Construction of the chronic temporomandibular disorder patients: the association between neural and psychological pathways

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ABSTRACT

Chronic temporomandibular disorder (cTMD) as a term based on the diagnostic criteria for temporomandibular disorders (DC/TMD) classification refers, in this paper, to the condition listed that has a non-mechanical association without any obvious organic cause. Specifically, this is the condition that falls under the International Classification of Diseases 11th revision (ICD-11) classification of chronic primary and chronic secondary pains. This implies that there is increased responsiveness of nociceptive neurons in the central nervous system, a phenomenon known as central sensitisation. cTMD patients may have their beginning with genetic susceptibility to pain. Although no single gene is exclusively linked to cTMD, various genes associated with nervous and musculoskeletal systems are believed to play a role. Environmental triggers and epigenetic changes are also thought to contribute to cTMD development. The biopsychosocial model emphasises the need to comprehensively address biological, psychological and social factors in cTMD assessment and management. In this study, we leverage the cyclic causation framework within the biopsychosocial model to illuminate the intricate interplay between biological and psychosocial factors in the context of cTMD. The conceptualisation of cTMD involves the dynamic evolution of genetic predispositions, influenced by life events and other biological susceptibilities. These factors collectively contribute to the emergence of nociplastic changes, ultimately manifesting as the distinctive features observed in individuals afflicted with cTMD.

Pain was described by the International Association for the Study of Pain (IASP) as "*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*".[1] While there is no precise boundary defining the transition from acute to chronic pain, the International Classification of Diseases (ICD) and International Classification of Orofacial Pain (ICOP) indicates that pain persisting beyond the anticipated healing period (lasting more than 3 months and occurring on at least 15 days per month) is considered pathological.[2,3]

Expanding upon this concept, we specifically designate chronic temporomandibular disorder (cTMD) in this article to encompass conditions outlined in the diagnostic criteria for temporomandibular disorders (DC/TMD) classification. This condition is characterised by a lack of mechanical origins and without clear organic causes. Temporomandibular disorder (TMD) is a comprehensive term encompassing various conditions causing pain and dysfunction in the orofacial region. In the decade since its inception, the DC/TMD classification has outlined various conditions, including mechanical aberrations tied to the temporomandibular joint such as disc displacement, disc perforations, condylar hyperplasia and certain tumours. Additionally, it addresses conditions linked to chronic pain, encompassing myogenous and arthrogenous sources, along with headaches associated with cTMD, among others collectively denoted as cTMD.[4] This second group encompasses the majority of patient cohorts frequently encountered in pain management clinics. cTMD specifically denotes individuals grappling with pain persisting for more than 3 months, a definition set forth by IASP. In contrast, the International Classification of Diseases 11th Revision (ICD-11), introduced by the World Health Organization in 2018, presents a more comprehensive framework that categorises this prevalent, non-mechanical cohort under the umbrella of chronic primary pain. This system integrates specific codes and classifications for a diverse range of diseases and conditions, including chronic pain disorders like cTMD. Recognising chronic pain, including cTMD, as a pathology, the

ICD-11 provides a clinically relevant perspective. The National Academy of Medicine (NAM) has underscored a critical gap in the assessment, diagnosis and management of both acute and chronic conditions, with a particular focus on cTMD.[5] It highlights the intricate, multisystem nature of cTMDs, necessitating a comprehensive, multidisciplinary approach to treatment. Unlike conventional medicine, which predominantly addresses diseases with discernible physiological mechanisms, the ICD-11's definition of chronic primary pain recognises the absence of pathology at the perceived pain site. This perspective challenges clinicians to adapt their approach to managing conditions where the pathology may not be immediately evident. In this context, the term TMD is deemed misleading, as it implies an association with the structures housing the pain and utilises the term "Disorder," which lacks a specific pathology for diagnosis.

Addressing the intertwined challenges of pain and psychological distress, common components of many diseases, proves to be a formidable task. Unlike conditions where pathology primarily affects peripheral organs, the origins of pain and distress are deeply embedded in intricate brain functions.[6] Remarkably, alterations in nerve function could manifest in individuals genetically predisposed to pain sensitivity and psychological distress.[7] When examining conditions like ICD-11 chronic primary pain associated with chronic temporomandibular disorder (CPP cTMD), it becomes crucial to unravel the intricate factors contributing to these patients' experiences. This deeper understanding is essential for the effective management of chronic pain sufferers, enabling healthcare professionals to devise more targeted and empathic interventions. Furthermore, cTMD has been integrated into the established biopsychosocial model employed for studying and managing various chronic pain conditions.[8] The findings from *Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA)* bolster the complexity of cTMD, emphasising the need for a nuanced approach. The alignment between OPPERA findings and the biopsychosocial framework affirms a non-local aetiology for cTMD, emphasising the multifaceted nature of this condition.[9]

A plausible model for understanding the development of cTMD involves commencing with a consideration of genetic predisposition to pain, for example the catechol-o-methyltransferase (COMT) gene in the case of cTMD. This genetic susceptibility may contribute to an individual possessing a distinct neuroanatomical makeup, rendering them more susceptible to experiencing pain. Variations among individuals could mean that some are more predisposed to undergoing "temporary" neuroplastic changes, eventually leading them to become chronic pain sufferers. This correlation has been demonstrated in conditions like fibromyalgia, where genetic factors potentially account for up to 50% of disease susceptibility.[10] Under the ICD-11 classification, cTMD and fibromyalgia share a similar pathogenesis.[2]

This intricate construction, rooted in the individual's genetic makeup, is further complicated by the influence of psychosocial factors, which also harbour genetic components and may be influenced by factors such as childhood trauma and other biological intervening variables (Figure 1).[11–13]

Biopsychosocial model

George Engel conceptualised the biopsychosocial model as a dynamic and interactive perspective on human experience, acknowledging the intricate interplay between the mind and body.[14] This model emphasises the mutual influence and interconnectedness of psychological, biological and social factors in shaping the human condition.[15] The notion of various system levels and the emergence of a whole that possesses information greater than the sum of its parts is the foundational concept of this model. In this framework, neural network activity serves as a foundational level from which psychological functions arise. Furthermore, biological, psychological and social factors relate in a cyclic manner, meaning that each can influence and affect the others in a continuous loop, which is a fundamental concept in the biopsychosocial model and systems theory. This recognition of bidirectional influences is an essential aspect of understanding the complexity of human experiences and interactions.[16,17] Such cyclic interaction between environment and genes have been also demonstrated.[18]

It is of interest then to consider causative paths between the three levels (biology, psychology and social). Both biological and social factors appear to play a role in shaping psychological aspects. For instance, neural networks, starting from membrane function and extending upwards, could serve as a model for understanding the parallel between biological and psychological modules. Additionally, interventions such as family and group therapy have demonstrated their impact on individual mental health. Numerous research studies highlight

potential continuous links from the cellular membrane (ion channels) level to the neuronal and network levels. An illustrative example is the cyclic nucleotide-gated channel, present in both the prefrontal cortex and the hippocampus. This channel is involved in recurrent information processing within individual neurons, providing valuable insights into the intricate connections between biological and psychological processes.[19–21] Significantly, the same regions of the brain play a crucial role in attention, memory and affective functions. Specifically, well-established association networks such as the central executive network, dorsal attentional network, salience network and default mode network (DMN) are pivotal in influencing cognitions associated with affect.[22] Hence, there is the potential to construct a nuanced comprehension of information processing, tracing it from the biological level (beginning with membrane function) to the generation of cognitive and affective functions by biological networks (akin to hardware), to the way learning acts as software or a form of self-programming. How psychological phenomena could affect social activity could be observed in how memes affect group social behaviour. However, the reverse—purely psychological phenomena directly influencing biological function—raises intriguing questions. While the observations of alterations in neural pathways due to psychotherapy are compelling, it's important to acknowledge potential objections rooted in social factors, particularly the dynamics between therapists and patients.[23] These interactions could introduce complexities, making it difficult to purely isolate the psychological impact. One potential avenue for exploring this connection lies in long-term, introspective practices devoid of social interference. For instance, individuals engaging in silent meditation over extended periods may offer valuable insights. Through practices like insight meditation, where individuals delve deeply into their own psyche, devoid of external social influences, we may gain a clearer understanding of how purely psychological experiences intricately influence biological functions. Such evidence has been demonstrated in scientific studies.[24] Mindfulness practice is known to assist in pain management.[25]

Engaging in mindfulness practice has been linked to the augmentation of grey matter in key brain regions, including the anterior cingulate, prefrontal cortex and hippocampus, while concurrently structural changing in the amygdala.[26,27] Additionally, mindfulness has been observed to improve the functioning of the DMN.[28] Notably, the DMN plays a role in directing attention towards pure sensations, effectively dampening the activity of other networks. This inhibition contributes to a reduction in cognitive and affective functions, potentially influencing distress and pain experiences.

In the realm of causation, the proximity of the temporal connection between cause and effect often determines the consideration of a more proximal cause. Nevertheless, cascades of causation can unfold, commencing with an early factor such as childhood trauma, which may engender vulnerabilities, thereby heightening the probability of succumbing to additional causes in the future. For instance, the experience of childhood trauma may lead to both psychological and biological impairments, rendering the individual more susceptible to subsequent traumas, whether they be of environmental, social or biological origin (Figure 1). These interconnected causes can set in motion a divergent cascade of events that eventually converge to influence a singular disorder, such as cTMD. A construct can be formulated to illustrate how the biopsychosocial model might alter the initial interplay between afferent and descending pathways of nociception. While the placebo and nocebo concepts offer a simplified explanation of the impact on the descending pathway through learning and other neural mechanisms, our proposition is to integrate these concepts within a broader biopsychosocial model (Figure 2).[29]

Chronic temporomandibular disorders

The concept of disease, defined as a bodily disruption or abnormality, is just a linguistic construct. Disease and illness share similar semantics, both pointing to human suffering and dissatisfaction with one's condition. Whether this suffering arises from purely biological factors within the brain or body, psychological factors rooted in one's thoughts and feelings or social factors related to interactions with the external world, all of these sources are valid and significant considerations in understanding the human experience of health challenges. The use of the term disorder is often an apt compromise when pathophysiology is not completely established.

Regarding cTMD, the journey starts with an individual's genetic makeup. Chronic pain sufferers often commence life with a genetic

predisposition to pain sensitivity, setting the stage for their unique pain experiences. While there have been studies exploring potential genetic links to cTMD, the field is complex, and no specific "TMD genes" have been universally identified. While there isn't a single gene that is exclusively associated with cTMD, several genes that code for receptors and proteins, such as serotonin and sensory neuron receptors, cytokines, matrix metalloproteinases, oestrogen receptor and calcitonin gene-related peptide in the nervous and musculoskeletal systems have been studied in relation to cTMD.[30–35] A systematic review has revealed a genetic overlap involving three specific genes—ESR1, MTHFR and COMT—in the genetic profiles of patients diagnosed with both primary headaches and cTMD.[36] The COMT gene is additionally linked to susceptibility to mood and anxiety disorders.[37,38]

However, cTMD is a multifactorial condition, meaning it is influenced by a combination of genetic, environmental and lifestyle factors. The triplet code of DNA, once thought to be entirely deterministic of the phenotype, does not exclusively dictate an organism's traits. Environmental influences could induce changes in DNA structure, driving evolutionary shifts. This dynamic interaction implies that lower-level factors (e.g., DNA) may shape outcomes at higher levels (complex network, e.g., Organism), creating a feedback loop of circular causation.[17] Furthermore, genetic information flows from DNA to RNA, but it's important to note that RNA could also influence DNA (Figure 3).[39] The field of epigenetics has unveiled a fascinating phenomenon: environmental factors, through processes like histone methylation, could modify gene expression.[40] Frequently, this modification may involve the recombination and relocation of genetic domains, resulting in the transmission of new traits down the germ line.

Environmental triggers and epigenetic changes

Genetic susceptibility plays a role in gastrointestinal tract sensitivity.[41] A gastrointestinal infection could trigger an immune response, not only against the infection itself but also against the gastrointestinal tract lining. This primed immune reaction could lead to peripheral nociception. This process, in turn, causes peripheral and central sensitisation through sacral, lumbar and thoracic pathways, contributing to conditions like irritable bowel syndrome.[42–44] These individuals may become predisposed to other chronic pains such as cTMD due to this priming, resulting in the development of chronic overlapping pain conditions.[45] Moreover, lifestyle factors like smoking may downregulate stress responses and inhibit serotonin synthesis, while alcohol use may increase dopamine and endogenous opioids synthesis (Figure 4).[46,47] Additionally, a high-fat diet may enhance reward-related circuitry.[48,49] These factors further contribute to the complexity of pain conditions, highlighting the intricate interplay between genetics, environmental triggers and lifestyle choices in the development of chronic pain conditions (Figure 4).

Pain perception is intricately influenced by alterations in modulators and receptors within the body. For instance, the Homer genes may have the potential to inhibit nociceptive signal transmission in the posterior horn of the spinal cord, modulating pain signals.[50] Prodynorphin (PDYN) has links to conditions such as depression, stress and substance addiction.[51–53] Stress triggers the release of norepinephrine and cortisol while simultaneously decreasing testosterone levels, potentially contributing to the higher prevalence of pain in females.[54,55] The impact of stress and its associated humoral response has the potential to induce changes in immune response, potentially affecting gut function. This cascade effect may contribute to sensitisation processes, ultimately predisposing individuals to chronic pain. Additionally, histone modification may lead to central sensitisation, amplifying pain signals.[56] Vitamin D deficiency has been associated with decreased pain threshold and tolerance.[57,58] Pronociceptive factors act as amplifiers, intensifying sensitisation processes.[59] These factors involve reactive oxygen species, proinflammatory cells and signals, adaptations in neuroimmune synapses, negative affective states, structural volume changes (hippocampus), loss of control systems, reduced positive interactions and decreased environmental exposure.[60–63] Peripheral injuries could activate both the innate and adaptive branches of the immune system to resolve tissue damage, but prolonged immune activation may contribute to the chronicity of pain.[64]

Pain processing and central sensitisation

The sensory-discriminative aspects of pain originating from trigeminal nociceptive neurons are processed in specific brain regions. These include the primary somatosensory cortex, posterior insular cortex and thalamus, all of which receive direct projections from these neurons in

the orofacial region (Figure 4).[65] In the thalamus, trigeminal nociceptive inputs undergo modulation before being transmitted to both cortical and subcortical structures, highlighting the intricate processing and integration of pain signals in the central nervous system.[66] The primary somatosensory cortex and insular cortex play crucial roles in encoding the intensity of painful stimuli. These regions exhibit graded increases in activity, directly corresponding to the intensity of the stimulus presented. This precise modulation reflects the brain's sophisticated processing of pain perception.[67,68] The prefrontal cortex, anterior cingulate cortex and secondary somatosensory cortex are integral to the comprehensive processing of pain signals, encompassing emotional, cognitive, sensory and spatial aspects of pain perception and modulation. The prefrontal cortex is involved in the emotional aspect of pain processing and is essential for cognitive evaluation of pain-related stimuli.[69,70] The anterior cingulate cortex is considered to be involved in a variety of cognitive and emotional processes such as pain and coping mechanisms, especially affective pain.[71] The secondary somatosensory cortex integrates and processes nociceptive information, enhancing the brain's ability to perceive and respond to pain signals, and contributes to the sensory-discriminative dimension of pain.[72,73]

In central sensitisation, the central nervous system becomes hyperresponsive to pain stimuli, involving complex changes in various brain regions. The exact pattern of activation or deactivation varies based on the individual or condition; however, several important brain regions are thought to be associated with central sensitisation. Chronic pain has the potential to alter the brain's structure, indicating that prolonged pain experiences might lead to observable changes in the brain's anatomy.[74] For example, research reveals chronic back pain correlates with reduced grey matter density in both the prefrontal cortex and thalamus.[69,75] This finding indicates structural changes in these brain regions, suggesting a link between persistent back pain and alterations in specific areas of the brain.[75] A study also showed a decrease in grey matter within regions, including the cingulate cortex, insula and prefrontal cortex, associated with pain processing in individuals experiencing chronic pain.[76] However, another study argued that structural brain changes observed in chronic pain patients likely do not indicate damage or atrophy. This suggests that alterations in the brain's structure related to chronic pain might be different in nature from traditional damage or degeneration.[77,78] cTMD has been associated with central sensitisation. For example, experimental pain studies showed individuals experiencing painful cTMD exhibit higher sensitivity to experimental pain stimuli. They demonstrate lower thermal and ischemic pain thresholds, along with reduced tolerance values, compared to individuals without cTMD symptoms.[79,80] Quantitative sensory testing in patients with painful cTMD have revealed lower pain thresholds and increased pain responses to various stimuli, supporting the presence of central sensitisation.[79,81] Functional magnetic resonance imaging studies have shown abnormal altered brain activity patterns in response to both innocuous and painful stimuli and altered connectivity in pain-related brain regions in individuals with cTMD, suggesting central nervous system involvement in cTMD-related pain.[82] Studies have demonstrated enhanced temporal summation of pain in cTMD patients, indicating an increased response to repeated noxious stimuli, which is a characteristic feature of central sensitisation.[83] Clinically, cTMD patients often report widespread pain and increased sensitivity to pressure, heat or cold, symptoms consistent with central sensitisation.[84–86] Treatments focussing on central sensitisation, such as cognitive behavioural therapy and medications acting on the central nervous system, have shown effectiveness in managing cTMD-related pain.[87] This offers indirect evidence supporting the involvement of central sensitisation in cTMD. In considering the previous section, it is apparent that a vicious cycle can emerge where physical and mental suffering reinforce each other.

A biopsychosocial model of cTMD

In the context of the biopsychosocial model, the Al-Khotani et al. study highlights significant connections between psychosocial, somatic and behavioural coexisting conditions and cTMD-related pain among children and adolescents.[88] Biological factors, including genetics, hormonal influences and anatomical variations, have been implicated in cTMD. Certain genetic markers and hormonal changes have been specifically associated with the development of cTMD symptoms, underscoring the disorder's biological basis.[89] Psychological factors such as stress, anxiety and depression, along with individual coping mechanisms, significantly influence the onset and

worsening of cTMD symptoms. Extensive research demonstrates a strong association between psychological distress and the severity of cTMD symptoms. Implementing stress management and relaxation techniques has proven effective in alleviating cTMD-related pain.[90] Social factors, encompassing socio-economic status, social support and cultural influences profoundly shape how individuals perceive and manage pain. Strong social support systems enhance coping mechanisms, especially in chronic pain conditions such as cTMD. Furthermore, cultural beliefs and attitudes toward pain significantly influence how cTMD symptoms are experienced and communicated.[91–95] Evidence from cognitive behavioural therapies, which address maladaptive pain beliefs and coping strategies, have been successful in managing cTMD-related pain, which is indirect evidence supporting the biopsychosocial model.[96] Treatment strategies for cTMD typically integrate dental, medical, psychological and physical therapies. Multidisciplinary programmes, rooted in the biopsychosocial model, have demonstrated significant success in enhancing pain management and overall quality of life for individuals dealing with cTMD.[97] The evidence supporting the biopsychosocial model in the context of cTMD is strong. It highlights the importance of addressing biological, psychological and social factors comprehensively in the assessment and management of cTMD.

Childhood trauma and sleep disorder in cTMD

Childhood trauma (emotional/physical) may be a contributing factor to the development of cTMD; however, it's important to note that the relationship between childhood trauma and cTMD is complex and multifaceted. Childhood trauma may lead to chronic stress, altered pain processing pathways and changes in the way the brain perceives and responds to pain.[98,99] Childhood trauma is a common antecedent of mood and anxiety disorders, which are co-morbid with pain disorders and could generate a vicious cycle.[100–102] These factors might contribute to the onset or exacerbation of cTMD symptoms. Moreover, individuals who have experienced childhood trauma may be at increased risk of parafunction habits such as bruxism.[103] This, in turn, could trigger epigenetic changes, further predisposing these individuals to the process of chronification. The influence of trauma, whether experienced in childhood or adulthood, has been minimally explored in relation to cTMD. Nevertheless, it is crucial to acknowledge the potential link between trauma, especially childhood trauma, and the establishment of chronic vulnerability to a cascade of future traumas, both social and biological.

Sleep plays a crucial role in chronic cTMD.[104] Conditions like obstructive sleep apnea (OSA) and insomnia, whether individually or in combination (comorbid insomnia and obstructive sleep apnea [COIMSA]), may worsen cTMD symptoms.[104–106] A healthy sleep routine of 7–9 hours is recommended, and chronic insomnia often involves underlying psychosocial and behavioural factors.[107] Managing sleep disorders involves various approaches. Continuous positive airway pressure and mandibular advancement appliances may be used for OSA, while cognitive behavioural therapy for insomnia is effective for insomnia.[108,109] A combination of these methods is often employed for COIMSA cases.[110] Studies suggest that more than one third of Australian adults experience nocturnal symptoms.[111] Notably, sleep disorders have genetic links and are associated with an increased risk of anxiety and depression.[112,113] Assessments, including detailed sleep history and diaries (digital, visual and text-based), provide valuable insights into cTMD.

Points of direction

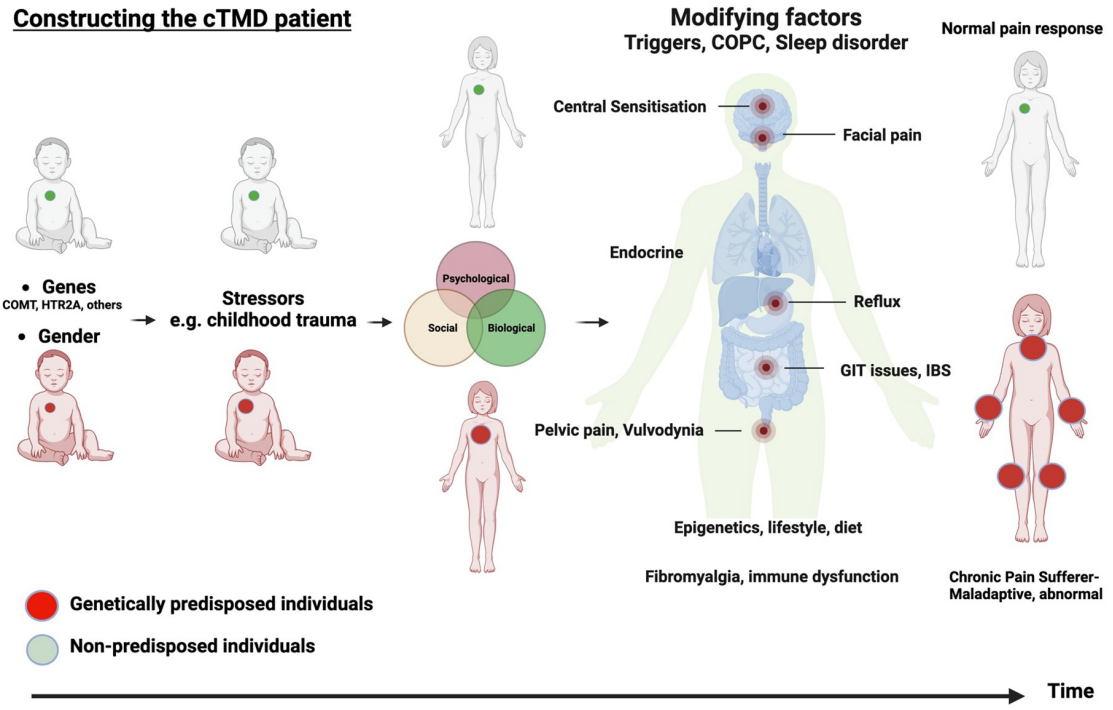
In this paper, we employ the biopsychosocial model to formulate a framework for understanding the pathological evolution of cTMD. Although the model is not exhaustive, it serves as an initial template to guide the construction of more intricate models for comprehending cTMD as a disorder. Our conceptualisation defines a disorder as any condition leading to a homeostatic imbalance from a biopsychosocial perspective. We assert the validity of the biopsychosocial model for both understanding the causation and managing the manifestations of diseases. Specific environmental and psychological factors play significant roles in triggering the persistence of neural mechanisms associated with cTMD. Consequently, we propose that this model could serve as a catalyst for further research in the field. Furthermore, our understanding and focus on the underlying process shows promising research into management of chronic pain in the future through fields like chemogenetics. Chemogenetics has been shown as a possible means to suppress the hyperexcitability and maladaptive changes seen in chronic pain.[114] We advocate for the integration of advanced

biological techniques with psychosocial interventions as an ongoing strategy for advancing research in cTMD. While biological research in cTMD is advancing rapidly, investigations into psychosocial causes and interventions lag behind. Recognising this gap, we emphasise the need for further research into childhood trauma and its cascading susceptibility to trauma as an area requiring more attention compared to general research in chronic pain. Furthermore, despite the longstanding use of mindfulness-based cognitive therapy as a treatment strategy in chronic pain for nearly 5 decades, its application in the field of cTMD warrants continued development. This highlights the importance of concurrently advancing both biological and psychosocial dimensions in cTMD research to comprehensively address the complexities of this disorder.

Conclusion

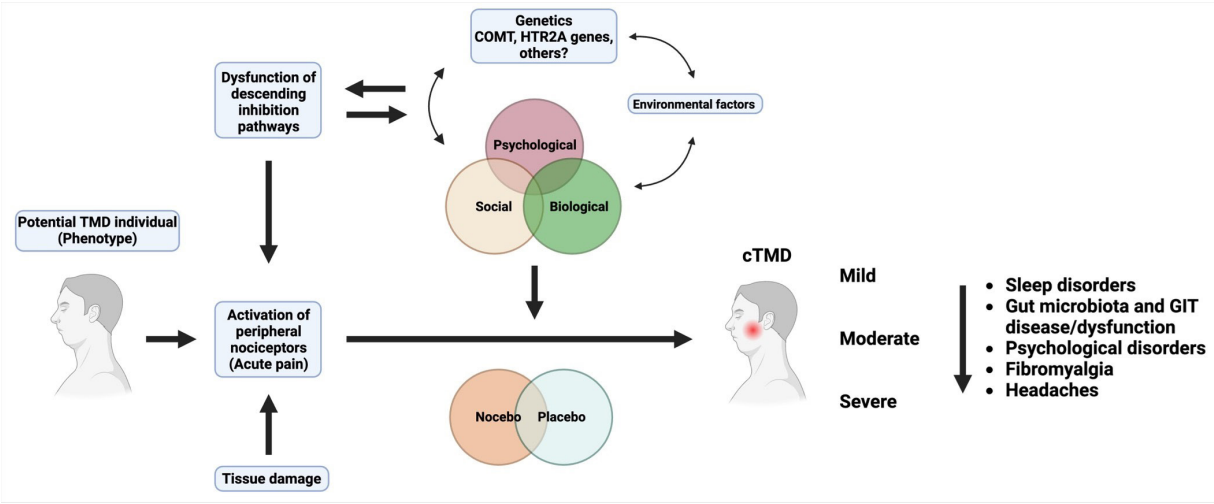
Genetics and epigenetics exert influence on both chronic pain and the psychological constitution of individuals, shaping neuroanatomical pathways and function. Chronic pain, characterised as pathological, is distinctly outlined in the ICD-11 classification, emphasising the absence of pathology at the pain site. Instead, the focus shifts to neural pathways, influenced by various factors such as psychological elements, sleep patterns, emotional trauma and immune system irregularities, which collectively contribute to the final experience of pain. Central sensitisation emerges as a pivotal factor in cTMD, playing a central role in amplifying pain perception and sensitivity among affected individuals. The supporting evidence for the biopsychosocial model in the context of cTMD is robust. We propose a tentative model illustrating the intricate interplay between biological and psychosocial factors, forming a cascade that culminates in cTMD as a disorder of neural and psychological pathways. This model underscores the imperative need to address biological, psychological and social factors comprehensively in the assessment and management of temporomandibular disorders.

Figure 1: Constructing the cTMD patient.



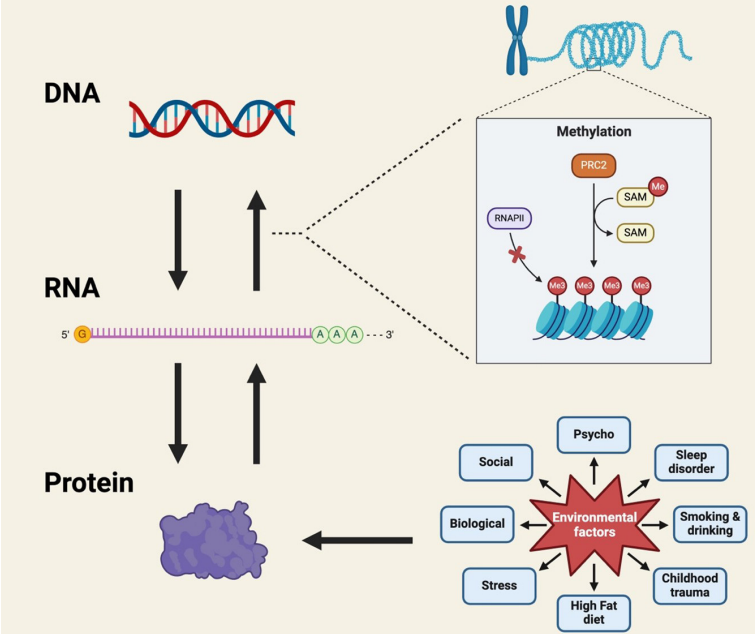
This model integrates both temporal (developmental) and biopsychosocial (construct) perspectives. It underscores the intricate interplay between genetic factors, which are influenced by psychosocial and other biological elements, culminating in noteworthy epigenetic changes. Created with BioRender.com

Figure 2: Transitioning to cTMD entails activation through diverse triggers.



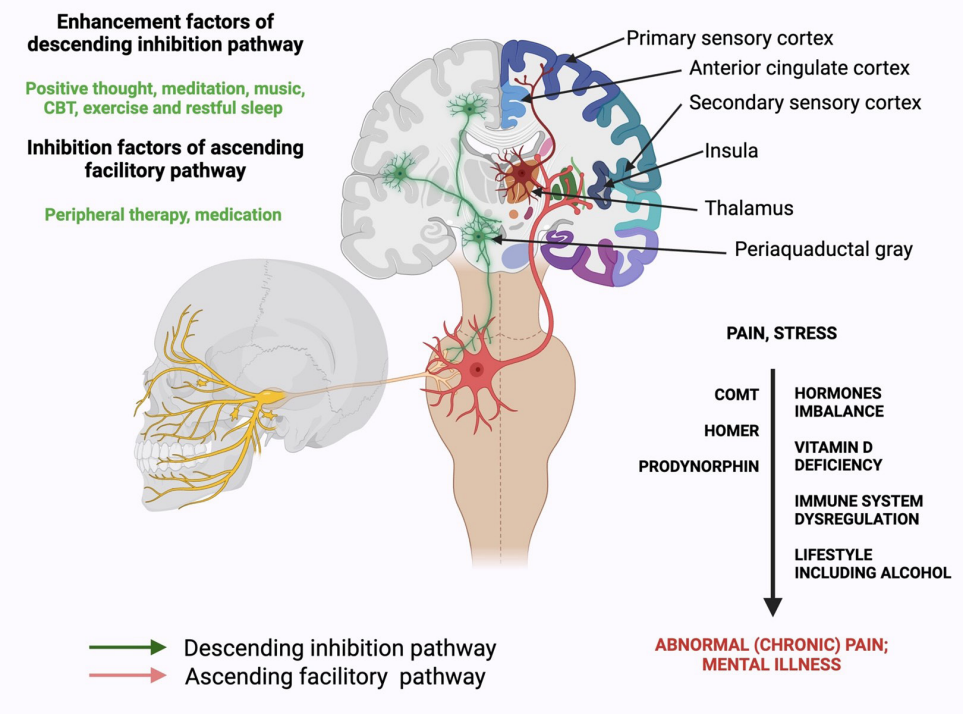
Transitioning to cTMD entails activation through diverse triggers. It elucidates the modelling of this intricate process, incorporating constructs from both the biopsychosocial model and the nocebo/placebo model. The severity of this transition is intricately shaped by a multitude of factors visually depicted in the figure. Created with BioRender.com

Figure 3: DNA, RNA and methylation.



Typically, the genetic programme follows the sequence from DNA to RNA; however, it is noteworthy that RNA also has the capacity to modify DNA. The realm of epigenetics has illuminated an intriguing phenomenon wherein environmental factors, utilising processes such as histone methylation, can exert influence on gene expression. Created with BioRender.com

Figure 4: The trigeminal pathway.



Environmental triggers, including hormonal imbalances, vitamin deficiencies, immune system dysregulation and lifestyle choices, have the potential to adversely impact pain. The modulation of descending inhibition can be augmented through self-directed interventions and medications, ultimately leading to a reduction in pain. Created with BioRender.com

COMPETING INTERESTS
The authors have no conflict of interest to declare.

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