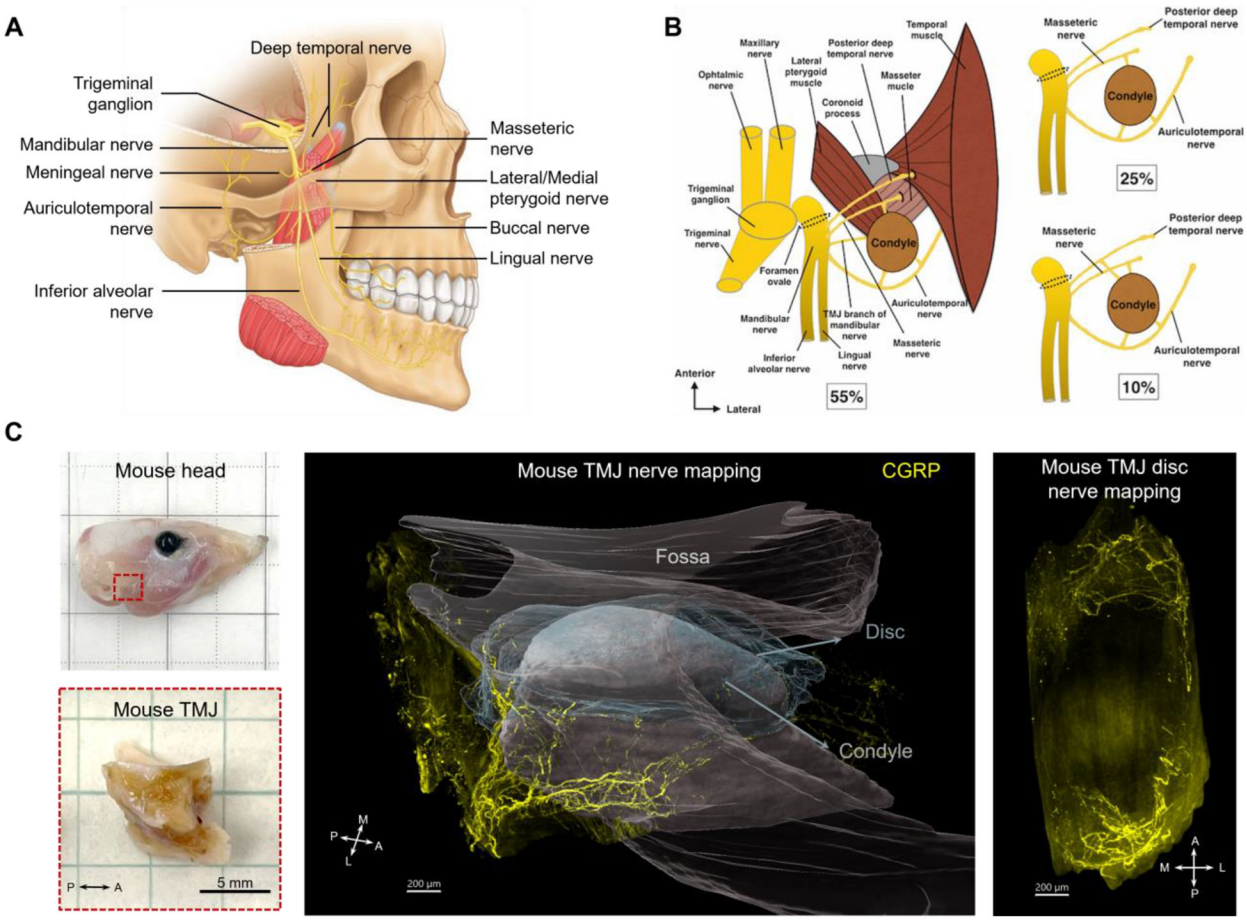

Figure 3. TMJ macroscale and microscale innervation.

(**A**) Schematic illustration of the nerve branches originating from the mandibular nerve. It comprises nine nerve branches: meningeal, auriculotemporal, lingual, inferior alveolar, masseteric, deep temporal, buccal, and the lateral and medial pterygoid nerves, each supplying specific joint tissues. This panel is modified from the work of Woods et al. (Woods and McIvor 2022) (**B**) Major mandibular nerve branches innervating human TMJ, including documented variations in TMJ innervation patterns: 55% of dissections showed innervation by the auriculotemporal nerve, masseteric nerve, and TMJ branches of the mandibular nerve; 25% exhibited innervation by the auriculotemporal and masseteric nerves; and 10% displayed innervation by the auriculotemporal, masseteric, and posterior deep temporal nerves. Adapted from the publication by Kucukguven et al. (Kucukguven et al. 2022). (**C**) 3D mapping of TMJ innervation in the mouse joint, visualizing the spatial distribution of nerve fibers within the whole joint. CGRP, calcitonin gene-related peptide. Figures adapted from our unpublished data (manuscript under review). A, anterior; P, posterior; M, medial; L, lateral.

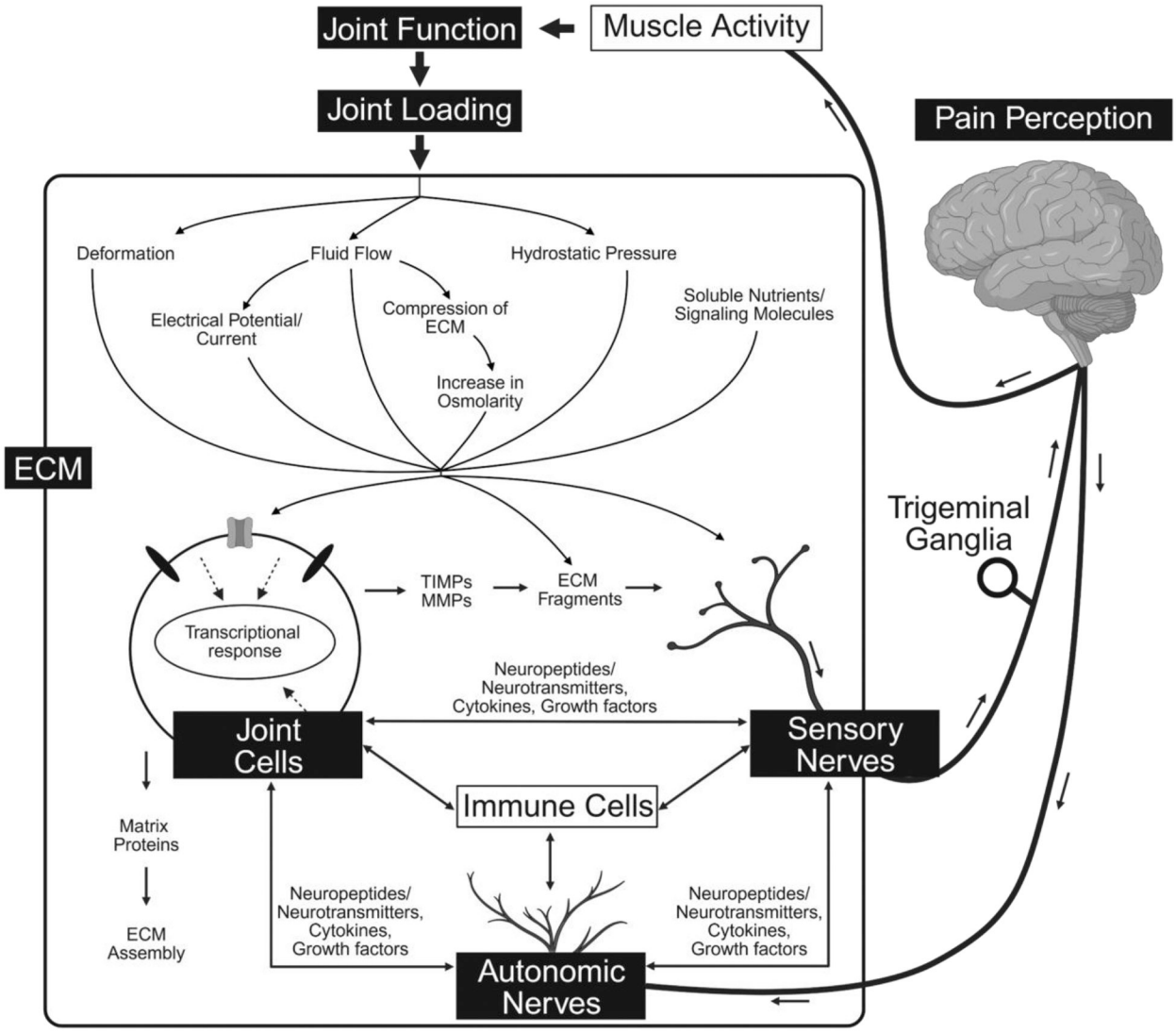

Figure 4. Conceptual schematic of interactions between joint structure, function, and pain.
During jaw movement, each TMJ tissue experiences varying mechanical loads. These loads induce extracellular matrix (ECM) responses, which activate resident cells, such as chondrocytes and fibroblast-like cells, and embedded nerve fibers, triggering downstream events including cytokine release and nociceptor activation. Excessive loading can cause microdamage, promote ECM turnover, and disrupt the balance between matrix metalloproteinases (MMPs) and their inhibitors (TIMPs), leading to ECM degradation and generation of bioactive fragments that further stimulate nociceptive nerves. Activated nerves release neuropeptides that influence surrounding joint cells, establishing bidirectional communication. Additionally, joint cells and nerves interact with innate immune components, collectively modulating tissue integrity and pain. Nociceptive signals are transmitted to the central nervous system, where pain is perceived. In turn, the brain regulates motor output and autonomic functions, adjusting muscle activity and joint mechanics, as well as cellular responses.

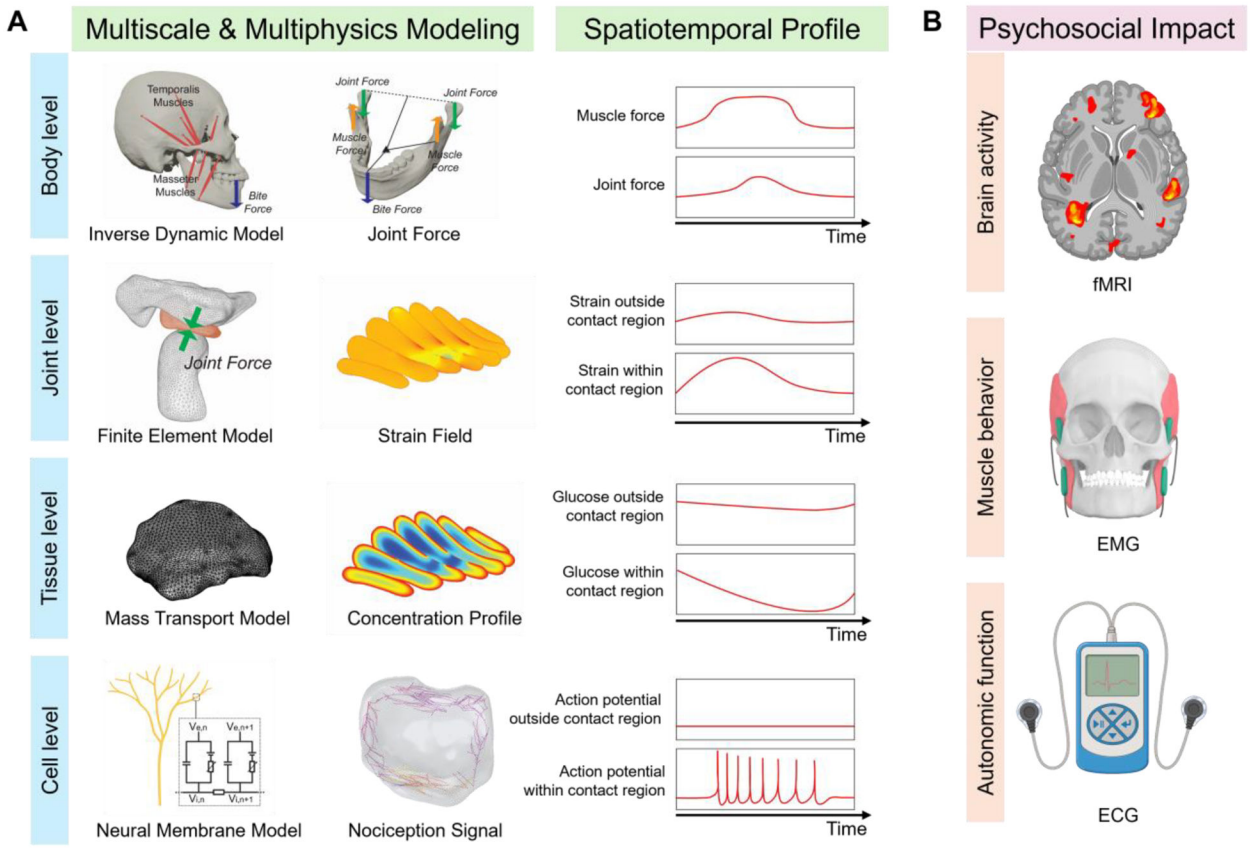

Figure 5. Integrated multiscale framework to assist in the quantitative understanding of joint structure, function, and pain relationship.

(**A**) Multiscale and Multiphysics Modeling concept. Body-level modeling captures the jaw motion and overall muscle and joint reaction forces. At the joint level, modeling enables the analysis of stress and strain distributions within articulating structures during mandibular movement. Tissue-level mass transport modeling provides insight into the spatial and temporal distribution of biomolecule concentrations within the joint tissues. At the cellular level, models such as neural membrane model allow for determining nerve action potential signals induced by changes of microenvironment. By integrating these approaches through multiscale and multiphysics modeling, the spatiotemporal dynamics of TMJ biomechanics, biochemical environments, and nociceptive responses can be quantitatively assessed. This comprehensive modeling framework facilitates a deeper understanding of the complex relationships between joint structure, function, and pain. Such tools and knowledge are critical for advancing our understanding of TMJ development, the onset and progression of joint disorders, and the mechanisms underlying chronic pain. (**B**) Incorporation of psychosocial factors. Brain activity and connectivity are monitored using emerging brain imaging technologies like functional MRI (fMRI), muscle activity during TMJ movement is accessed with an electromyography (EMG), and autonomic function is measured through an electrocardiography (ECG). (**C**) The clinical implications and key knowledge gaps of the integrated multiscale model.

Table 1.

TMJ structure, function, and innervation in health and disease

Anatomical Structure	Primary Function	Main ECM Components	Innervation in Health	Structural Changes in Disease	Neural Plasticity in Disease
Cartilage	Shock absorption Load redistribution	Collagen I & II GAGs Elastin	No nerve	Degeneration Loss of GAGs Collagen breakdown	--
Bone	Load bearing Joint stability	Collagen I Hydroxyapatite	CGRP+, SP+ TH+, NPY+	Bone loss Bone edema Osteophyte formation	TH+, CGRP+ nerves increase [mouse UAC model] (Ma et al. 2025) No significant changes [mouse CFA model] (Jariyasakulroj et al. 2025)
TMJ disc	Shock absorption Load redistribution	Collagen I GAGs Elastin	CGRP+ *, SP+ * TH+ *, NPY+ *	Displacement, Disorganized & thickened collagen fibers	CGRP+ nerves increase [rat CFA model] (Shinoda et al. 2003) No significant changes [mouse CFA model] (Jariyasakulroj et al. 2025) CGRP+ nerves increase [rat liquid diet model] (Takei et al. 2008)
Retrodiscal tissue	Disc stability	Collagen I GAGs Elastin	CGRP+ TH+ Htr3a+, Mrgpr+	Inflammation Rupture Decreased elastin	CGRP+ nerves increase [mouse CFA model] (Jariyasakulroj et al. 2025)
Synovial membrane	Lubrication	Collagen I & III GAGs	CGRP+ TH+ *, NPY+ *, VIP+ *	Inflammation Hyperplasia Fibrosis	CGRP+ nerves increase [mouse CFA model] (Jariyasakulroj et al. 2025) CGRP+ nerves increase [human sample] (Sato et al. 2004)
Capsule	Joint stability	Collagen I GAGs Elastin	CGRP+ TH+ *, NPY+, VIP+ Htr3a+	Inflammation Laxity	CGRP+ nerves decrease [sheep surgical model] (Tahmasebi-Sarvestani et al. 2001)
Ligament	Joint stability	Collagen I GAGs Elastin	--	Sprain Loss of elasticity Calcification Laxity	--
Muscle	Driving force for joint movements	Collagen I & III GAGs Elastin	CGRP+, SP+ TH+, NPY+ TRPV1+, TRPV2+, P2X3+	Degeneration Atrophy Hypertrophy	CGRP+ nerves increase [rat myositis model] (Carleson et al. 2004)

*: inconsistent reports on the presence of the nerve type in literature

--: no relevant research has been found

GAGs: glycosaminoglycans

CGRP: calcitonin gene-related peptide; SP: substance P; TH: tyrosine hydroxylase; NPY: neuropeptide Y; VIP: Htr3a: 5-hydroxytryptamine receptor 3A; Mrgpr: Mas-related G-protein coupled receptor; TRPV: transient receptor potential vanilloid; P2X3: P2X purinoceptor 3

UAC: unilateral anterior crossbite; CFA: complete Freund's adjuvant