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Temporomandibular disorders and mental health: shared etiologies and treatment approaches

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Abstract

The biopsychosocial model suggests that temporomandibular disorders (TMDs) often coexist with mental health disorders, particularly depression and anxiety, affecting a significant portion of the global population. The interplay between TMDs and mental health disorders contributes to a complex comorbidity, perpetuating a cycle of mutual influence and reinforcement. This review investigates the neurobiological mechanisms and epidemiological evidence supporting the shared etiology of TMDs and mental health disorders, exploring potential shared vulnerabilities and bidirectional causal relationships. Shared vulnerabilities between TMDs and mental health disorders may stem from genetic and epigenetic predispositions, psychosocial factors, and behavioral aspects. Inflammatory cytokines, neurotransmitters, neurotrophins, and neuropeptides play pivotal roles in both peripheral and central sensitization as well as neuroinflammation. Brain imaging studies suggest that TMDs and mental health disorders exhibit overlapping brain regions indicative of reward processing deficits and anomalies within the triple network model. Future research efforts are crucial for developing a comprehensive understanding of the underlying mechanisms and confirming the reciprocal causal effects between TMDs and mental health disorders. This review provides valuable insights for oral healthcare professionals, stressing the importance of optimizing treatment strategies for individuals dealing with concurrent TMDs and mental health issues through a personalized, holistic, and multidisciplinary approach.

Keywords Temporomandibular disorders, Mental health disorders, Depression, Anxiety, Peripheral sensitization, Central sensitization, Neuroinflammation, Brain reward system, Triple network model

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Introduction

Temporomandibular disorders (TMDs) encompass a range of conditions affecting the temporomandibular joint (TMJ), masticatory muscles, and related tissues. These disorders are typically characterized by pain and functional impairments [1]. TMDs represent a significant public health concern, ranking as the second most prevalent source of musculoskeletal pain behind low back pain, with prevalence estimating ranging from 5 to 12% [2]. Although the prevalence of TMDs symptoms is not age-specific, the age group most affected is adults aged 20 to 40 years [3]. Additionally, epidemiological studies have demonstrated that women are significantly more likely than men to experience TMDs symptoms [3]. Despite the complexity and incomplete understanding of TMDs etiology, a biopsychosocial model is often employed to elucidate the interplay between biological, psychosocial factors in these conditions [4]. According to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), TMDs are classified into two main categories: ① pain-related conditions, which include myalgia, arthralgia, and TMDs-related headache; ② joint disorders, which consist of various types of disc displacement, degenerative joint disorders, and subluxation [5]. Chronic pain conditions beyond headaches are also commonly associated with TMDs, including fibromyalgia, myofascial pain, and orofacial neuralgia following whiplash-associated trauma [6, 7]. These conditions may serve as differential diagnoses in clinical assessments. Acute painful TMDs are typically self-limiting and have a favorable prognosis, while chronic painful TMDs are associated with persistent functional impairment and mental health disorders [8]. Additionally, the Graded Chronic Pain Scale (GCPS) serves as a biopsychosocial screening tool for the subtyping of painful TMDs [9, 10].

Both chronic pain and mental health disorders contribute to approximately 11% of global disability, underscoring their combined detrimental effects on overall health as well as their significant societal and economic impacts [11, 12]. A systematic review found that the prevalence of moderate-to-severe somatization and depression was high among TMDs patients, while severe physical impairment was rarely reported [13]. Manfredini et al. found the association between Axis I diagnoses and pain-related impairment was not significant [14]. Predictors of high pain-related disability were mainly associated with psychosocial factors including severe depression, somatization, and elements related to the pain experience, such as chronic pain lasting more than six months and a tendency to seek treatment [14]. What's more, higher levels of pain-related impairment were associated with the most severe scores of depression and somatization [15].

Persistent pain can lead to maladaptive thought patterns and behaviors, impair daily functioning, increase psychological distress, and potentially exacerbate the pain experience. A recent study suggested that a cohort of patients diagnosed with persistent orofacial pain (POFP) who began treatment at age 25 could only expect to accumulate a mere 18 Quality-Adjusted Life Years (QALYs) per individual before their demise. This alarming projection served to underscore the profound and far-reaching long-term consequences associated with this disorder [16]. In TMDs patients, various mental health disorders have been found to be linked to heightened levels of pain and disability. These factors include psychological distress, pain catastrophizing, fear-avoidance behaviors, depression, anxiety, and passive coping strategies. Numerous cross-sectional studies have highlighted these associations [17–19], but the mechanisms underlying their comorbidity remain unclear. It is essential to explore whether the relationship between TMDs and mental health disorders is causal in nature and what factors mediate this causality, as this has significant clinical implications.

Generally, the mechanisms underlying comorbidities can be categorized as follows [20]: (1) one disease precipitates the onset of another; (2) pharmacological treatment for the initial disease induces the subsequent disease; (3) a common risk factor contributes to the development of both diseases; (4) a secondary disease facilitates the emergence of both primary diseases; or (5) correlated risk factors, each independently contributing to the onset of one of the diseases. The mechanisms mentioned above may more or less be present in the interaction between TMDs and mental health disorders, where they influence and reinforce each other, ultimately leading to a "vicious circle" (Fig. 1). In this review, we explored the potential comorbid mechanisms between TMDs and mental health disorders by examining both clinical and preclinical evidence, aiming to offer more comprehensive approaches to their treatments and managements. This review places its emphasis on the painful TMDs within the classification of TMDs, and primarily focuses on the symptoms of depression and anxiety as key types of mental health disorders.

Potential shared vulnerabilities

Potential shared vulnerabilities of TMDs and mental health disorders may involve genetic/epigenetic predisposition, psychosocial and behavioral factors.

Genetic/epigenetic predisposition

At present, there is limited evidence that TMDs and mental health disorders share genetic or epigenetic risk factors. The Val158Met polymorphism (rs4680) in the catechol-O-methyltransferase (COMT) gene may help explain the frequent coexistence of mental health disorders and TMDs [21–23]. An animal study demonstrated

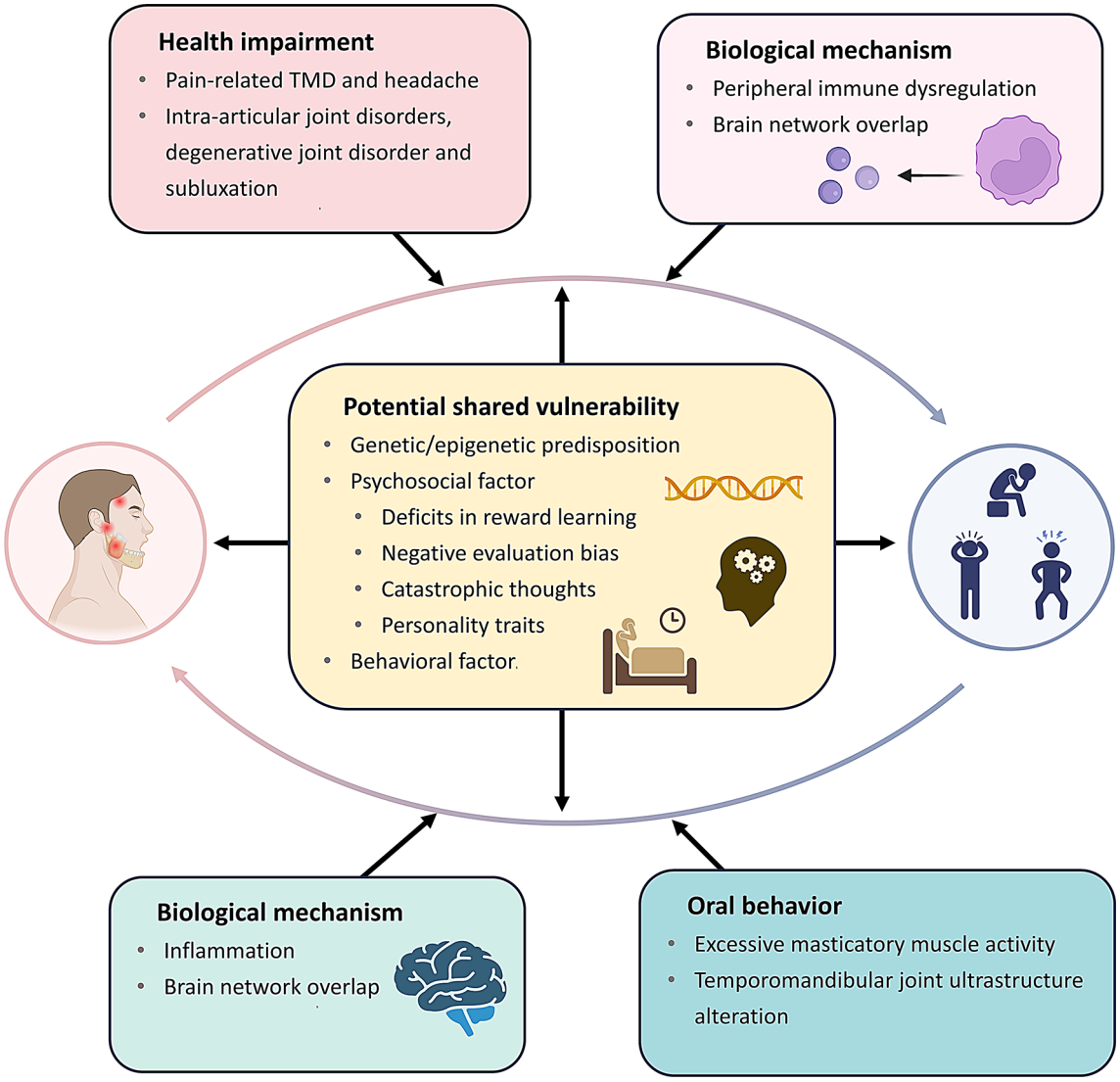

Fig. 1 Potential aetiopathogenic mechanisms of the interaction between TMDs and mental health disorders

that low levels of COMT, combined with stress, exacerbate functional pain and depressive behaviors, particularly in female mice [24]. Additionally, Slade et al. found that low-activity COMT diplotype interacts with increased environmental stress, which elevates the risk of developing TMDs [25]. In a prospective cohort study, 2,737 individuals without TMDs underwent assessment for common genetic variation in 358 genes associated with affective distress, nociceptive pathways and inflammation. While no single nucleotide polymorphism (SNP) was significantly associated with the risk of TMDs onset after correction for multiple comparisons using the Bonferroni method, several SNPs, such as prostaglandin-endoperoxide synthase 1 (PTGS1) and amyloid-β (A4) precursor protein (APP), exceeded the thresholds for association with intermediate phenotypes predictive of TMDs onset when applying the false discovery rate approach [26]. *PTGS1* was found to be associated with global psychological symptoms, playing a pivotal role in regulating neuronal sensitivity to pain and mediating inflammatory responses. In addition, it was suggested that *APP* polymorphisms might contribute to impairments in coping mechanisms for stressful life events among individuals affected by TMDs.

Psychosocial factors

Deficits in reward learning

Deficits in reward learning predispose individuals to maladaptive responses to chronic pain and depression, particularly following psychological or somatic trauma [27]. These deficits not only exacerbate reward processing dysfunction but also increase vulnerability to both conditions. Clinical outcomes are significantly influenced by patients' expectations for pain relief and quality of life

improvement; higher expectations are associated with better results [28]. Additionally, deficits in reward learning predisposed individuals to depression. A longitudinal study demonstrated that dysfunction in reward processing acted as a biobehavioral predictor for adolescent depression [29]. Evidence also supported that anhedonia served as a possible predictor of treatment outcomes and remission times in depression patients [30, 31]. Increased affective distress often correlates with lower expectations of pain relief, underscoring the interconnectedness of reward processing, pain, and depression.

Negative evaluation bias

Chronic pain patients are inclined to perceive ambiguous stimuli as pertaining to pain or illness. And this bias towards negative interpretations is a known risk factor for developing mental health disorders [32]. Trait anxiety, somatosensory amplification, and hypervigilance are three psychological constructs linked to TMDs, forming a significant triad connecting various psychosocial states [33]. Trait anxiety, characterized by perceiving situations as threatening, avoiding anxiety-provoking scenarios, and exhibiting high baseline physiological arousal, may potentially result in increased masticatory muscle activity and more severe episodes of tooth clenching during waking hours [34]. Individuals with somatosensory amplification tended to experience normal bodily sensations intensely, perceiving them as painful and bothersome. Individuals with heightened somatosensory amplification tended to experience abnormal occlusal sensitivity [35, 36]. This phenomenon might be attributed to threat-related attentional bias. Individuals with heightened somatosensory amplification might perceive occlusal or dental changes as potential threats, resulting in distinct sensory processing and behavioral responses compared to those who do not [35]. Bucci et al. found that patients with painful TMDs exhibited enhanced occlusal tactile sensitivity compared to healthy controls. This heightened sensitivity might be associated with patients' perception of pathological signals, which could in turn be linked to increased symptom severity [37].

Catastrophic thoughts

Catastrophic thoughts, including rumination, magnification, and helplessness, are pivotal in the development of mental health disorders [38]. Magnification, which involves worries about the severity of potential outcomes, and rumination, characterized by persistent reflection on the pain, are linked to primary appraisal processes. This highlights how individuals tend to focus on and amplify the threatening nature of painful stimuli. In contrast, helplessness, where individuals believe they cannot alleviate pain intensity, is associated with secondary appraisal processes, reflecting negative self-assessments of coping capacity [39]. Patients with TMDs who have pain-related disability tended to exhibit higher levels of catastrophic thoughts compared to those without disability [19]. These findings emphasized a strong association between pain catastrophizing and disability in chronic TMDs sufferers.

Personality traits

The influence of personality traits on the onset of TMDs and mental health disorders is another area worthy of further investigation. The personality trait of neuroticism is associated with anxiety and depression. In a recent study, Zhang and colleagues found that both MDD and subjective well-being were strongly genetically associated with neuroticism, supported by significant bidirectional causal effects and shared genetic enrichment, indicating common genetic factors [40]. Neuroticism also has an effect on the quality of life related to oral health. Individuals with higher neuroticism levels are associated with heightened TMDs pain perception and increased parafunctional behaviors [41–43]. Furthermore, individuals with high emotional stability and conscientiousness personality traits were significantly less associated with TMDs symptoms [41, 43]. In addition, low extraversion was associated with various symptoms (limited jaw movements, joint sounds, and masticatory muscle tenderness), and high extraversion was associated with a specific oral habit—teeth clenching behavior [41, 43].

Behavioral factors

Poor subjective sleep quality is a significant predictor of TMDs, surpassing traditional risk factors [44]. Insomnia can lead to hyperalgesia and may trigger or worsen spontaneous pain symptoms. It is also crucial to recognize that insomnia contributes to the onset of mental health disorders [45]. A systematic review and meta-analysis further revealed the mediating effect of sleep quality on the relationship between depression and chronic pain [46]. Additionally, Yang et al. found the mediating effect of sleep quality on the association between mental health disorders and TMDs pain [47].

Bidirectional casual relationship between TMDs and mental health disorders

The relationship between TMDs and mental health disorders is likely bidirectional and mutually reinforcing. However, some studies provide only partial support for this hypothesis [48, 49].

Some Mendelian randomization (MR) studies and Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) studies have found that anxiety, depression, and somatic symptoms are risk factors for TMDs [48–51]. Fillingim et al. conducted an analysis of 26 psychosocial measures, identifying the frequency of somatic

symptoms as the most significant predictor of TMDs incidence. In comparison, pain-coping strategies and mental health disorders, such as psychological stress, anxiety, and obsessive-compulsive feelings, were found to have a comparatively weaker impact on predicting TMDs incidence [52]. In addition, mental health disorders are closely associated with increased jaw motor responses, potentially mediated through the paraventricular hypothalamic nucleus and the trigeminal premotor area circuit [53]. Oral behaviors, such as clenching or grinding, can increase the load and mechanical stress on the TMJ, leading to pathological changes in the joint and surrounding tissues [54]. However, whether oral behaviors directly cause TMDs pain remains controversial. Svensson et al. reported that TMDs pain caused by clenching or grinding was typically mild and transient, which did not explain persistent orofacial pain [55]. While psychological factors may exacerbate pain by inducing oral behaviors, Yang et al. didn't observe the mediating effect of oral behaviors on the association between mental health disorders and TMDs pain [47]. In addition, a case-control study demonstrated that there was no association between sleep bruxism, as diagnosed by polysomnographic examination, and TMDs [56]. However, further longitudinal studies are needed to clarify the causal relationship.

In general, chronic pain is significantly associated with mental health disorders such as depression and anxiety. Long-term pain not only reduces quality of life and daily activities but also leads to a decline in hedonic pleasure and motivation. More severe pain is often linked to a further decrease in pleasure, which can eventually trigger or worsen mental health problems [57]. However, in a recent bidirectional two-sample MR study, Que et al. found that genetically predicted depression had a causal effect on TMDs, while anxiety disorder did not, and there was no strong evidence of TMDs causing depression or anxiety [49]. Another MR study discovered that major depressive disorder (MDD) and panic disorder were associated with a heightened risk of TMDs, yet failed to identify any causal link between TMDs and these psychiatric conditions on the reverse MR analysis [48].

In summary, to clarify the nature of the bidirectional interaction, the etiological model emphasizes the need for longitudinal research to establish temporal precedence. At present, the quality of the available evidence is inadequate, and establishing causality in this area remains challenging.

Neurobiological mechanism overlap

Pathophysiological mechanisms

Painful TMDs activate both the ascending pain pathway and the descending pain regulation system [58] (Fig. 2). Pain signals are conveyed through primary sensory neurons in the trigeminal nerve to the trigeminal ganglion (TG). These signals are then relayed to the spinal trigeminal nucleus caudalis (SpVc) through spinal trigeminal tract. From the brainstem, the signals ascend to ventral posterior medial nucleus in the thalamus (VPM) through trigeminal-thalamic tract. The VPM then project to various cortical areas, such as the primary and secondary somatosensory cortices (S1 and S2), the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), insular cortex (IC) and the amygdala. The nociceptive input transmitted to the SpVc also projects to the parabrachial nucleus (PBN), which further relays signals to the VPM, the periaqueductal gray (PAG), the amygdala.

Ascending afferent pain signals activate descending pathways from the PAG in the midbrain, modulating pain perception. The PAG receives projections from the S1 and S2, the PFC, the ACC, the IC, and the amygdala. The rostral ventromedial medulla (RVM) is a critical nucleus in the descending inhibitory and facilitatory systems, receiving inputs from the PAG, PBN, and locus coeruleus (LC). Neuronal activity within the RVM can produce either inhibitory or facilitatory effects on pain. This integrated network ensures precise pain perception and modulation, maintaining a balanced nociceptive response. Anomalies in descending pain modulation may enhance pain perception in patients suffering from painful TMDs.

Peripheral sensitization and central sensitization are two key mechanisms for the exacerbation and chronicity of painful TMDs. Peripheral sensitization increases the responsiveness and lowers the pain threshold of nociceptive neurons to stimulation in the fields of tissue damage [59] (Fig. 3). Tissue injury releases inflammatory chemical mediators, which subsequently activate immune cells, such as neutrophils, mast cells and macrophages. Activated immune cells subsequently produce inflammatory mediators like serotonin (5-HT), Prostaglandin E2 (PGE_2), nerve growth factor (NGF), adenosine triphosphate (ATP), tumor necrosis factor-α (TNF-α), and Interleukin-1β (IL-1β), which stimulate receptors on nociceptive terminals more frequently, perpetuating the inflammatory process. In addition, inflammatory mediators acting on TG neuron nociceptors can upregulate the expression of transient receptor potential vanilloid subtype 1 (TRPV1) channel, inducing calcium influx and releasing neuropeptides such as Substance P (SP) and calcitonin gene-related peptide (CGRP). These neuropeptides affect the vasculature and directly attract and activate immune cells, contributing to sustained nociceptor activation [60].

In the TG, the interaction between TG neurons and satellite glial cells (SGCs) is vital for promoting peripheral sensitization [61]. SP released from TG neurons activates SGCs via the ERK1/2 and p38 signaling pathways,

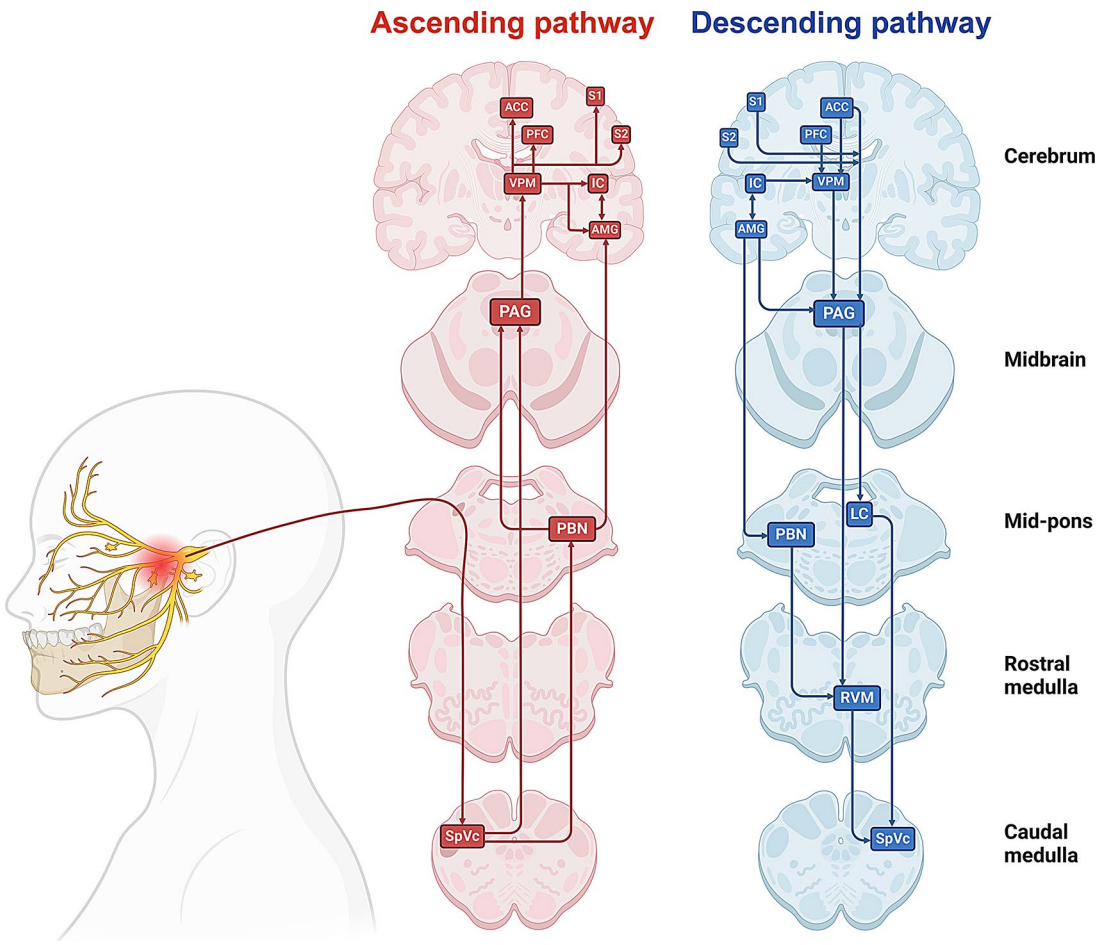

Fig. 2 The ascending and descending pathway of pain. Abbreviations: S1, the primary somatosensory cortices; S2, the secondary somatosensory cortices; PFC, prefrontal cortex; ACC, anterior cingulate cortex; IC, insular cortex; AMG, amygdala; PAG, periaqueductal gray; RVM, rostral ventromedial medulla; SpVc, spinal trigeminal nucleus caudalis; LC, locus coeruleus; PBN, parabrachial nucleus; NAc, nucleus accumbens; VTA, ventral tegmental area. Created with BioRender.com

facilitating the secretion of pro-inflammatory cytokines such as IL-1β, TNF-α, and CCL2 [62]. Similarly, CGRP acting on SGCs can induce the expression of pro-inflammatory factors like TNF-α and IL-1β [63]. The activation of IL-1R and TNFR can upregulate voltage-gated sodium channel 1.7 ($Na_v1.7$) and TRPV1 channels in TG neurons [64]. Abnormalities in glutamate and extracellular K^+ levels are anticipated to enhance neural activity, while peripheral inflammation decreases inwardly rectifying potassium channel 4.1 (Kir4.1) currents in SGCs [65]. When glutamate binds to N-methyl-D-aspartate receptor (NMDAR), it triggers Ca^{2+} influx, promoting cAMP production and activating the ERK-CREB signaling pathway in response to inflammatory stimuli [66]. Additionally, SGCs communicate through gap junctions, while neurons communicate via signals such as NGF, NO, and ATP, leading to the activation of adjacent TG neurons [61]. The P2Y14 receptor in the TG may contribute to orofacial inflammatory pain by regulating SGCs activation and the release of cytokines including IL-1β, TNF-α, and CCL2, along with phosphorylating ERK1/2 and p38 [67].

Central sensitization refers to the increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent signals [68]. This phenomenon typically occurs in tissues without harmful conditions [59, 69] (Fig. 4). Nociceptive input induces the release of ATP, glutamate, and SP from the terminals of primary neurons. The sustained release of glutamate and SP facilitates Ca^{2+} entry into the neuron, activating intracellular pathways [70]. Under normal conditions, inhibitory interneurons continuously release gamma-aminobutyric acid (GABA) and/or glycine to decrease the excitability of secondary neurons [70]. The descending pain modulation system releases 5-HT and norepinephrine (NE), which not only decrease the release of glutamate and SP from primary neurons but also act on inhibitory interneurons, prompting them to release endogenous opioid peptides (EOPs), thereby alleviating pain [71–74]. Additionally, ATP, fractalkine, and

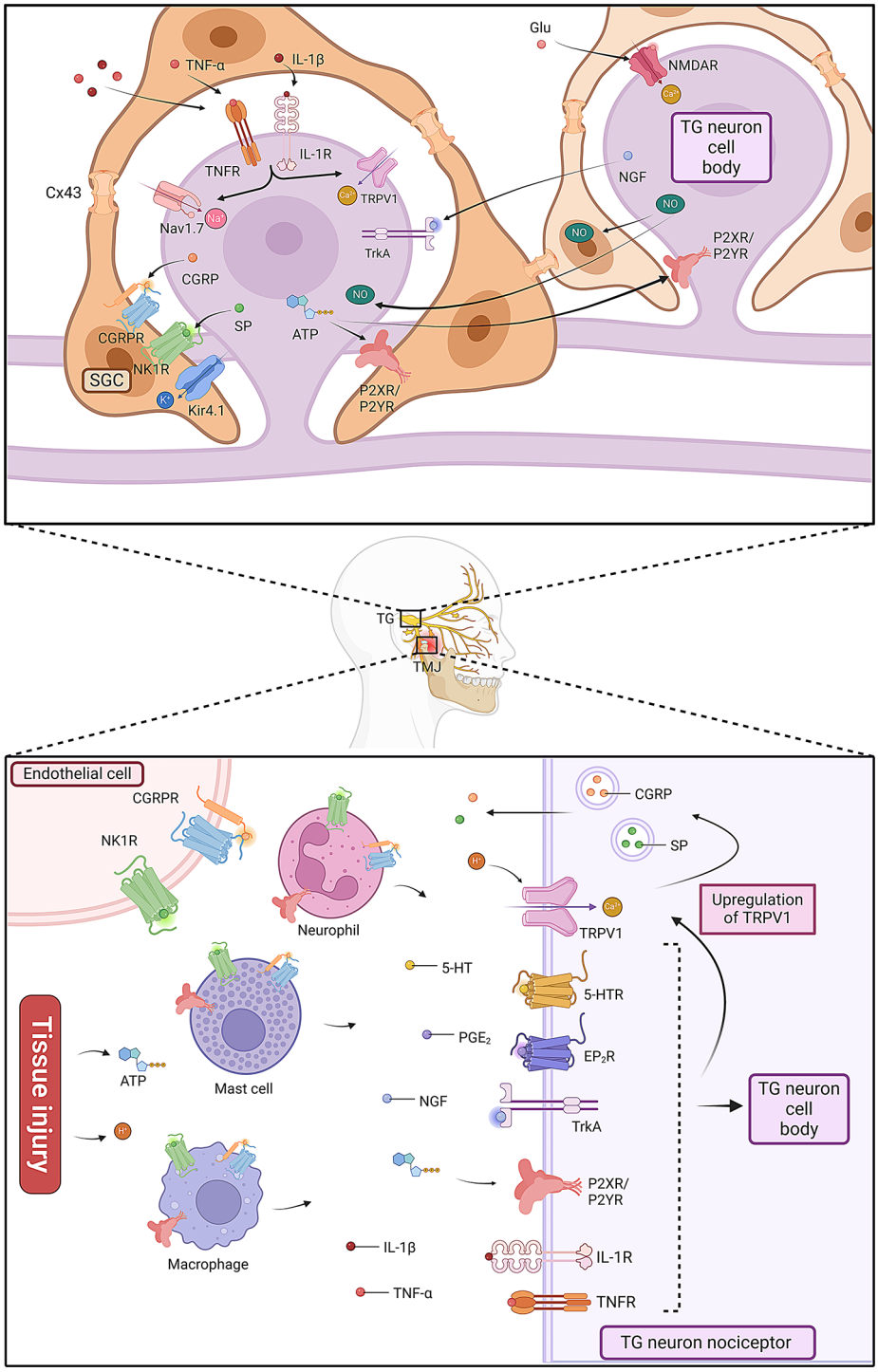

Fig. 3 Mechanisms of peripheral sensitization. Abbreviations: TG, trigeminal ganglion; TMJ, temporomandibular joint; ATP, adenosine triphosphate; SP, substance P; CGRP, calcitonin gene-related peptide; NK1R, neurokinin-1 receptor; 5-HT, serotonin (5-hydroxytryptamine); PGE_2, Prostaglandin E2; NGF, nerve growth factor; IL-1β, Interleukin-1β; TNF-α: tumor necrosis factor-α; TRPV1, transient receptor potential vanilloid 1; EP_2R, E-prostanoid 2 receptor; TrkA, tropomyosin receptor kinase A; P2XR/P2YR, P2X/Y receptor; SGC, satellite glial cells; Cx43, connexin 43; $Na_v1.7$, voltage-gated sodium channel 1.7; Kir4.1, inwardly rectifying potassium channel 4.1; Glu, glutamate; NMDAR, N-methyl-D-aspartate receptor. Created with BioRender.com

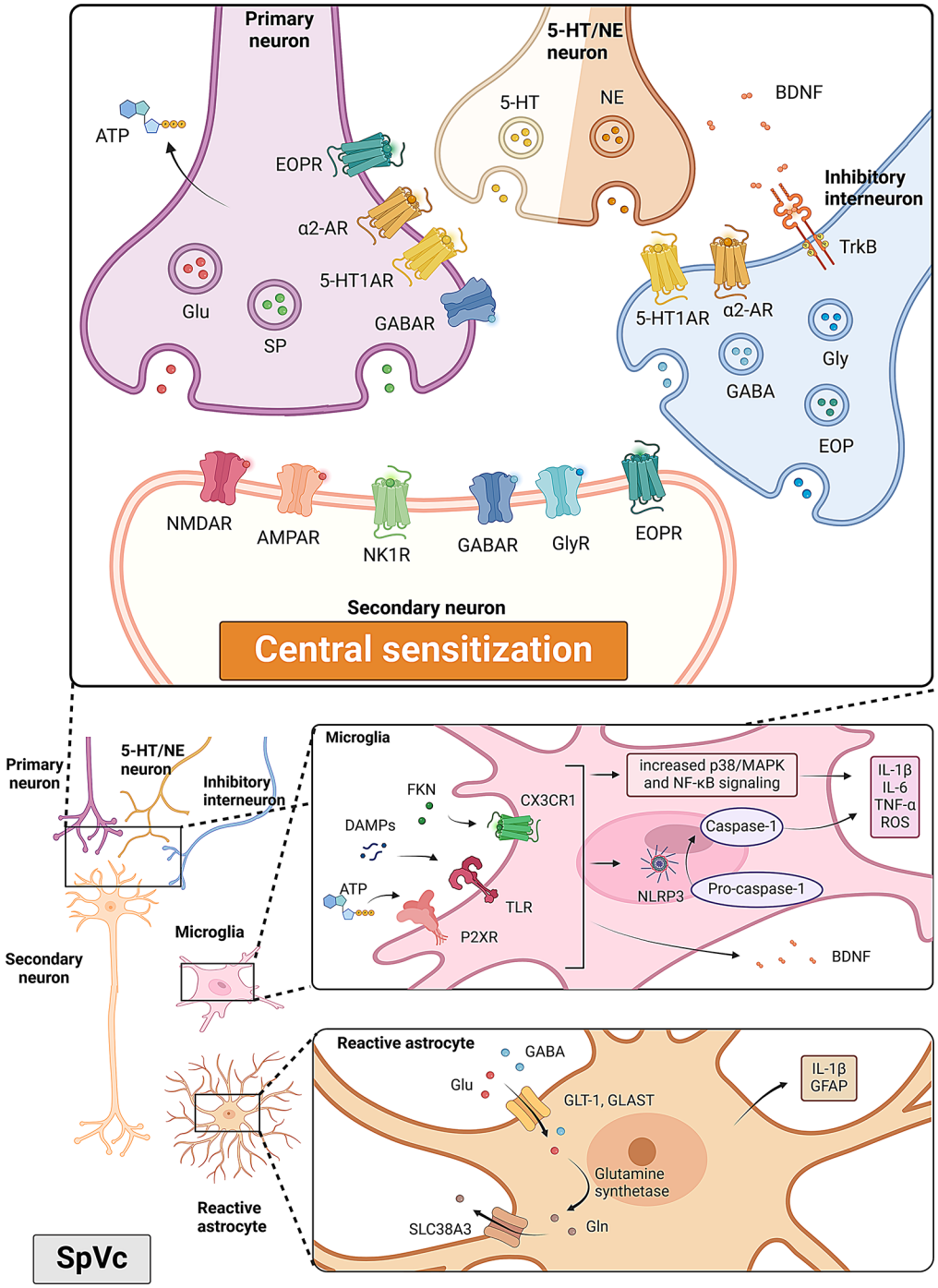

Fig. 4 Mechanisms of central sensitization. Abbreviations: ATP, adenosine triphosphate; SP, substance P; Glu, glutamate; EOPR, endogenous opioid receptor; α2-AR, alpha-2 adrenergic receptor; 5-HT1AR, 5-hydroxytryptamine 1 A receptor; GABAR, gamma-aminobutyric acid receptor; 5-HT, serotonin (5-hydroxytryptamine); NE, norepinephrine; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; GABA, gamma-aminobutyric acid; Gly, glycine; EOP, endogenous opioid peptide; NMDAR, N-methyl-D-aspartate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NK1R, neurokinin-1 receptor; GlyR, glycine receptor; DAMPs, damage-associated molecular patterns; FKN, frac-talkine; P2XR, P2X receptor; TLR, Toll-like receptor; CX3CR1, CX3C chemokine receptor 1; NLRP3, NOD-like receptor family pyrin domain containing 3; GLAST, glutamate transporters glutamate-aspartate transporter; GLT-1, glutamate transporter-1; Gln, Glutamine; GFAP, glial fibrillary acidic protein; SLC38A3, solute carrier family 38 member 3; SpVc, spinal trigeminal nucleus caudalis. Created with BioRender.com

damage-associated molecular patterns (DAMPs) can bind to P2X receptor (P2XR), CX3C chemokine receptor 1 (CX3CR1), and Toll-like receptors (TLR) on the surface of microglia, respectively. This binding results in microglial inflammatory activation, which causes an abnormal increase in the release of proinflammatory cytokines and brain-derived neurotrophic factor (BDNF). BDNF acts on inhibitory interneurons, causing them to become excitatory, leading to allodynia [75]. In addition, inflammatory processes can activate the p38 MAPK/NF-κB pathway and induce the transcription of NLRP3 in microglia, resulting in an abnormal increase in the release of ROS and inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which contribute to central sensitization [76, 77]. What's more, reactive astrocytes release glial fibrillary acidic protein (GFAP) and IL-1β. The astroglia glutamate-glutamine shuttle is a critical mechanism supporting central sensitization [78]. Activation of astrocytes can lead to an imbalance in glutamate and GABA levels, resulting in an unequal input from excitatory and inhibitory neurons, thereby amplifying pain signals.

Under pathological pain conditions, inflammation stimulates the expression of indoleamine 2,3-dioxygenase 1 (IDO1) in macrophages and dendritic cells, leading to an increase in kynurenine metabolites and a simultaneous reduction in tryptophan and 5-HT levels [79]. Elevated plasma kynurenine crosses the blood-brain barrier, encouraging microglia to produce excitotoxic compounds, such as quinolinic acid, which further reduces 5-HT synthesis within the brain [80]. Additionally, quinolinic acid contributes to neuronal excitotoxicity and induces the production of reactive oxygen species and nitric oxide, causing oxidation of tetrahydrobiopterin and diminishing dopamine synthesis in the brain [81]. This upregulation of the kynurenine pathway and a subsequent decrease in dopamine synthesis in the brain heighten the risk of developing depression [82]. Moreover, some cytokines, including IL-1, IL-6, TNF, CCL2, CCL11 and cytokine-induced neutrophil chemoattractant-1, and peripheral immune cells like neutrophils, macrophages are capable of crossing the blood-brain barrier under pathological conditions [83]. Moreover, the interaction between astrocytes and microglia plays a crucial role in neuroinflammation [84]. These mechanisms may lead to the damage of neurons and oligodendrocytes, potentially resulting in the comorbidity of painful TMDs and mental health disorders (Fig. 5).

Specifically, inflammatory cytokines, neurotransmitter, neurotrophins, and neuropeptide play an important role in the pathophysiological mechanism of TMDs and mental health disorders.

Inflammatory cytokines

Shared inflammatory cytokines may be a common mechanism underlying the comorbidity of TMDs and mental health disorders (Fig. 6). Patients with TMDs exhibit elevated levels of pro-inflammatory cytokines, including IL-1α, IL-1β, IL-6, IL-8, TNF-α and TNF-β, as well as anti-inflammatory cytokines such as IL-4, IL-10, IL-13, interleukin-1 receptor antagonist (IL-1ra), in both plasma and masticatory muscles [85]. When the production of pro-inflammatory cytokines is reduced, patients often experience significant improvements in pain symptoms [86]. The presence of elevated anti-inflammatory cytokines indicates a localized production aimed at counteracting inflammation. However, this compensatory response may be insufficient. Additionally, chronic inflammation affects collagen structures, leading to the deterioration of the ultrastructure and nanomechanical properties of TMJ discs [87]. Elevated levels of collagenases (MMP-1, MMP-8, MMP-9, MMP-13), matrix metalloproteinase-3 (MMP-3), and gelatinases (MMP-2, MMP-7) can be detected in the synovial fluid of the TMJ [85].

Dysregulation of the peripheral immune system may represent an essential mechanism driving brain alterations that underpin the pathophysiology of mental health disorders [88, 89]. The levels of IL-1β, IL-6, and TNF-α entering the bloodstream from the brain can be significant enough to elevate their concentrations in the blood [83]. In addition, as previously mentioned, neuroinflammation may play a role in causing depression. Therefore, it seems reasonable to assume that peripheral immune dysregulation associated with TMDs may serve as a potential pathway for eliciting functional and structural brain alterations, leading to mental health disorders. In turn, pro-inflammatory cytokines enhanced by mental health disorders possibly mediate muscle and joint hyperalgesia, potentially increasing pain sensitivity by sensitizing nociceptors in peripheral nerves.

Neurotransmitter

Glutamate Glutamate plays an important role in pain processing, peripheral and central sensitization. A case-control study demonstrated elevated plasma and salivary glutamate concentrations in TMDs-myalgia patients, though these levels lacked significant association with self-reported pain intensity [90]. Notably, the study additionally identified reduced salivary NGF and BDNF, alongside elevated plasma BDNF levels, which exhibited a significant association with psychological maladjustment [90]. Increased expression of peripheral NMDARs in women might be associated with heightened pain sensitivity in the masseter muscle [91]. There is a functional, bidirectional interaction between glutamate receptors and TRP channels that influences the modulation of tri-

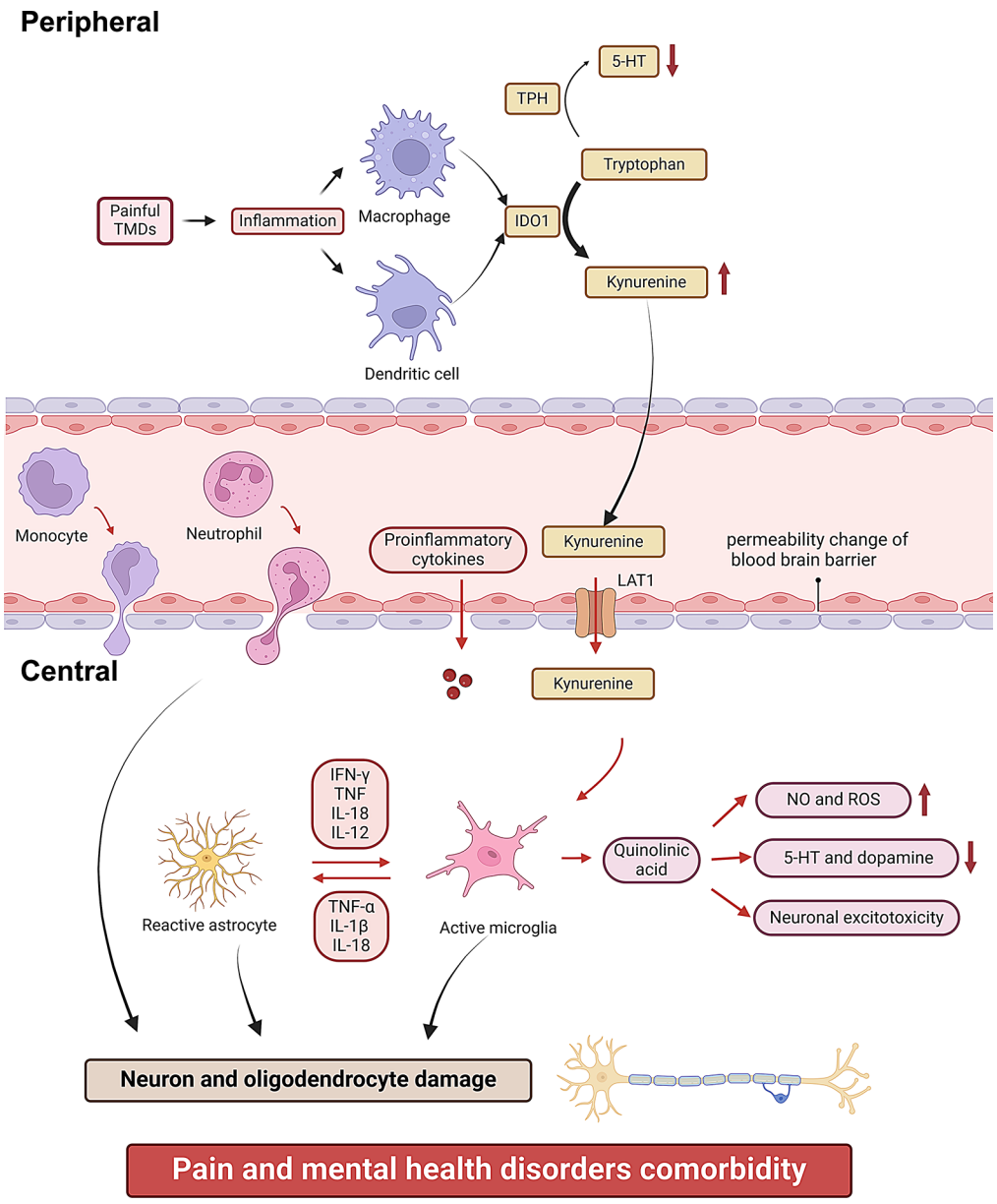

Fig. 5 Mechanisms of neuroinflammation. Abbreviations: TPH, tryptophan hydroxylase; IDO1, indoleamine 2,3-dioxygenase 1; 5-HT, serotonin (5-hydroxytryptamine); LAT1, large amino acid transporter 1; TNF-α: tumor necrosis factor-α; IL-1β, Interleukin-1β; IFN-γ, Interferon-γ; NO, nitric oxide; ROS, reactive oxygen species. Created with BioRender.com

geminal nociceptors. When glutamate receptors are activated, they trigger protein kinase C, which phosphorylates TRPV1. The combined sensitization of TRPV1 by both inflammatory mediators and glutamate receptors, alongside endogenous ligands, played a role in the development of masseter muscle hyperalgesia [92]. Additionally, concentrations of the glutamate and its precursor glutamine in pain-related brain regions showed a positive correlation with individual pain sensitivity [93].

GABA GABAergic neurons encompass both projection neurons and interneurons. In peripheral nervous system, Antonopoulos et al. found that the expression of $GABA_B$ receptor subunits ($GABA_{B1}$ and $GABA_{B2}$) in the TG was reduced in the model of chronic TMDs [94]. In addition, the activation of $GABA_B$ receptors in satellite glial cells within the TG has been shown to alleviate inflammatory facial allodynia. This activation also suppresses the ele-

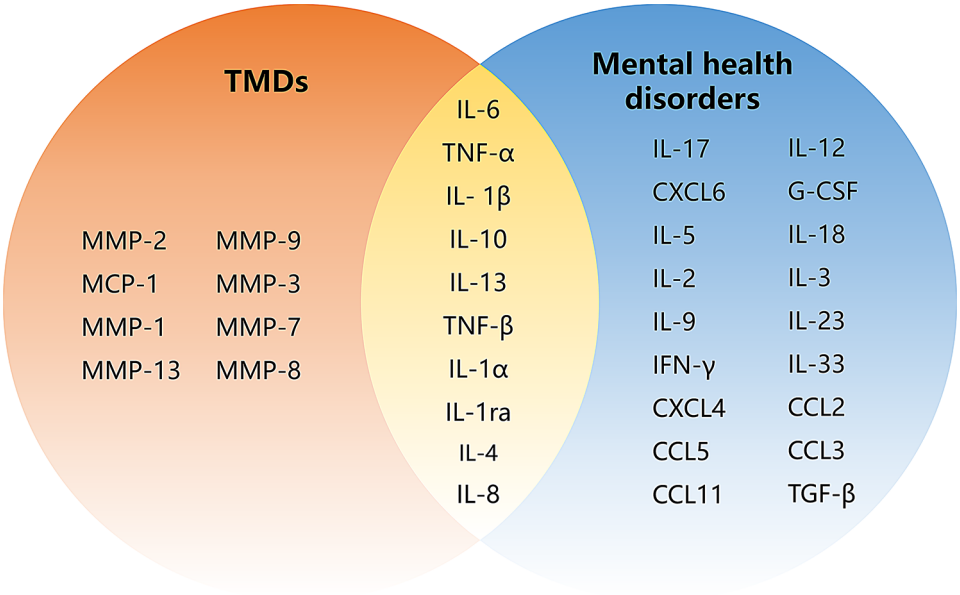

Fig. 6 Common inflammatory cytokines involved in TMDs and mental health disorders. The background color of the inflammatory cytokines indicates the frequency of abnormal changes observed in studies: darker shades represent inflammatory cytokines with a higher frequency of abnormalities, while lighter shades indicate lower frequencies. Data from [85, 88, 89]. MMP, matrix metalloproteinase; MCP, monocyte chemoattractant protein; IL, interleukin; TNF, tumor necrosis factor; CXCL, chemokine, CXC motif; CCL, chemokine, CC motif; IFN, interferon; TGF, transforming growth factor

vated expression of IL-1β in satellite glial cells observed during inflammatory allodynia [78].

In central nervous system, evidence suggested that inter-regional projections involving glutamatergic and GABAergic neurons played a crucial role in pain and mental health disorders. Xue et al. found that most rostral ventromedial medulla (RVM) neurons projecting to SpVc were either GABAergic, inhibiting craniofacial nociception, or glutamatergic, facilitating it [95]. Manipulating these pathways, either by activating GABAergic neurons or inhibiting glutamatergic neurons in SpVc, effectively reversed inflammation-induced masseter hyperalgesia. Zhu et al. identified that GABAergic neurons from the central amygdala projected to glutamatergic neurons in the parafascicular nucleus, highlighting the involvement of this pathway in regulating pain symptoms associated with depression through connections to the S2 [96]. Yan et al. observed increased excitation of a pathway involving glutamatergic neurons from layer 5 of the hindlimb S1 projecting to GABAergic neurons in the caudal dorsolateral striatum in mice with persistent inflammatory pain and comorbid anxiety symptoms [97]. Additionally, GABAergic neurons in the lateral septum were found to be hyperactivated under pathological conditions, where increased inhibitory output from the lateral septum to downstream brain regions contributed to the development of pain and anxiety. The GABAergic projections from the lateral septum to the lateral hypothalamus were particularly significant in regulating comorbid pain and anxiety [98]. Overall, disruptions in the glutamatergic and GABAergic systems within the central nervous system can lead to the onset of chronic pain and mental health disorders.

Monoamine Monoamine neurotransmitters, such as 5-HT, NE, and dopamine, are essential for the functioning of the nervous system [99]. The traditional monoamine hypothesis suggests that, alongside common pathogenic factors, a deficiency in these neurotransmitters is a primary contributor to depression [100].

Activation of 5-HT1A autoreceptors leads to reduced firing of serotonergic neurons, providing feedback control over 5-HT synthesis and release [101]. The activation of 5-HT1A heteroreceptors on neurons within the SpVc decreases the release of glutamate and SP at nociceptive terminals, thereby attenuating pain signals transmitted to the brain [74]. Similarly, the activation of 5-HT1A heteroreceptors on GABAergic neurons in brain regions reduces GABA-mediated inhibition of dopaminergic neurons, enhancing excitatory effects on the reward pathway, and thereby exerting an antidepressant effect [74]. Females exhibit a higher lifetime prevalence of mental health disorders and TMDs, which may be related to the influence of sex hormones on 5-HT [102]. Estrogen can regulate 5-HT synthesis, release, reuptake, and 5-HT1A receptor expression, thereby increasing central 5-HT levels. Progesterone, on the other hand, reduces the expression of the monoamine oxidase gene, increasing 5-HT levels in the synaptic space, which can help alleviate depression and pain [102]. In addition, Christidis et

al. discovered that female patients with myofascial TMDs had a higher number of putative nociceptors expressing the 5-HT3 receptor in the masseter muscle compared to healthy female controls, indicating a potential up-regulation of 5-HT3 receptors in myofascial TMDs [103].

The primary source of norepinephrine in the central nervous system is the LC-noradrenergic system, which becomes dysfunctional in chronic pain, contributing to pain amplification [104]. Notably, bilateral elevation of noradrenaline in the PFC has been linked to persistent pain, suggesting excessive activation of the noradrenergic system in chronic pain conditions [105]. Furthermore, projections from the LC to the basolateral amygdala are implicated in the encoding of traumatic memories, indicating that similar dysregulation may also occur in post-traumatic stress disorder and chronic pain scenarios [106, 107].

The plasma dopamine levels in patients with painful TMDs are significantly higher than in healthy individuals, and this increase correlates with both pain intensity and mental health disorders [108]. Conversely, patients exhibit reduced cerebrospinal fluid (CSF) dopamine concentrations, likely due to the long-term suppression of dopamine responses to pain by elevated tonic levels [108]. Chronic pain has been shown to significantly impair mesolimbic dopamine function, leading to disruptions in motivated behavior [109]. Pharmacological interventions that increase synaptic dopamine levels can enhance endogenous pain inhibition associated with reward and heighten pain facilitation linked to punishment [110]. Disturbances in dopaminergic control are associated with a lack of motivation and anhedonia, key features of depression [111].

BDNF

BDNF is widely distributed in the central nervous system, with particularly high expression in the hippocampus, cortex, and prefrontal areas, which is involved in pain and mental health disorders [112]. The antinociceptive effect of BDNF may be mediated centrally rather than peripherally [113]. Wang et al. demonstrated that BDNF increased T-type currents by activating TrkB, which in turn activated the PI3K-p38-PKA signaling pathway [114]. This process led to heightened neuronal excitability in TG neurons and contributed to pain hypersensitivity in rats [114]. Additionally, Liu et al. demonstrated that BDNF modulated depression and pain in a projection-specific manner within mesolimbic circuits during chronic mild stress (CMS)-induced depression [115]. The role of BDNF in the VTA→mPFC pathway was primarily reflected in the regulation of depressive-like behaviors, where the restoration of BDNF in the mPFC alleviated depressive symptoms. In contrast, in the VTA→NAc pathway, BDNF primarily influenced the regulation of pain, with an increase in BDNF in the NAc enhancing pain perception [115]. Furthermore, Kim et al. have demonstrated that activating the BDNF/TrkB pathway in the hippocampus and PFC can ameliorate depressive and anxiety-like behaviors [116]. However, elevated BDNF levels in the NAc are linked to the development of depression-like behaviors [117].

Neuropeptides

Several neuropeptides, such as CGRP, SP and EOP, playing crucial roles in pain perception, cognitive function, and emotional regulation.

Peripheral damage can trigger the release of CGRP by neurons in the TG. This released CGRP acts on adjacent sensory neurons via paracrine signaling, initiating a ganglion inflammatory cascade [118]. In TMDs mouse models, Suttle et al. discovered that activating TRPV4-expressing TG neurons led to the secretion of CGRP. This was linked to elevated CGRP levels in the masseter muscle, peri-TMJ tissues, the SpVc, and plasma [119]. In addition, CGRP heightens anxiety-like behaviors and neural activity by inhibiting anterolateral sector of BNST (BNST-AL) cells [120].

Upon receiving stimuli from inflammation or injury, SP is released and primarily binds to neurokinin-1 receptor (NK1R), which are widely expressed in the central nervous system, specifically in the PFC, amygdala, hippocampus, and hypothalamus [60]. SP can enhances the effects of glutamate within the synapse, thereby modulating pain. Furthermore, SP activates the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis, contributing to anxiogenic effects [121].

Trigeminal dynorphin could modulate TMDs-like masseter hypersensitivity, highlighting a female-specific role in the comorbidity of TMDs and migraine-like pain [122]. Research by Feldreich et al. demonstrated that reduced plasma β-endorphin levels were correlated with decreased TMJ pain following surgery [123]. Additionally, κOR antagonists have potential as novel treatments for MDD, especially in individuals who do not respond adequately to conventional antidepressants [124].

Brain network

The existence of overlapping brain networks involved in pain processing and emotion regulation may provide an explanation for the high comorbidity between TMDs and mental health disorders. Neuroimaging techniques, particularly magnetic resonance imaging (MRI), have been utilized to identify brain changes. A multimodal meta-analysis of 320 studies revealed that in MDD, ANX and CP, there was a common decrease in gray matter volume (GMV) in the dorsomedial PFC, lateral PFC, bilateral insula cortex, bilateral ACC, superior temporal gyrus (STG), and SMA. However, this analysis did not identify

any common increase in GMV or intrinsic Fc changes [125]. This section will explore the key brain regions overlap involved in TMDs and mental health disorders.

Mental health disorders are characterized by dysregulation across multiple brain regions, which are crucial for cognitive and emotional processes. Key areas involved include the PFC, the insula cortex, the ACC, the limbic system and so on (Supplemental Table 1). Alterations in brain function and structure also exist in patients with painful TMDs. In addition to the sensory-discriminative regions associated with pain, the affective-motivational and cognitive-evaluative regions are also involved [126] (Supplemental Table 2). There are several overlaps in the altered brain regions involved in TMDs and mental health disorders (Fig. 7A).

The identified comorbid abnormal pattern largely corresponds to the reward processing deficits (Fig. 7B), as well as the anomalies in the triple network model (Fig. 7C).

Impairments in brain's reward system, including reward deficiency and anti-reward, are common vulnerability factors for MDD, anxiety disorders (ANX), and chronic pain. These impairments contribute to negative moods, heightened anxiety, and reduced pain relief from external rewards [27]. The brain's reward system includes essential components such as the striatum, the VTA, the mPFC, the amygdala, the orbitofrontal cortex (OFC), and the ACC [127]. The striatum is divided into dorsal and ventral regions. The dorsal striatum consists of the caudate and the putamen, while the ventral striatum, commonly

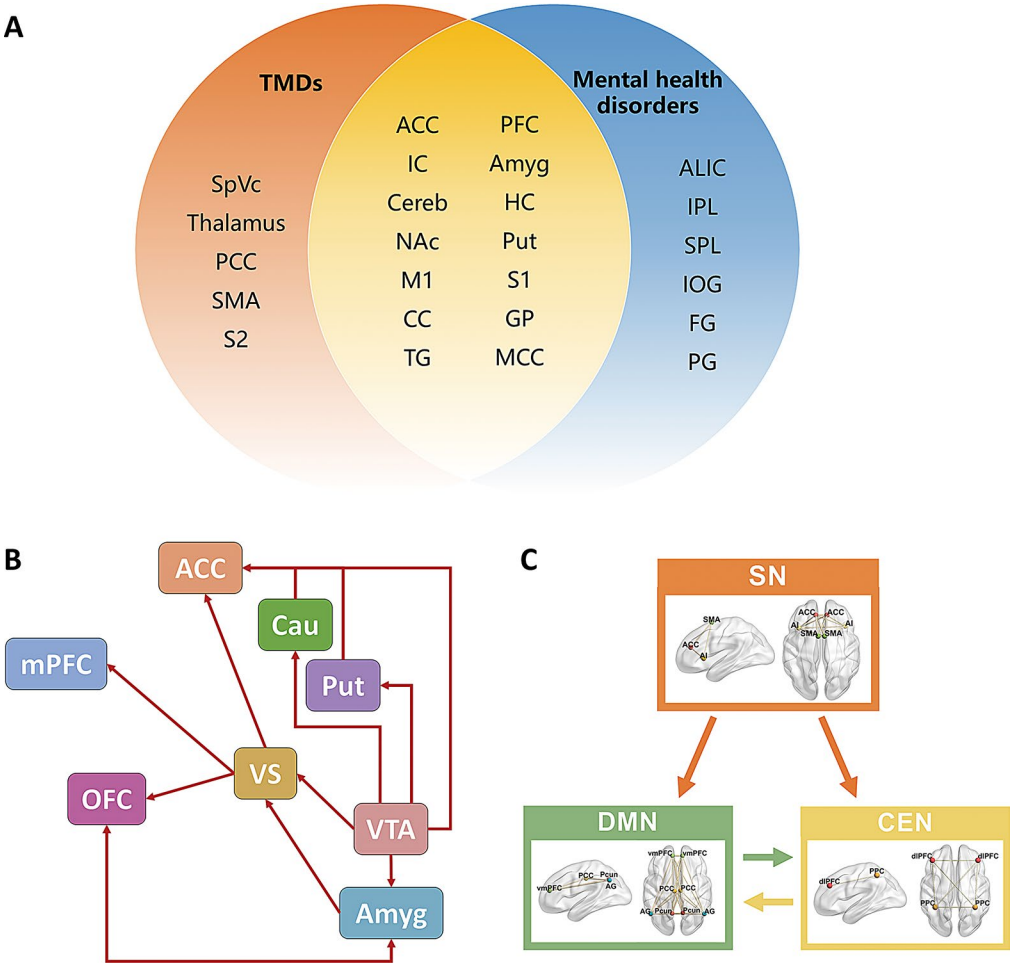

Fig. 7 Overlapping brain networks involved in TMDs and mental health disorders. (**A**) Overlaps of altered brain regions. The background color of the brain regions indicates the frequency of abnormal changes observed in MRI studies: darker shades represent regions with a higher frequency of abnormalities, while lighter shades indicate lower frequencies. (**B**) Brain reward system. (**C**) Triple network model. Abbreviations: SpVc, superior parietal lobule; PCC, posterior cingulate cortex; SMA, supplementary motor area; S2, secondary somatosensory cortex; ACC, anterior cingulate cortex; PFC, prefrontal cortex; IC, insular cortex; Amyg, amygdala; ALIC, anterior limb of the internal capsule; Cereb, cerebellum; HC, hippocampus; NAc, nucleus accumbens; M1, primary motor cortex; CC, corpus callosum; TG, temporal gyri; Put, putamen; S1, primary somatosensory cortex; GP, globus pallidus; MCC, middle cingulate cortex; IPL, inferior paietal lobule; SPL, superior parietal lobule; IOG, inferior occipital gyrus; FG, fusiform gyrus; PG, parietal gyri; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; Cau, caudate; VS, ventral striatum; VTA, ventral tegmental area; vmPFC, ventral medial prefrontal cortex; AG, angular gyrus; Pcun, precuneus; dlPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; AI, anterior insula cortex

referred to as the NAc, plays a key role in dopamine-mediated behaviors such as reward and pleasure [128]. Both regions receive dopamine signals from the midbrain, specifically from the VTA, which is involved in processing pain and regulating emotion [129]. Frauke et al. found that dorsal striatum responses associated with anhedonia and impaired reward processing might predict the onset of chronic pain, regardless of genetic predisposition [130]. There was also a decrease in GMV in the left putamen, along with decreased dynamic FC between the left putamen and the ACC in TMDs patients [131]. However, the decrease in GMV in NAc in TMDs patients was not significant [131]. Furthermore, Chen et al. discovered that abnormal functional connectivity (Fc) within the left striatal-orbitofrontal pathway could serve as a mediator linking pain and depressive symptoms in patients with TMDs [132]. In MDD, there was a reduction in GMV in the bilateral anterior cingulate cortex and right striatum, while in ANX, there was a decrease in GMV in the left striatum and amygdala [133]. Ding et al. found decreased FC within the reward system in recurrent MDD [134]. Furthermore, Bore et al. conducted an analysis of evidence derived from neuroimaging meta-analyses and discovered that both adults and adolescents diagnosed with depression demonstrated reductions in activity within the caudate and subgenual ACC [135]. In addition, Zhou et al. found that a significant negative correlation between the pgACC-caudate hypoconnectivity and percentage of female MDD patients [136].

The triple network model of psychopathology, which includes the salience network (SN), central executive network (CEN), and default mode network (DMN), was first proposed by Menon in 2011 [137]. The SN plays a crucial role in regulating the switch between the brain's two primary control networks: the DMN, associated with internal processing, and the CEN, associated with external processing. In a healthy brain, these two networks are not simultaneously active or operating. The key functional regions of the SN are primarily located in the ACC, anterior insula cortex (AIC), and pre-SMA [138]. Hyperactivity of the SN is associated with both physical and psychological vulnerabilities. Specifically, excessive activity in the AIC-dorsal ACC pathway is primarily related to emotional disorders, particularly heightened anxiety and neuroticism [139]. In individuals with depression, responses to negative stimuli are characterized by increased activity in the AIC, ACC, and amygdala [140]. Furthermore, activation of the ACC, insula cortex, and S1 is commonly observed in cases of orofacial pain [141]. The AIC, which serves a central role within the SN consists of three distinct regions, each with specialized functions: the posterior AIC is involved in sensorimotor processing, the dorsal AIC participates in cognitive control and redirects information to the dlPFC -posterior parietal cortex loop, and the ventral AIC is engaged in affective processes, directing affective stimuli to specific areas within the limbic cortex and mPFC [138]. The mPFC and insula cortex are also involved in both the learning and persistence of threat responses and their regulation [142, 143]. In patients with TMDs, the levels of anxiety and perceived pain were associated with variations in individual insula activity [144, 145].

The DMN comprises several key brain regions, including mPFC, the posterior cingulate cortex (PCC)/precuneus, inferior parietal lobule, and bilateral temporal cortex [146]. In the brain's resting state, when it is not actively engaged in focused, goal-directed tasks, the activity of the DMN increases, facilitating the processing of internal thoughts [147]. Dysfunctions in the DMN may be linked to cognitive and behavioral impairments seen in painful TMDs patients [148]. Kuyci et al. used fMRI to show that painful TMDs patients who frequently ruminated on pain exhibited increased Fc between the mPFC and various DMN regions, such as PCC/precuneus, retrosplenial cortex, and parts of the visual cortex [149]. Additionally, DMN dysregulation, which is mediated by key aspects of depression-related cognitive impairment, serves to underpin the neurobiological risk for recurrent depression [150]. In a meta-analysis, Briley et al. identified reduced connectivity between the amygdala and the DMN in patients with anxiety and depression [151]. Furthermore, in patients with recurrent MDD, disrupted NAc FCs in the DMN were observed [134].

The CEN comprises primarily the dlPFC and posterior parietal cortex, critical for executing functions and demanding cognitive tasks aligned with specific goals. Among patients with TMDs, the corpus callosum exhibited increased FC with the frontal pole but decreased connectivity with the dlPFC [152, 153]. Chen et al. discovered reduced FC between the dlPFC and the amygdala, along with abnormal FC in the left striatal-orbitofrontal pathway, potentially mediated the relationship between pain and depressive symptoms, possibly due to a greater engagement in internally-directed cognitive processes [132]. Additionally, Picó-Pérez et al. observed that individuals with anxiety disorders engage the regulatory CEN to a certain extent during cognitive reappraisal, albeit with reduced activation levels [154]. Moreover, Xu et al. noted hypo-connectivity between the affective network and both CEN and the DMN, alongside a disconnection of CEN from DMN [155]. In patients with comorbid anxiety and MDD, decreased FC was detected not only between the amygdala and both DMN and CEN, potentially associated with feelings of low mood, impaired concentration, and heightened sensitivity to negative stimuli [151].

Recent studies employing MR analyses have sought to explore the causal relationships between brain

resting-state networks (RSNs) dysfunctions and TMDs or mental health disorders. For example, Lin et al. found that, in the forward MR analysis, specific brain regions like the left caudal middle frontal gyrus (reduced thickness) and the right superior frontal gyrus (increased GMV) demonstrated significant causal effects on TMDs [156]. In the reverse MR analysis, TMDs showed notable causal impacts on various brain regions, including the left medial orbitofrontal cortex (reduced thickness), left magnocellular nucleus (reduced volume), and the right inferior-lateral ventricle (reduced intensity) [156]. Furthermore, the anterior division of the left superior temporal gyrus exhibited increased GMV due to TMDs [156]. Regarding mental health disorders, Huang et al. identified that structural connectivity within the limbic network, characterized by increased white matter integrity, might serve as an etiological factor for depression. However, they did not find evidence supporting a causal effect of depressive disorders on the structural connectivity of the limbic network [157]. Additionally, Zanoaga et al. reported that a reduced area of the right PCC and decrease in GMV in the right anterior STG directly affect ANX [158]. It is essential to acknowledge that these findings may not be universally generalizable across diverse populations or conditions, given their context specificity.

Clinical therapy

The etiology of TMDs is biopsychosocial and multifactorial, necessitating the adoption of a comprehensive approach to their management [4]. The comorbidity between TMDs and mental health disorders implies that treating TMDs could have positive effects on mental health, and conversely, managing mental health conditions could help reduce TMDs symptoms. Present clinical interventions vary; some aim at relieving TMDs symptoms specifically, while others target mental health improvement. Moreover, certain therapeutic strategies can effectively address symptoms of both TMDs and mental health disorders (Fig. 8).

Impact of TMDs treatment on mental health

Treatment for TMD symptoms typically includes a combination of non-invasive interventions, such as physical modality therapy, manual therapy, therapeutic exercises, and occlusal splints. While invasive interventions, such as open TMJ surgery, arthroscopy, and minimally invasive muscular and intra-articular injections [159], may be considered in more severe or refractory cases, non-invasive treatments are often the first-line approach for most patients [4]. A guideline analysis has identified moderate to high-level evidence supporting the effectiveness of several interventions for managing moderate chronic pain associated with TMDs [160]. These interventions include cognitive behavioral therapy (CBT), therapist-assisted mobilization, manual trigger point therapy, supervised postural exercises, and supervised jaw exercises and stretching. The guideline strongly recommends these interventions for adult patients suffering from moderate chronic pain, measured at 4 to 6 cm on a 10 cm pain scale. It is well known that reducing symptoms of disease can reduce pain, restore normal social functioning, and consequently improve mental health. In a five-year follow-up study of 234 participants with chronic TMDs, results showed that 49% of participants achieved complete recovery, while 14% reported more than a 50% reduction in pain [161]. Participants who were pain-free at the five-year mark had consistently low levels of psychopathology from baseline to follow-up [161]. Those who experienced at least a 50% reduction in pain initially had higher levels of depression, anxiety and somatization, but these psychological symptoms showed significant improvement over the follow-up period [161].

Current clinical trials primarily assessed outcomes related to pain intensity, mechanical sensitization, and mandibular function [162, 163]. However, numerous studies indicated a weak association between the reduction of pain intensity and the success of treatments for TMDs [164, 165]. In contrast, other research highlighted a stronger association between treatment success and factors such as jaw movements, patient characteristics, and comorbidities, including depression, anxiety, and somatization [164, 165]. Therefore, a multidimensional approach to evaluating treatment outcomes is essential, encompassing behavioral, psychosocial, and mental health aspects [163–166].

Effectiveness of mental health interventions on TMDs

The biopsychosocial model serves as a crucial framework for understanding the complex nature of chronic pain and informing care strategies. Within this model, psychological processes are identified as key factors that influence both risk and resilience. This emphasis has prompted extensive research into psychological interventions designed to alter the underlying processes associated with pain, distress, and disability [167].

Cognitive behavioral therapy (CBT) can improve the dysfunction of brain regions associated with pain processing, including the PFC, ACC, insula cortex, and amygdala [168]. Moreover, CBT enhances top-down pain control by releasing neurotransmitters such as opioids, 5-HT, and NE, which inhibit nociceptive signaling [169]. A recent RCT suggested that repetitive CBT delivered via smartphone applications might help alleviate clinical symptoms in TMDs patients [170]. A systematic review of RCTs (primarily CBT-based) found CBT might reduce pain intensity more than alternative therapies (e.g., oral appliances, medication) or controls at long-term follow-up, but not post-treatment. For pain disability outcomes,

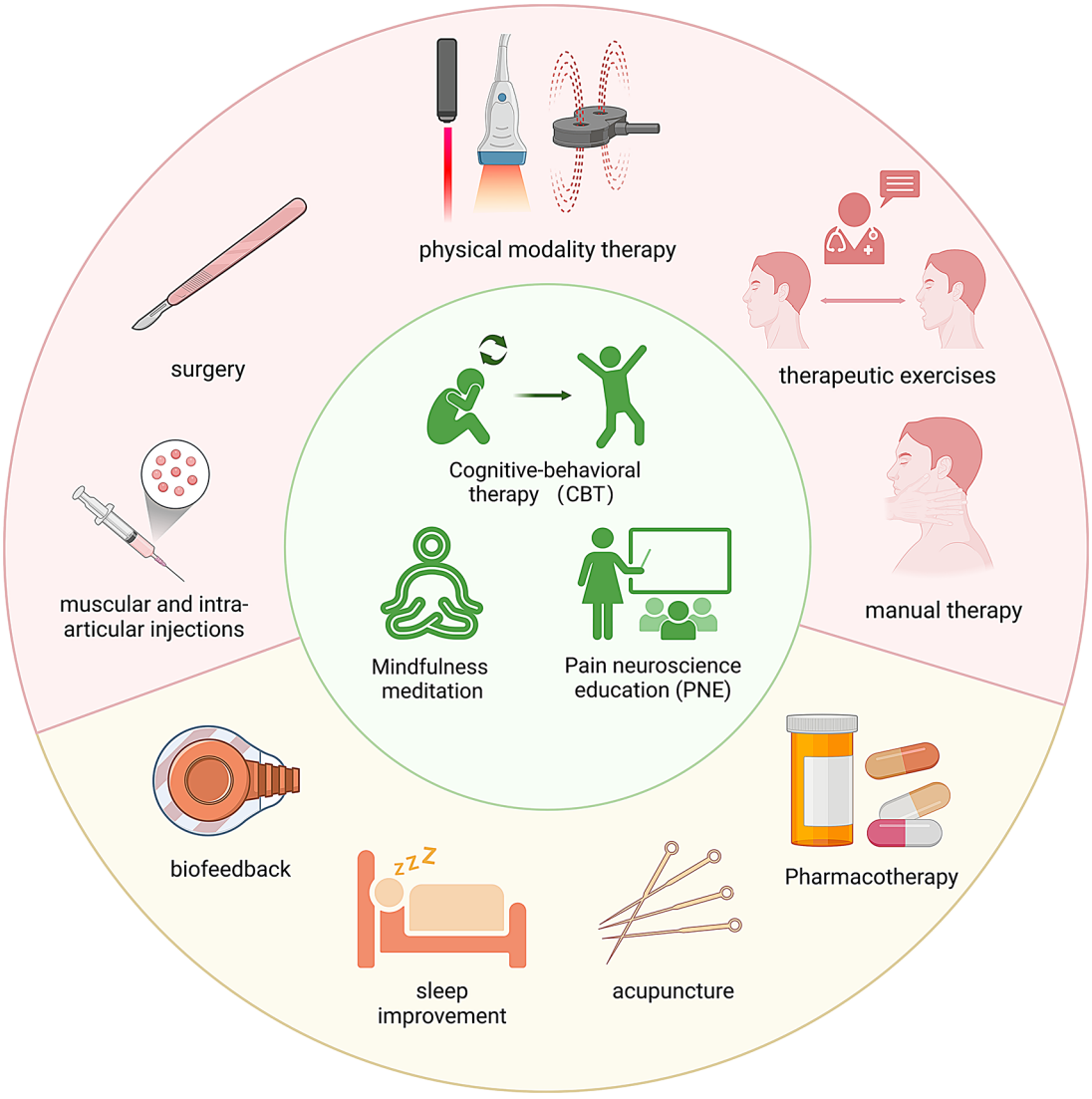

Fig. 8 Clinical therapy for managing TMDs symptoms and mental health disorders

CBT showed no significant advantage over other treatments or controls [171]. However, these observations could not overcome the overarching limitation of low-certainty evidence; therefore, current evidence remains insufficient to confirm the efficacy of CBT for painful TMDs [171]. High-quality RCTs are required to establish effectiveness. In addition, the CBT protocol requires refinement to enhance its effectiveness in treating TMDs. It should not only focus on managing negative emotions but also address kinesiophobia, cognitive distortions, and deficiencies in reward mechanisms [172]. This comprehensive approach is essential for improving treatment outcomes.

In addition to CBT, mindfulness practices and pain neuroscience education (PNE) are significant mental health interventions. Neuroimaging studies have explored the neurological mechanisms behind mindfulness, highlighting brain regions such as the PCC that are involved in self-referential processing [173]. A RCT conducted in India with chronic patients demonstrated that mindfulness positively influenced pain intensity, pain acceptance, and perceived stress [174]. In addition, a meta-analysis showed that while mindfulness-based interventions were not superior to traditional cognitive-behavioral therapies for chronic pain, they were valuable alternatives [175]. Recent meta-analyses indicated that PNE durations of 100, 200, and 400 min were found to surpass the minimum clinically important differences for reducing kinesiophobia, anxiety symptoms, and catastrophizing [176]. These findings suggest that clinicians can use PNE to provide tailored education that helps patients reconceptualize pain and address pain-mediating factors, possibly by adjusting the duration of PNE based on specific clinical goals.

Psychological treatments demonstrated comparable efficacy to standard interventions (e.g., occlusal appliances, pharmacological approaches, jaw exercises) in reducing TMDs-related pain intensity, as evidenced in a recent meta-analysis [177]. However, combining psychological treatments with standard approaches appeared to yield even better results. This suggested that psychological therapies could serve as a promising supplementary treatment option for painful TMDs [177]. Nevertheless, further high-quality RCTs are required to validate these findings. In addition, future psychological research on chronic pain should consider adopting a more individualized and process-oriented approach, which focuses on theoretically grounded and evidence-supported mechanisms of change.

Therapeutic approaches for managing TMDs symptoms and mental health disorders

Previous methods primarily focused on TMDs symptoms or mental health disorders. The following approaches will each address both TMDs symptoms and mental health disorders through similar or different pathways.

In addition to the injectable medications previously mentioned, several oral medications are available for the treatment of TMDs and mental health disorders. These include non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, anticonvulsants, antidepressants, and corticosteroids. A systematic review suggested that for painful TMDs of musculoskeletal origin, evidence supported the use of therapies such as botulinum toxin, granisetron, platelet-rich plasma, and muscle relaxants, while for painful TMDs of arthrogenous origin, pharmacological approaches like NSAIDs, glucocorticosteroids, hyaluronic acid, and dextrose were effective [178]. Antidepressants can modulate pain perception and transmission. Their primary mechanism of action involves increasing the inhibition of afferent pathways to the supraspinal and spinal regions, as well as enhancing the levels of NE and 5-HT at the synaptic junction [179]. Consequently, antidepressants possess analgesic properties that operate independently of their mood-regulating effects. Barakat et al. reviewed the potential of fluoxetine in managing nociceptive pain, particularly when combined with morphine [180]. Pain often comes with other symptoms, and antidepressants can also help with muscle relaxation, mood enhancement, and improved sleep quality [181]. Furthermore, antidepressants exhibit anti-inflammatory effects. A 26-week study on patients with depression found significant reductions in 17 out of 27 inflammatory markers during treatment [182]. However, the risk of side effects underscores the necessity for cautious use of these medications.

Biofeedback is a technique that provides patients with real-time biological information, allowing them to respond effectively and mitigate negative effects [183]. A RCT examined the efficacy of a full-occlusion biofeedback splint in treating sleep bruxism and TMDs. The study revealed a statistically significant reduction in both the frequency and duration of bruxing activity [184]. Furthermore, the intervention led to a decrease in pain experienced in the masticatory muscles. Beyond its applications in physical health, biofeedback is also employed in the treatment of mental health disorders. It has proven to be an effective intervention for individuals with MDD and depressive symptoms, despite its relatively modest impact on these symptoms. In addition to traditional techniques such as electromyography (EMG) biofeedback, innovative approaches like gamified biofeedback on mobile devices have emerged as tools for stress management [185].

Acupuncture, a traditional Chinese medicine practice, involves inserting fine needles into targeted acupoints to achieve therapeutic outcomes. The choice of acupoints is tailored to the specific condition being addressed. It is frequently used in managing chronic pain and is also known to reduce stress and anxiety by promoting relaxation. In a double-blind RCT by Liao et al., the effectiveness of acupuncture tailored for pain and depression was examined. The study demonstrated that both types of acupoints were effective in treating patients with co-occurring pain and depression [186].

Good sleep quality is a crucial factor in mental health and effective pain management. A prospective cohort study revealed that patients with obstructive sleep apnea (OSA) experienced notable reductions in the intensity of pain-related TMDs and headaches attributed to TMDs after 18 months of OSA treatment [187]. However, as a non-randomized study, potential selection bias and confounding factors might limit causal conclusions. Further RCTs are required to validate these findings. Furthermore, a meta-analysis encompassing 65 trials and 8,608 participants found that improving sleep positively impacted mental health, irrespective of the severity of mental health difficulties or the presence of comorbid conditions [188].

Conclusion

A substantial body of evidence from epidemiological studies supports the association between TMDs and mental health disorders. This review has explored the mechanisms through which these conditions can adversely affect each other. Potential shared vulnerabilities between TMDs and mental health disorders may arise from genetic and epigenetic predispositions, as well as psychosocial and behavioral factors. Additionally, there is considerable overlap in pathophysiology mechanisms and brain regions involved in both conditions, suggesting a biological basis for their mutual influence.

Treatment approaches informed by these mechanisms have shown promising results, although definitive causal relationships and the specific mediating and moderating factors remain underexplored. Therefore, future prospective research is necessary to further elucidate the causal pathways between TMDs and mental health disorders.

Effective treatment requires a multidisciplinary approach. Healthcare professionals from various disciplines, such as neurology, pain medicine, psychiatry, psychology, otolaryngology, and physical therapy, should be involved. This collaboration ensures a holistic treatment plan that addresses the complexity of both TMDs and mental health disorders. Moreover, prioritizing personalized medical interventions that address both physical and mental health is crucial. Individualized treatment involves tailoring nursing and management strategies to align with each patient's clinical condition and psychological characteristics. This approach not only enhances patient comfort and compliance but also promotes early and sustained recovery. In addition, it is of great importance to adopt conservative, personalized, and non-invasive treatment methods due to the psychological vulnerability of TMDs patients [189]. Avoiding irreversible interventions is crucial, as excessive or inappropriate treatments may worsen the condition [190, 191].

In summary, while current evidence underscores the interconnectedness of TMDs and mental health disorders, further research is required to gain a comprehensive understanding of the underlying mechanisms and to optimize treatment strategies. A multidisciplinary, individualized approach remains the most effective path forward, ensuring that each patient's unique needs and circumstances are met.

Supplementary Information

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Supplementary Material 1

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Author contributions
J. W. and X. F. conceived the idea and J. W. drafted the manuscript. J. W., X. F. and J. L. contributed to the manuscript revisions. J. L., T. Z., F. C., S. J., Z. W., X. F., Q. C. and X. C. provided supervision and critical feedback. All authors reviewed and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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