An Integrated Multiscale Framework to Bridge Structure Function Pain in Musculoskeletal Joints

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INTRODUCTION: Musculoskeletal diseases, such as back pain, temporomandibular joint disorders, and osteoarthritis, are the leading cause of disability, affecting approximately 1.7 billion people worldwide and resulting in an estimated annual healthcare cost of $980 billion in the United States alone. The musculoskeletal joint is a diverse and multiscale system comprising an array of different joint tissues (i.e., bones, connective tissues, and muscles), each with unique tissue structures that support their complex functional demands. Alterations in these structures are often linked to joint dysfunction, with pain being one of the most prevalent symptoms. However, the mechanisms underlying joint pain and their relationship with structural deterioration or functional impairment remain poorly understood. A comprehensive understanding of the interplay between joint structure, function, and pain is essential for uncovering disease mechanisms and developing effective therapies. To date, musculoskeletal 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 inconsistent correlations among joint structural changes, dysfunctions, and pain. Some individuals with radiographic joint changes remain asymptomatic, while others experience pain despite no detectable joint degeneration, complicating diagnosis and treatments. To address these gaps, this study aims to bridge these traditionally fragmented areas by synthesizing current knowledge across macroscopic and microscopic scales. We propose a multiscale and multiphysics framework that integrates joint and tissue biomechanics, biochemical signals, cellular responses, nociception, and psychosocial influences. This approach enables holistic and quantitative assessment of the spatiotemporal dynamic processes in the musculoskeletal joints. Realizing this vision requires a transdisciplinary effort and the development and adaptation of advanced methods to study joint at unprecedented resolution and details. By unifying structural, functional, and pain-related data, this integrated multiscale approach holds promises for elucidating new mechanisms of joint 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.

METHODS: The interplays among musculoskeletal joint structure, function, and pain are extensively reviewed and explored from a multiscale perspective based on both existing literature and our own research. Using the temporomandibular joint (TMJ) as an example, we employ a chair-side functional assessment toolkit to quantitatively assess the spatiotemporal dynamics of joints across scales, which captures the joint kinetics, records muscle activities and autonomic functions, and derives the joint and muscle forces. Finite element joint models are further developed to determine joint tissue biomechanics and biochemical environment. In addition, our recently developed whole joint tissue clearing and 3D imaging methods are used to map the joint cellular and molecular structures. Neural membrane model is also used to predict the nociception signals during joint movement, providing critical insights into pain mechanisms.

RESULTS: Musculoskeletal joints comprise spatially proximate cellular, extracellular, and neural components that undergo multiscale, spatiotemporal changes and interactions. During joint movement, these components experience complex mechanical loading, triggering mechanical, neural, and immune responses that interact bidirectionally to influence joint integrity and pain (Fig. 1A). In turn, the brain modulates motor output and autonomic function, further impacting joint mechanics and cellular and nociceptive responses (Fig. 1A). Using the TMJ as an example, we outline a multiscale and multiphysics framework 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 (Fig. 1B). The psychosocial impact can also be incorporated into the framework by monitoring central brain activities and connectivity through emerging brain imaging methods, muscle activities during TMJ movement using electromyography, and autonomic function with electrocardiography (Fig. 1B). To enable such analyses, we have developed a chair-side functional assessment toolkit that captures the joint kinetics, records muscle autonomic activities, and determines the joint and muscle forces (Fig. 1C) and have invented a 3D whole joint tissue clearing and imaging technique to map the cellular and molecular structures (e.g., pain-sensing nerves labeled with CGRP and blood vessels labeled with CD31) across the entire joint (Fig. 1C). By integrating experimental and modeling data, we can comprehensively and holistically characterize the joint in both health and diseased conditions to decipher the complex relationship between joint structure, function, and pain.

DISCUSSION: This study seeks to bridge the joint structure, function, and pain. Our findings reveal complex interactions among joint components, including joint cells, sensory and autonomic nerves, immune systems, and central brain modulation. Connecting TMJ structure, function, and pain requires holistic, multiscale integration of spatiotemporal biomechanical, biochemical, and nociceptive information. This necessitates a transdisciplinary approach encompassing assessments from the body to the cellular level while also accounting for psychosocial contributions. The techniques and methods developed in our lab provide a platform to achieve this goal. This integrated multiscale framework proposed here links upstream and downstream mechanisms, offering new insights into diagnostic and treatment development. A deeper understanding of the joint structure–function–pain relationship will enable patient stratification for more personalized care. Moreover, it lays a scientific foundation for evaluating and optimizing treatment strategies, such as force-based manipulation, neuromodulation, and combination therapy as envisioned in Centers of Excellence. Much research remains to be conducted to collect these various layers of information. Incorporating in vitro human joint models into this framework will further enhance its capacity to validate and refine findings.

SIGNIFICANCE/CLINICAL RELEVANCE: Understanding the relationships between joint structure, function, and pain in the context of the biopsychosocial framework presents a promising approach to uncovering the fundamental mechanisms of joint disorders and developing comprehensive therapeutic strategies, whether structural, functional, neurological, behavioral, or combined.

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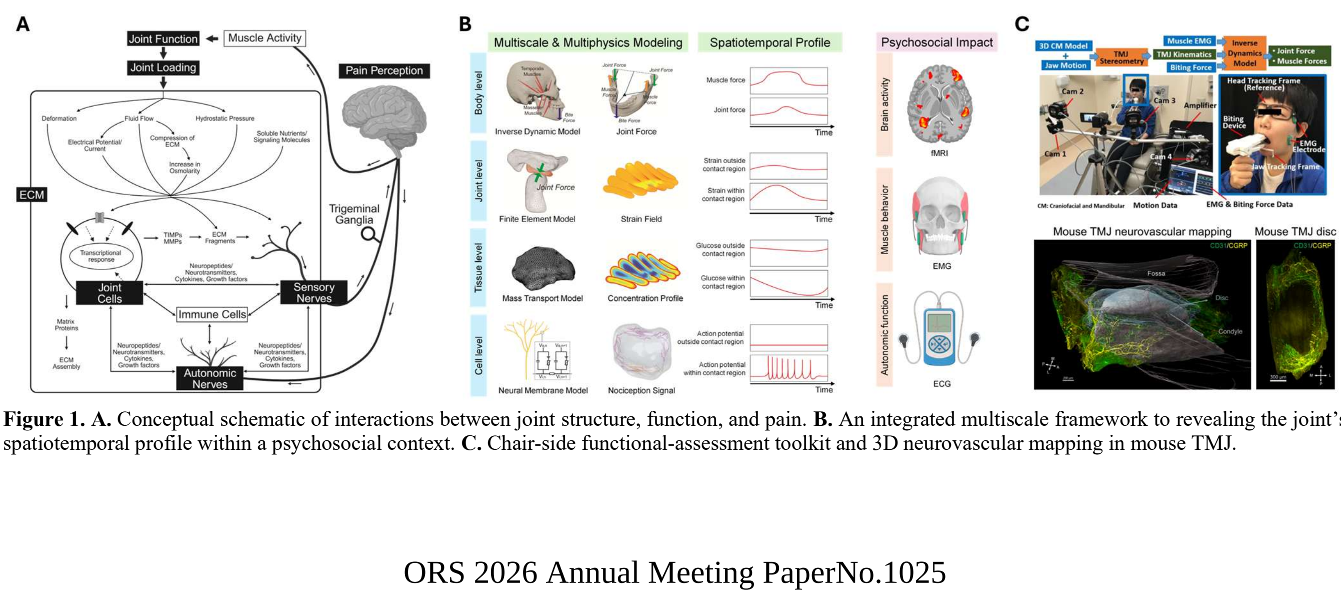

Figure 1. A. Conceptual schematic of interactions between joint structure, function, and pain. **B.** An integrated multiscale framework to revealing the joint's spatiotemporal profile within a psychosocial context. **C.** Chair-side functional-assessment toolkit and 3D neurovascular mapping in mouse TMJ.